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Pine bark (*Pinus* spp.) extract for treating chronic disorders (Review)

Robertson NU, Schoonees A, Brand A, Visser J

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[Intervention Review]

Pine bark (*Pinus* spp.) extract for treating chronic disorders

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ABSTRACT

Background

Pine bark (*Pinus* spp.) extract is rich in bioflavonoids, predominantly proanthocyanidins, which are antioxidants. Commercially-available extract supplements are marketed for preventing or treating various chronic conditions associated with oxidative stress. This is an update of a previously published review.

Objectives

To assess the efficacy and safety of pine bark extract supplements for treating chronic disorders.

Search methods

We searched three databases and three trial registries; latest search: 30 September 2019.

We contacted the manufacturers of pine bark extracts to identify additional studies and hand-searched bibliographies of included studies.

Selection criteria

Randomised controlled trials (RCTs) evaluating pine bark extract supplements in adults or children with any chronic disorder.

Data collection and analysis

Two authors independently assessed trial eligibility, extracted data and assessed risk of bias. Where possible, we pooled data in meta-analyses. We used GRADE to evaluate the certainty of evidence.

Primary outcomes were participant- and investigator-reported clinical outcomes directly related to each disorder and all-cause mortality. We also assessed adverse events and biomarkers of oxidative stress.

Main results

This review included 27 RCTs (22 parallel and five cross-over designs; 1641 participants) evaluating pine bark extract supplements across 10 chronic disorders: asthma (two studies; 86 participants); attention deficit hyperactivity disorder (ADHD) (one study; 61 participants); cardiovascular disease (CVD) and risk factors (seven studies; 338 participants); chronic venous insufficiency (CVI) (two studies; 60 participants); diabetes mellitus (DM) (six studies; 339 participants); erectile dysfunction (three studies; 277 participants); female sexual dysfunction (one study; 83 participants); osteoarthritis (three studies; 293 participants); osteopenia (one study; 44 participants) and traumatic brain injury (one study; 60 participants).

Two studies exclusively recruited children; the remainder recruited adults. Trials lasted between four weeks and six months. Placebo was the control in 24 studies. Overall risk of bias was low for four, high for one and unclear for 22 studies.

In adults with asthma, we do not know whether pine bark extract increases change in forced expiratory volume in one second (FEV₁) % predicted/forced vital capacity (FVC) (mean difference (MD) 7.70, 95% confidence interval (CI) 3.19 to 12.21; one study; 44 participants; very low-certainty evidence), increases change in FEV₁ % predicted (MD 7.00, 95% CI 0.10 to 13.90; one study; 44 participants; very low-certainty evidence), improves asthma symptoms (risk ratio (RR) 1.85, 95% CI 1.32 to 2.58; one study; 60 participants; very low-certainty evidence) or increases the number of people able to stop using albuterol inhalers (RR 6.00, 95% CI 1.97 to 18.25; one study; 60 participants; very low-certainty evidence).

In children with ADHD, we do not know whether pine bark extract decreases inattention and hyperactivity assessed by parent- and teacher-rating scales (narrative synthesis; one study; 57 participants; very low-certainty evidence) or increases the change in visual-motoric coordination and concentration (MD 3.37, 95% CI 2.41 to 4.33; one study; 57 participants; very low-certainty evidence).

In participants with CVD, we do not know whether pine bark extract decreases diastolic blood pressure (MD -3.00 mm Hg, 95% CI -4.51 to -1.49; one study; 61 participants; very low-certainty evidence); increases HDL cholesterol (MD 0.05 mmol/L, 95% CI -0.01 to 0.11; one study; 61 participants; very low-certainty evidence) or decreases LDL cholesterol (MD -0.03 mmol/L, 95% CI -0.05 to 0.00; one study; 61 participants; very low-certainty evidence).

In participants with CVI, we do not know whether pine bark extract decreases pain scores (MD -0.59, 95% CI -1.02 to -0.16; one study; 40 participants; very low-certainty evidence), increases the disappearance of pain (RR 25.0, 95% CI 1.58 to 395.48; one study; 40 participants; very low-certainty evidence) or increases physician-judged treatment efficacy (RR 4.75, 95% CI 1.97 to 11.48; 1 study; 40 participants; very low-certainty evidence).

In type 2 DM, we do not know whether pine bark extract leads to a greater reduction in fasting blood glucose (MD 1.0 mmol/L, 95% CI 0.91 to 1.09; one study; 48 participants; very low-certainty evidence) or decreases HbA1c (MD -0.90 %, 95% CI -1.78 to -0.02; 1 study; 48 participants; very low-certainty evidence). In a mixed group of participants with type 1 and type 2 DM we do not know whether pine bark extract decreases HbA1c (MD -0.20 %, 95% CI -1.83 to 1.43; one study; 67 participants; very low-certainty evidence).

In men with erectile dysfunction, we do not know whether pine bark extract supplements increase International Index of Erectile Function-5 scores (not pooled; two studies; 147 participants; very low-certainty evidence). In women with sexual dysfunction, we do not know whether pine bark extract increases satisfaction as measured by the Female Sexual Function Index (MD 5.10, 95% CI 3.49 to 6.71; one study; 75 participants; very low-certainty evidence) or leads to a greater reduction of pain scores (MD 4.30, 95% CI 2.69 to 5.91; one study; 75 participants; very low-certainty evidence).

In adults with osteoarthritis of the knee, we do not know whether pine bark extract decreases composite Western Ontario and McMaster Universities Osteoarthritis Index scores (MD -730.00, 95% CI -1011.95 to -448.05; one study; 37 participants; very low-certainty evidence) or the use of non-steroidal anti-inflammatory medication (MD -18.30, 95% CI -25.14 to -11.46; one study; 35 participants; very low-certainty evidence). We do not know whether pine bark extract increases bone alkaline phosphatase in post-menopausal women with osteopenia (MD 1.16 ug/L, 95% CI -2.37 to 4.69; one study; 40 participants; very low-certainty evidence).

In individuals with traumatic brain injury, we do not know whether pine bark extract decreases cognitive failure scores (MD -2.24, 95% CI -11.17 to 6.69; one study; 56 participants; very low-certainty evidence) or post-concussion symptoms (MD -0.76, 95% CI -5.39 to 3.87; one study; 56 participants; very low-certainty evidence).

For most comparisons, studies did not report outcomes of hospital admissions or serious adverse events.

Authors' conclusions

Small sample sizes, limited numbers of RCTs per condition, variation in outcome measures, and poor reporting of the included RCTs mean no definitive conclusions regarding the efficacy or safety of pine bark extract supplements are possible.

PLAIN LANGUAGE SUMMARY

Using pine bark supplements to help treat a variety of chronic diseases

Review question

Can pine bark antioxidant supplements help to treat chronic diseases?

Background

The main ingredients in pine bark extract supplements are proanthocyanidins, which are antioxidants. These supplements are marketed to prevent or treat a wide range of chronic diseases. This is an update of a previously published review, where we assessed how well these supplements work for treating chronic diseases, as well as their safety.

Search date

The evidence is current to 30 September 2019.

Study characteristics

We included 27 studies (1641 participants) across 10 chronic diseases. These included: asthma (two studies; 86 participants), attention deficit hyperactivity disorder (ADHD) (one study; 61 participants), heart disease and risk factors (seven studies; 332 participants), chronic venous insufficiency (leg veins not working effectively; two studies; 60 participants), diabetes (six studies; 336 participants), erectile dysfunction (three studies; 227 participants), female sexual dysfunction (one study; 75 participants), osteoarthritis (cartilage damage in joints; three studies; 293 participants), osteopenia (beginning of bone mass loss; one study; 44 participants) and traumatic brain injury (one study; 56 participants). Two of the studies were conducted exclusively in children; the others were in adults. Studies compared pine bark supplements with placebo (i.e. a dummy supplement) or non-antioxidant interventions and participants were randomly selected for one treatment or the other. The duration of treatment ranged from four weeks to six months.

Key results

For most outcomes across the different chronic diseases we only included one study with a small number of participants. In adults with asthma, we do not know whether pine bark extract increases lung function, improves asthma symptoms or increases the number of people able to stop using albuterol inhalers (a specific type of asthma pump).

In children with ADHD, we do not know whether pine bark supplements decrease inattention and hyperactivity (assessed by parents and teachers) or whether it increases co-ordination and concentration.

In people with heart disease we do not know if pine bark supplements decrease blood pressure and LDL cholesterol (the bad type) or whether it increases HDL cholesterol (the good type).

In adults with chronic venous insufficiency we do not know whether pine bark supplements decrease pain, increase the number of people free of pain, or how well doctors think the treatment works. In people with type 2 diabetes, we do not know whether pine bark supplements improve blood sugar levels or HbA1c levels (the long-term marker for measuring blood sugar control); we also do not know if pine bark supplements decrease HbA1c in people with type 1 or type 2 diabetes.

In men with erectile dysfunction, we do not know if pine bark supplements increase erectile function. Similarly, in women with sexual dysfunction, we do not know if pine bark supplements increase sexual satisfaction or reduce pain.

In adults with osteoarthritis, it is not clear if pine bark supplements improve pain, swelling or stiffness in the knee, or whether it decreases the use of anti-inflammatory drugs. We also do not know if pine bark supplements increase bone formation in postmenopausal women with weakened bones. Lastly, in people with a traumatic brain injury, it is not clear if pine bark supplements improve memory and post-concussion symptoms.

For most comparisons, studies did not report outcomes of hospital admissions or serious adverse events.

With the available studies, we cannot clearly say how well (or not) pine bark supplements work and whether they are safe.

Quality of the evidence

The overall risk of bias was low for four studies, high for one and unclear for 22 studies. By this we mean the extent to which the methods used in a study enable it to determine the truth. The certainty of evidence was very low for all outcomes across all chronic diseases in the included studies.

SUMMARY OF FINDINGS

Summary of findings 1. Pine bark extract compared to placebo for the treatment of Asthma

Pine bark extract compared to placebo for the treatment of asthma

Patient or population: children and adults with asthma diagnosed by American Thoracic Society criteria

Setting: outpatient clinics (USA and Iran)

Intervention: pine bark extract tablets 1 mg/lb/day for 4 weeks

Comparison: placebo tablets for 4 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pine bark extract				
Participant-reported						
Decrease in asthma symptoms	Study population		RR 1.85 (1.32 to 2.58)	60 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b, c}	It is not known whether pine bark extract supplements improve asthma symptoms.
Follow-up: 3 months	533 per 1000	987 per 1000 (704 to 1000)				Results from a small, single paediatric study in the USA.
Participants off albuterol inhaler	Study population		RR 6.00 (1.97 to 18.25)	60 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,d}	It is not known whether pine bark extract supplements increase the number of individuals who stop using albuterol inhalers.
Follow-up: 3 months	100 per 1000	600 per 1000 (197 to 1000)				Results from a small, single paediatric study in the USA.
Investigator-reported						
Change in FEV ₁ % predicted	The mean change in FEV ₁ % predicted was 70%.		-	44 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{b,d,e}	It is not known whether pine bark extract supplements increase FEV ₁ % predicted slightly, where an increased FEV ₁ % means improvement.
Follow-up: 1 month						Results from a small, single study in adults in Iran.

Change in FEV ₁ % predicted/FVC	The mean change in FEV ₁ % predicted/FVC was 65.5%.	MD 7.70 % higher (3.19 higher to 12.21 higher).	-	44 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{b,c,e}	It is not known whether pine bark extract supplements increase the ratio FEV ₁ % predicted/FVC, where an increased ratio means improvement Results from a small, single study in adults in Iran.
Follow-up: 1 month						
All-cause mortality	No studies reported this outcome.					
Serious adverse events	No studies reported this outcome.					

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FEV₁**: forced expiratory volume in 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **RCT**: randomised controlled trial; **RR**: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for risk of bias: concerns about selection bias.

^b Downgraded once for indirectness: single study only.

^c Downgraded once for imprecision: optimal information size not met.

^d Downgraded twice for imprecision: optimal information size not met and 95% CI includes both little or no difference or an important benefit.

^e Downgraded once for risk of bias: concerns regarding selection, performance and detection bias.

Summary of findings 2. Pine bark extract compared to placebo for the treatment of ADHD

Pine bark extract compared to placebo for the treatment of ADHD

Patient or population: children with ADHD

Setting: outpatients (Slovakia)

Intervention: oral pine bark extract tablets 1 mg/kg once daily

Comparison: placebo tablets once daily

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pine bark extract

Participant-reported					
Inattention assessed with: CAP, CTRS and CPRS scores Follow-up: 1 month	After treatment the mean CAP score was 0.44 lower than baseline.	After treatment the MD in CAP scores was 1.92 lower (95% CI 3.33 lower to 0.51 lower) than in the placebo group.	57 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements decrease inattention as measured by CAP, CTRS and CPRS scores, where a lower score indicates improvement.
	After treatment the mean CTRS score was 0.24 higher than baseline.	After treatment the MD in CTRS scores was 1.03 lower (95% CI 5.77 lower to 3.71 higher) than in the placebo group.			
	After treatment the mean CPRS score was 0.93 lower than baseline.	After treatment the MD in CPRS scores was 0.41 higher (95% CI 6.62 lower to 7.44 higher) than in the placebo group.			
Hyperactivity assessed with: CAP, CTRS and CPRS scores Follow-up: 1 month	After treatment the mean CAP score was 0.06 higher than baseline.	After treatment the MD in CAP scores was 1.62 lower (95% CI 9.03 lower to 5.79 higher) than in the placebo group.	57 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,c,d}	It is not known whether pine bark extract supplements decrease hyperactivity as measured by CAP, CTRS and CPRS scores, where a lower score indicates improvement.
	After treatment the mean CTRS score was 1.04 lower than baseline.	After treatment the MD in CTRS scores was 0.69 lower (95% CI 2.51 lower to 1.13 higher) than in the placebo group.			
	After treatment the mean CPRS score was 0 (indicating no change from baseline).	The MD as measured by CPRS scores was 1.85 lower (95% CI 3.91 lower to 0.21 higher).			
Investigator-reported					
Change in visual-motoric coordination and concentration score Follow-up: 1 month	The visual-motoric coordination and concentration score increased by 2.91 points.	With pine bark the change in score was 3.37 points higher (2.41 higher to 4.33 higher).	- 57 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,c}	It is not known whether pine bark extract supplements increase the visual-motoric coordination and concentration score (a higher score indicates improvement).

All-cause mortality	No studies reported this outcome.
Serious adverse events	No studies reported this outcome.

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ADHD: attention deficit hyperactivity disorder; **CAP:** child attention problems; **CI:** confidence interval; **CPRS:** Conner's Parent Rating Scale; **CTRS:** Conner's Teacher Rating Scale; **MD:** mean difference.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for indirectness: single study only.

^b Downgraded twice for imprecision: optimal information size not met and 95% CI includes the possibility of an important harm, as well as an unimportant and an important benefit.

^c Downgraded once for risk of bias: concerns regarding performance and detection bias, with an outcome of subjective nature.

^d Downgraded twice for imprecision: optimal information size not met; and the 95% CI includes an important benefit as well as an unimportant and important harm.

Summary of findings 3. Pine bark extract compared to placebo for the treatment of CVD

Pine bark extract compared to placebo for the treatment of CVD

Patient or population: adults with CVD

Setting: not reported

Intervention: pine bark extract 1x 10 g pouch daily, taken orally once sachet contents dissolved in 180 mL water resulting in an isotonic solution

Comparison: placebo 1x 10 g pouch daily, taken orally once sachet contents dissolved in 180 mL water resulting in an isotonic solution

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pine bark extract				
Participant-reported	No studies reported this outcome.					
Investigator-reported						

Diastolic blood pressure (mm Hg) Follow-up: 2 months	The mean diastolic blood pressure was 92 mm Hg.	MD 3.00 mm Hg lower (4.51 lower to 1.49 lower).	-	61 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements decrease diastolic blood pressure.
HDL cholesterol (mmol/L) Follow-up: 2 months	The mean HDL cholesterol was 0.96 mmol/L.	MD 0.05 mmol/L higher (0.01 lower to 0.11 higher).	-	61 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements increase HDL cholesterol.
LDL cholesterol (mmol/L) Follow-up: 2 months	The mean LDL cholesterol was 1.01 mmol/L.	MD 0.03 mmol/L lower (0.05 lower to 0.00).	-	61 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements decrease LDL cholesterol.
All-cause mortality	No studies reported this outcome.					
Serious adverse events: hospitalisation	Hospitalisation of 1 participant occurred in the pine bark extract supplement group of each included study.			176 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,b,d}	It is not known whether pine bark extract supplements increase hospitalisation.

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CVD**: cardiovascular disease; **HDL**: high-density lipoprotein; **LDL**: low-density lipoprotein; **RR**: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for indirectness: single study only.

^b Downgraded once for risk of bias: concerns regarding selection bias.

^c Downgraded once for imprecision: optimal information size not met.

^d Downgraded twice for imprecision: optimal information size not met; very few events and the 95% CI is very wide.

Summary of findings 4. Pine bark extract compared to placebo for the treatment of CVI

Pine bark extract compared to placebo for the treatment of CVI

Patient or population: adults with CVI

Setting: clinical centre (Italy)

Intervention: pine bark extract 100 mg 3 capsules per day for 2 months
Comparison: placebo 3 capsules per day for 2 months

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pine bark extract				
Participant-reported						
Pain scores Follow-up: 60 days	The mean pain score increased from base-line by 1.17 points.	The mean pain score with pine bark was 0.59 lower (1.02 lower to 0.16 lower).		40 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements decrease pain scores.
Disappearance of pain Follow-up: 60 days	Study population		RR 25.00 (1.58 to 395.48)	40 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,c,d}	It is not known whether pine bark extract supplements increase the disappearance of pain.
	None of the 20 participants in the placebo group reported that pain had disappeared.	12 out of 20 participants in the pine bark group (600 per 1000 reported pain had disappeared).				
Investigator-reported						
Treatment efficacy as judged by physician Follow-up: 2 months	Study population		RR 4.75 (1.97 to 11.48)	40 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,c,d}	It is not known whether pine bark extract supplements increase treatment efficacy, as judged by physician.
	200 per 1000.	950 per 1000 (394 to 1000).				
All-cause mortality	No studies reported this outcome.					
Serious adverse events	No studies reported this outcome.					

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CVI:** chronic venous insufficiency; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

- ^a Downgraded once for indirectness: one study only.
^b Downgraded once for imprecision: optimal information size not met.
^c Downgraded once for risk of bias: concerns regarding selection, performance and detection bias.
^d Downgraded twice for imprecision: optimal information size not met and the 95% CI is extremely wide.

Summary of findings 5. Pine bark extract compared to control for the treatment of diabetes mellitus type I

Pine bark extract compared to control for the treatment of diabetes mellitus type I

Patient or population: adults with diabetes mellitus type I

Setting: not reported (Italy)

Intervention: Pycnogenol® 50 mg capsule 3x per day orally for 6 weeks together with 100 mg powder from 2x 50 mg capsules placed on ulcerated area

Comparison: only standard ulcer care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with pine bark extract				
Participant-reported						
Microcirculation-related symptom scores: oral and local Pycnogenol® Follow-up: 6 weeks	The mean microcirculation-related symptom score for oral and local Pycnogenol® increased from baseline by 5.1	The mean microcirculation-related symptom score was 2.9 lower (5.4 lower to 0.4 lower).		16 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether oral and local Pycnogenol® decrease microcirculation-related symptom scores.
Investigator-reported						
Area of ulceration: oral and local Pycnogenol® Follow-up: 6 weeks	The mean area of ulceration with oral and local Pycnogenol® was 34 mm².	The mean area of ulceration was 23 mm² lower (27.44 lower to 18.56 lower).	-	16 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,d}	It is not known whether oral and local Pycnogenol® decrease the area of ulceration.
All-cause mortality	No studies reported this outcome.					
Serious adverse events	No studies reported this outcome.					

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for risk of bias: concerns regarding selection, performance and detection bias.

^b Downgraded once for indirectness: one study only.

^c Downgraded twice for imprecision: optimal information size not met and 95% CI includes both an unimportant and important benefit.

^d Downgraded once for imprecision: optimal information size not met.

Summary of findings 6. Pine bark extract compared to placebo for the treatment of diabetes mellitus type II

Pine bark extract compared to placebo for the treatment of diabetes mellitus type II

Patient or population: adults with diabetes mellitus type II

Setting: USA; not reported in other two studies

Intervention: Pycnogenol[®] for two studies and Diaberet for one

Comparison: placebo or untreated control group

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pine bark extract				
Participant-reported						
Visual acuity	Study population		RR 34.04 (2.17 to 533.19)	46 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements increase visual acuity.
Follow-up: 2 months	None of the 22 participants reported any change in visual acuity.	18 out of 24 participants (750 per 1000 reported "vision improvement").				
Investigator-reported						
Reduction in fasting blood glucose levels (mmol/L)	The mean reduction in fasting blood glucose levels was 0.32 mmol/L.	The reduction in fasting blood glucose was 1.0 mmol/L greater (0.91 greater to 1.09 greater).	-	48 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,c,d}	It is not known whether pine bark extract supplements lead to a greater reduction in fasting blood glucose levels.
Follow-up: 12 weeks						

HbA1C levels (%) Follow-up: 12 weeks	The mean HbA1C levels were 8%.	The mean HbA1C levels were 0.9% lower (1.78 lower to 0.02 lower).	-	48 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,c,d}	It is now known whether pine bark extract supplements decrease HbA1C levels.
Central macular thickness (μm) Follow-up: 6 months	The mean central macular thickness was 209.44 μm.	The mean central macular thickness was 8.94 μm lower (35.85 lower to 17.97 higher).	-	68 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,e,f}	It is not known whether pine bark extract supplements decrease central macular thickness.
All-cause mortality	No studies reported this outcome.					
Serious adverse events	No studies reported this outcome.					

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HbA1C**: glycated haemoglobin; **MD**: mean difference; **RCT**: randomised controlled trial; **RR**: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for indirectness: one study only.

^b Downgraded twice for imprecision: optimal information size not met and the 95% CI is extremely wide.

^c Downgraded once for risk of bias: concerns regarding selection, performance and detection bias.

^d Downgraded once for imprecision: optimal information size not met.

^e Downgraded once for risk of bias: concerns regarding selection bias.

^f Downgraded twice for imprecision: optimal information size not met and the 95% CI includes both an important harm and an important benefit.

Summary of findings 7. Pine bark extract compared to placebo for the treatment of diabetes mellitus type I and II combined

Pine bark extract compared to placebo for the treatment of diabetes mellitus type I and II combined

Patient or population: adults with diabetes mellitus type I and II combined

Setting: optometric practice focused on diabetic eye care

Intervention: DiVFuSS formula 2 capsules daily taken orally

Comparison: placebo 2 canola oil soft gel capsules daily taken orally

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pine bark extract				
Participant-reported						
Diabetic peripheral neuropathy symptom score: number of participants who showed no change	Study population		RR 0.78 (0.58 to 1.04)	67 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b}	It is not known whether pine bark extract supplements decrease the number of participants showing no change in diabetic peripheral neuropathy symptoms.
Follow-up: 6 months	821 per 1000.	641 per 1000 (476 to 854).				
Investigator-reported						
Change in HbA1C (%)	The mean increase in HbA1C (%) was 0.1.	The mean change in HbA1C was 0.2 lower (1.83 lower to 1.43 higher).	-	67 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,c}	It is not known whether pine bark extract supplements decrease change in HbA1C from baseline.
Follow-up: 6 months						
All-cause mortality	No studies reported this outcome.					
Serious adverse events	No studies reported this outcome.					

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DiVFuSS**: Diabetes Visual Function Supplement Study; **HbA1C**: glycated haemoglobin; **MD**: mean difference; **RCT**: randomised controlled trial; **RR**: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for indirectness: one study only.

^b Downgraded twice for imprecision: optimal information size not met and 95% CI includes both an important benefit and unimportant harm.

^c Downgraded twice for imprecision: optimal information size not met and 95% CI includes both an important benefit and an important harm.

Summary of findings 8. Pine bark extract compared to placebo for the treatment of erectile dysfunction

Pine bark extract compared to placebo for the treatment of erectile dysfunction

Patient or population: men with erectile dysfunction

Setting: outpatient urology clinics in Europe.

Intervention: IDIProst® Gold, 1x 950 mg capsule per day (Cai); Pycnogenol® 2x 20 mg pills 3x per day (Durackova); Prelox®, 4x tablets daily (Ledda)

Comparison: Serenoa repens in the study that gave IDIProst® Gold (Cai); placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Pine bark extract				
Participant-reported						
IIEF-5 score Follow-up: 3 months	2 studies reported improved IIEF-5 scores (not pooled).		-	147 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,b,c,d}	It is not known whether pine bark extract supplements increase IIEF-5 scores.
IIEF erectile function domain score Follow-up: 6 months	The mean IIEF erectile function domain score was 19.1 points.	The mean IIEF erectile function domain score was 8.1 points higher (7.12 higher to 9.08 higher).	-	111 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{c,e,f}	It is not known whether pine bark extract supplements increase IIEF erectile function domain scores.
Investigator-reported						
Total plasma testosterone (nmol/L) Follow-up: 6 months	The mean total plasma testosterone was 17.3 nmol/L.	The mean total plasma testosterone was 1.6 nmol/L higher (0.68 higher to 2.52 higher).	-	111 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{c,e,f}	It is not known whether pine bark extract supplements increase total plasma testosterone levels.
Systolic blood pressure (mm Hg) Follow-up: 6 months	The mean systolic blood pressure was 135.00 mm Hg.	Mean systolic blood pressure was 3.90 mm Hg lower (6.44 lower to 1.36 lower).	-	111 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{c,e,f}	It is not known whether pine bark extract supplements decrease systolic blood pressure.
Diastolic blood pressure (mm Hg) Follow-up: 6 months	The mean diastolic blood pressure was 85.40 mm Hg.	Mean diastolic blood pressure was 3.40 mm Hg lower (5.36 lower to 1.44 lower).	-	111 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{c,e,f}	It is not known whether pine bark extract supplements decrease diastolic blood pressure.
All-cause mortality	No studies reported this outcome.					

Serious adverse events

No studies reported this outcome.

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; IIEF: International Index of Erectile Dysfunction; MD: mean difference RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for inconsistency: considerable heterogeneity ($I^2 = 76\%$).

^b Downgraded once for indirectness: pine bark extract compared with Serenoa repens.

^c Downgraded once for imprecision: optimal information size not met.

^d Downgraded once for risk of bias: concerns regarding selection, performance and detection bias.

^e Downgraded once for indirectness: only one study.

^f Downgraded once for risk of bias: concerns regarding selection bias.

Summary of findings 9. Pine bark extract compared to control for the treatment of female sexual dysfunction

Pine bark extract compared to control for the treatment of female sexual dysfunction

Patient or population: women with sexual dysfunction

Setting: not reported

Intervention: Lady Prelox® 2 capsules 2x daily taken orally

Comparison: placebo 2 capsules 2x daily taken orally

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with pine bark extract				
Participant-reported						
FSFI satisfaction domain score Follow-up: 8 weeks	The mean FSFI satisfaction domain score was 6.0.	The mean FSFI satisfaction domain score was 5.1 higher (3.49 higher to 6.71 higher).	-	75 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements increase FSFI satisfaction domain scores.

FSFI pain domain score Follow-up: 8 weeks	The mean FSFI pain domain score was 6.8.	The mean FSFI pain domain score was 4.3 higher (2.69 higher to 5.91 higher).	-	75 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements lead to a greater reduction of pain scores.
Investigator-reported	No studies reported this outcome.					
All-cause mortality	No studies reported this outcome.					
Serious adverse events	No studies reported this outcome.					

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FSFI**: female sexual function index; **MD**: mean difference; **RR**: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for indirectness: only one study.

^b Downgraded once for risk of bias: concerns regarding selection bias.

^c Downgraded once for imprecision: optimal information size not met.

Summary of findings 10. Pine bark extract compared to placebo for the treatment of osteoarthritis

Pine bark extract compared to placebo for the treatment of osteoarthritis

Patient or population: adults with osteoarthritis of the knee

Setting: Outpatient clinics in Europe and Asia

Intervention: Pycnogenol® 50 mg pills 3 capsules per day for 3 months taken orally

Comparison: placebo 3 capsules per day for 3 months taken orally

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pine bark extract				
Participant-reported						

Composite WOMAC score Follow-up: 90 days	The mean composite WOMAC score was 1455 points.	The mean composite WOMAC score was 730 points lower (1011.95 lower to 448.05 lower).	-	37 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements decrease composite WOMAC scores, with a lower score being better
Change in NSAIDs and COX-2 inhibitor usage (mean number of pills taken per month) Follow-up: 90 days	The mean number of NSAIDs and COX-2 inhibitor pills taken monthly increased by 3.6 pills.	The mean number of NSAIDs and COX-2 inhibitor pills taken monthly was 18.30 lower (25.14 lower to 11.46 lower).	-	35 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,c,d}	It is not known whether pine bark extract supplements decrease the number of NSAIDs and COX-2 inhibitor pills taken per month.
Investigator-reported	No studies reported this outcome.					
All-cause mortality	No studies reported this outcome.					
Serious adverse events						
Withdrawal from study because of pine bark extract supplements	Study population		RR 0.40 (0.08 to 1.97).	100 (1 RCT)	⊕⊕⊕⊕ MODERATE ^c	Pine bark extract supplements probably make little or no difference to withdrawal from studies.
	100 per 1000	40 per 1000 (8 to 197)				

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **COX-2:** cyclooxygenase-2; **NSAIDs:** nonsteroidal anti-Inflammatory drugs; **RR:** risk ratio; **WOMAC:** Western Ontario and McMaster Universities.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for indirectness: only one study.

^b Downgraded twice for imprecision: optimal information size not met and extremely wide 95% CI.

^c Downgraded once for risk of bias: concerns regarding selection, performance and detection bias.

^d Downgraded once for imprecision: optimal information size not met.

Summary of findings 11. Pine bark extract compared to control for osteopenia

Pine bark extract compared to control for osteopenia

Patient or population: post-menopausal women with osteopenia
Setting: Shariati Hospital affiliated with Tehran University of Medical Sciences (Iran)
Intervention: Oligopin® 250 mg/day given as 5 capsules per day
Comparison: placebo 5 capsules daily

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with pine bark extract				
Participant-reported	No studies reported this outcome.					
Investigator-reported						
Bone alkaline phosphatase (ug/L) Follow-up: 12 weeks	The mean bone alkaline phosphatase level was 13.87 ug/L.	The mean bone alkaline phosphatase level was 2.21 ug/L higher (0.58 higher to 3.84 higher).	-	40 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements increase bone alkaline phosphatase, where an increase indicates an improvement.
Procollagen type 1 N-terminal propeptide (ng/mL) Follow-up: 12 weeks	The mean procollagen type 1 N-terminal propeptide level was 486.2 ng/mL.	The mean procollagen type 1 N-terminal propeptide level was 73.0 ng/mL higher (17.03 higher to 128.97 higher).	-	40 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,d}	It is not known whether pine bark extract supplements increase levels of procollagen type 1 N-terminal propeptide, where an increase indicates an improvement.
C-terminal telopeptide of type I collagen (ng/mL) Follow-up: 12 weeks	The mean c-terminal telopeptide of type I collagen level was 0.31 ng/mL.	The mean c-terminal telopeptide of type I collagen level was 0.08 ng/mL lower (0.19 lower to 0.03 higher).	-	40 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,e}	It is not known whether pine bark extract supplements decrease levels of c-terminal telopeptide of type I collagen, where a lower level indicates improvement.
All-cause mortality	No studies reported this outcome.					
Serious adverse events	No studies reported this outcome.					

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for indirectness: one study only.

^b Downgraded once for risk of bias: concerns regarding selection bias.

^c Downgraded once for imprecision: optimal information size not met.

^d Downgraded twice for imprecision: optimal information size not met and extremely wide 95% CI.

^e Downgraded twice for imprecision: optimal information size not met and 95% CI includes both an important benefit and an unimportant harm.

Summary of findings 12. Pine bark extract compared to placebo for the treatment of traumatic brain injury

Pine bark extract compared to placebo for the treatment of traumatic brain injury

Patient or population: adults with a traumatic brain injury

Setting: participants' home (New Zealand)

Intervention: Enzogenol® 2 capsules daily

Comparison: placebo 2 capsules daily

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pine bark extract				
Participant-reported						
Cognitive failure questionnaire scores Follow-up: 6 weeks	The mean score from the cognitive failure questionnaire was 46.07.	The mean score from the cognitive failure questionnaire was 2.24 points lower (11.17 lower to 6.69 higher).	-	56 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements lead to lower cognitive failure questionnaire scores, where lower scores are better.
Rivermead post-concussion symptom questionnaire (RPQ-13) scores	The mean score from the Rivermead post-concussion symptom questionnaire was 24.18.	The mean score from the Rivermead post-concussion symptom questionnaire was 0.76 points lower (5.39 lower to 3.87 higher).	-	56 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements decrease Rivermead post-concussion symptom questionnaire

Follow-up: 6 weeks						scores, where lower scores are better.
Investigator-reported						
California verbal learning test: long-delay free recall scores Follow-up: 6 weeks	The mean standardised end score on the California Verbal learning test long-delay free recall was 0.51.	The mean standardised end score on the California Verbal learning test long-delay free recall was 0.28 points higher (0.26 lower to 0.82 higher).	-	56 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements increase California verbal learning test long-delay free recall scores, where higher scores are better.
California verbal learning test (mean total accuracy) (%) Follow-up: 6 weeks	The mean score for the California verbal learning test (mean total accuracy) was 86.02%.	The mean score for the California verbal learning test (mean total accuracy) was 2.04 higher (4.37 lower to 8.45 higher).	-	56 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements increase the California verbal learning test: mean total accuracy score, where a higher % is better.
Wechsler adult intelligence scale (letter number sequencing scores) Follow-up: 6 weeks	The mean score for the Wechsler adult intelligence scale (letter number sequencing) was 9.31.	The mean score for the Wechsler adult intelligence scale (letter number sequencing) was 0.39 lower (1.49 lower to 0.71 higher).	-	56 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	It is not known whether pine bark extract supplements increase the Wechsler adult intelligence scale: letter number sequencing scores, where higher scores are better.
All-cause mortality	No studies reported this outcome.					
Serious adverse events	No studies reported this outcome.					

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^a Downgraded once for indirectness: one study only.

^b Downgraded once for imprecision: optimal information size not met.

^c Downgraded once for risk of bias: concerns regarding selection bias.

BACKGROUND

Description of the condition

Oxidative stress is a state caused by a disruption in the homeostasis between the production and build up of reactive oxygen species (ROS) and the bodies ability to detoxify itself of them through antioxidant defences (Preiser 2012). ROS is a collective term for free radicals which include superoxide radicals, hydrogen peroxide, hydroxyl radicals and singlet oxygen (Cos 2004; Pizzino 2017). These are molecules with an unpaired electron that can exist independently (Sies 2017). Owing to the unpaired electron, free radicals are highly reactive species capable of damaging the membranes and nucleus of biologically relevant molecules such as DNA, proteins, carbohydrates, and lipids (Lobo 2010). ROS are naturally generated endogenously by essential metabolic processes either through non-enzymatic reactions, e.g. during cellular respiration of mitochondria or enzymatic reactions involved in the respiratory chain, prostaglandin synthesis, phagocytosis, and cytochrome P450 system (Pizzino 2017). ROS can also be derived exogenously through exposure to X-rays, ozone, cigarette smoke, alcohol, air pollutants, industrial chemicals and certain cooking methods (Whitney 2002). ROS may cause significant damage in large amounts; but despite the potentially harmful effect of ROS, they are beneficial in low to moderate concentrations as they perform important functions within cells synthesizing some cellular structures and are used by the host defence system namely phagocytes to fight pathogens. Another beneficial effect includes a regulatory role of ROS in intracellular signalling cascades, in several cell types such as fibroblasts, endothelial cells, vascular smooth muscle cells, cardiac myocytes, and thyroid tissue. One of the most common free radicals is nitric oxide plays a vital role in vasodilation. Damage to cellular structures may ensue, leading to the development of disease (Ammar 2009; Cos 2004; Watson 2006; Whitney 2002). Oxidative stress naturally increases during aging and physical activity (Preiser 2012).

Oxidative stress has been implicated in the development of a number of conditions including cardiovascular disease (CVD), arthritic and rheumatic disorders, cancer, inflammatory bowel disease, Alzheimer's disease, Parkinson's disease and renal disease (Bjorklund 2017; Litchford 2008). While the exact role of ROS in the pathogenesis of these diseases remains unclear, the following are some mechanisms that are thought to be important.

- Oxidative DNA damage is one of the known stimuli responsible for the development of cancer. Oxidative stress can also promote cancer by chromosomal abnormalities and oncogene activation. Hydrolysis of DNA as a by-product of DNA oxidation is a prominent occurrence in chemical carcinogenesis (Nijveldt 2001; Whitney 2002).
- Early endothelial inflammation causes atheromatous plaque formation leading to ROS generation by macrophages recruited in situ. These ROS then oxidise circulating low-density lipoprotein (LDL) cholesterol molecules which result in foam cell formation, lipid accumulation and ultimately the formation of an atherosclerotic plaque (Nijveldt 2001; Whitney 2002).
- Oxidation of poly-unsaturated fatty acids in cell membranes may hinder blood flow and contribute to cardiovascular problems (Whitney 2002).
- Oxidative stress encourages telomere (the non-gene terminal end of a chromosome which protects the chromosome

from destruction) instability and dysfunction in chondrocytes (cartilage cells), which may result in cartilage ageing and the development of osteoarthritis (Yudoh 2005).

- Dopamine-derived ROS and oxidized dopamine metabolites are toxic to neurons of the substantia nigra (part of the brain stem that release neurotransmitters, such as dopamine, that is important for the control of movement and coordination) which may lead to Parkinson's disease (Hald 2005).
- Chronic oxidative stress results in an initial stage of inflammation and later the formation of abundant fibrotic kidney tissue potentially leading to renal failure. Additionally, cyclosporine, tacrolimus, gentamycin, and bleomycin are medication that are known to be nephrotoxic as they cause lipid peroxidation via increased free radical levels and oxidative stress.

Chronic disease is a leading cause of death and disability globally, and a big cost to health systems (CDC 2017). The pathophysiology of chronic diseases are multifactorial, thus making them difficult to prevent and treat. There is no uniform definition of a "chronic disease", "chronic disorder", or "chronic illness", and it specifically varies across regions and disciplines (Bernell 2016). Aspects from various definitions include (Bernell 2016; Martin 2007; Zwar 2006):

- long duration, lasting three months or more;
- a long development period, often with no symptoms;
- multi-factorial aetiology;
- cannot just disappear;
- having no definite cure;
- cannot be prevented by vaccines;
- gradual changes over time;
- leave residual disability; and
- may be expected to require a long period of supervision, observation, or care.

Chronic illness, while similar sounding, has been described as the "lived experience of long-term bodily or health disturbance, whether related to a communicable or non-communicable disease, condition, syndrome, or disorder; and how people live and cope with the disruption" (Martin 2007), and includes fatigue, weakness, confusion or social stigma (Walker 2001).

Description of the intervention

Procyanidin, the main active ingredient in pine bark extract, is a member of the proanthocyanidin class of flavonoids, a subgroup of polyphenols with potent antioxidant properties. Dietary sources include berries, apples, nuts, cinnamon, cocoa beans and red wine. The sources of pine bark (*Pinus* spp.) extract come from various species and countries including *Pinus pinaster* from France, *Pinus radiata* from USA and *Pinus densiflora* from Korea (Li 2015). These are marketed under various brand names including Pycnogenol®, ProVens®, PineXol®, Flavangenol®, Prelox®, Lady Prelox®, Enzogenol®, and Oligopin®. These supplements also vary in the amount of procyanidin and non-antioxidant ingredients which are added; which may additionally explain any observed changes in health. Although marketed as dietary supplements, pine bark extracts are often promoted for therapeutic use in chronic conditions. Pycnogenol® was one of the first supplements to be launched globally and is standardised to contain a mean (standard deviation (SD)) level of 70% (5%) procyanidin. Pine bark extract

supplements are available in either liquid, tablet or capsule form (Kegin 2014; Oliff 2010).

How the intervention might work

Three antioxidant mechanisms have been attributed to proanthocyanidin:

- free radical scavenging, i.e. proanthocyanidin is oxidized by free radicals, resulting in more stable, less-reactive radicals (Cos 2004; Kegin 2014; Kruger 2014; Nijveldt 2001);
- proanthocyanidin binding of iron and copper, which are cofactors of several enzymes involved in oxygen metabolism, thus limiting the formation of free radical reactions (Cos 2004);
- direct inhibition of pro-oxidative enzymes such as lipoxygenase, nitric oxide synthase, and xanthine oxidase (Cos 2004; Kruger 2014).

There are three levels of mechanisms by which procyanidin can protect the body against oxidative stress:

- prevention - as antioxidants reduce hydroperoxides and hydrogen peroxide to alcohols and water, respectively, without generation of free radicals;
- scavenging - as lower redox potentials of the polyphenols are thermodynamically able to reduce highly oxidised free radicals because of their capacity to bond metal ions (irons, copper, etc.) and free radicals; and
- repair - as proteolytic enzymes, proteinases, proteases, and peptidases, present in the cytosol and in the mitochondria recognize, break down and remove oxidatively altered proteins and prevent the accumulation of oxidized proteins.

It is important to recognise that ROS have several important beneficial functions in cells including:

- mediation of apoptosis (programmed cell death, also known as cellular suicide) (Rauf 2019);
- mediation of detoxification reactions;
- defending cells against pathogenic viruses and bacteria;
- mediation of other specific biochemical reactions (Salganik 2001; Whitney 2002); and
- modulation of transcription of genes by allowing extracellular stimuli to change cell physiology (Preiser 2012).

It is therefore possible that excessive amounts of antioxidants may negatively affect these important physiological processes (Bjelakovic 2007). This implies that a balance between ROS and antioxidants may be critical for maintaining health.

Why it is important to do this review

According to the proposed mechanism of action of antioxidants, specifically procyanidin, it may be expected to show potential benefits in the aetiology and progression of many chronic disorders. Dietary supplements are a multibillion dollar industry with pine bark extract supplements specifically marketed to prevent the onset of and to alleviate and slow disease progression of chronic disorders (Bjelakovic 2007; Donma 2005; Lichtenstein 2005; Tonks 2007). As researchers and healthcare professionals it is our responsibility to provide the public with evidence-based recommendations on the use and safety of pine bark extract supplements.

Our original version of this review only included Pycnogenol® as this is a standardised product, and most of the trials at that stage had investigated Pycnogenol® (Schoonees 2012a). We included 15 trials with a total of 791 participants that evaluated Pycnogenol® for treating seven different chronic disorders (Schoonees 2012a). We found that with the available evidence-base at that time no definitive conclusions regarding the efficacy or safety of Pycnogenol® could be made. Subsequently, we have identified new trials on Pycnogenol®, as well as new trials in other supplements containing pine bark extract. With this updated review, we have broadened our question to also include other types of pine bark extract supplements, regardless of brand.

OBJECTIVES

To assess the efficacy and safety of pine bark extract supplements for treating chronic disorders.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) investigating the efficacy or safety (or both) of pine bark extract supplements. We excluded quasi-randomised trials (i.e. trials that used an inadequate method of randomisation, such as date of birth, medical record number or alternation).

Types of participants

Adults and children with any chronic disorder, regardless of geographical location or setting. We defined a chronic disorder as a disease (e.g. heart disease, stroke, cancer, diabetes mellitus (DM), HIV/AIDS, etc.) or non-specific illness (e.g. fatigue, pain, etc.) of more than three months duration, that does not often resolve spontaneously and is rarely cured completely (Drum 2014).

Types of interventions

Experimental

Supplements containing pine bark extract, alone or in combination with other supplements, as long as the comparison group(s) received the same treatment apart from the pine bark extract supplement. Any dose or route of administration was deemed acceptable, but the pine bark extract supplement should have been used for at least one month (four weeks).

Control

We compared the active intervention to placebo, or no intervention or other supplement(s) (excluding those with antioxidant properties).

Types of outcome measures

For each chronic disorder we assessed the following efficacy outcomes.

Primary outcomes

1. Any clinical outcome directly related to the disorder, stratified as
 - a. participant-reported outcomes (e.g. joint pain in individuals with osteoarthritis)

- b. investigator-reported outcomes (e.g. serum cholesterol levels in people with hyperlipidaemia, retinal blood flow with diabetic retinopathy)
2. All-cause mortality

Secondary outcomes

1. Adverse events
2. Biomarkers of oxidative stress (e.g. antioxidant activity in plasma, oxidized glutathione concentration)

Search methods for identification of studies

We used a comprehensive and exhaustive search strategy in order to identify all relevant studies regardless of language, year or publication status (published, unpublished, in press and in progress).

Electronic searches

1. Journals and trials databases

We searched the following databases and study registries:

- Cochrane Central Register of Controlled Trials (www.cochranelibrary.com/central; CENTRAL; 2019, Issue 9) in the Cochrane Library (searched 30 September 2019);
- PubMed (www.ncbi.nlm.nih.gov/pubmed/; 1946 to 30 September 2019);
- Embase Ovid (1974 to 30 September 2019);
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; searched 30 September 2019);
- ISRCTN Registry (www.isrctn.com/; searched 30 September 2019); and
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; searched 30 September 2019).

For details of our search strategies please see [Appendix 1](#).

Searching other resources

We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant studies.

In the initial review we contacted the manufacturer of Pycnogenol®, Horphag Research (UK) Ltd, via email to request a list of completed clinical trials. This was received on 21 July 2010. For the update, in July 2018 we contacted the following manufacturers via email to request a list of completed clinical trials: Horphag Research (UK) Ltd, Toyo Bio-Pharma (Japan), ENZO Nutraceuticals Limited (New Zealand), DRT Nutraceuticals (France), Unimed Pharma (Romania), NutraPharm Co (Korea) and Canadian Health Products International Inc.

Data collection and analysis

Selection of studies

The review authors (for the initial review: AS and JV; for the 2020 update: NR and AS) independently screened the title and abstract of studies identified by the searches and applied the pre-specified criteria in order to identify eligible studies. Where at least one

author considered a study to be relevant, we obtained the full-text and independently assessed it for eligibility. Where there was missing information or where we needed clarity, we contacted the study authors. We resolved any remaining disagreement by consensus among the whole review team. We listed studies at first thought to be relevant but which were later excluded in the table 'Characteristics of excluded studies' together with reasons for exclusion.

Data extraction and management

The review authors (for the initial review: AS and JV; for the 2020 update: NR and AB) independently extracted data using a standardized, pre-piloted extraction form. For each study we collected the following items: administrative details; study methodology; participant characteristics; interventions; outcomes; study findings; ethical approval and funding sources. For the initial review, the third author (AM) also independently extracted data for outcomes and results. For the 2020 update, NR and AB used Covidence to independently extract information ([Covidence](#)). We resolved disagreements by consensus. Where reported information was unclear or contradictory, or where important data were missing, we contacted the study author(s) via email.

We planned to group data based on duration of follow-up as follows:

- short-term (less than three months);
- medium-term (three months to 12 months);
- long-term (13 months onwards).

Due to mostly one included study per outcome, we instead reported exact time points as presented in the included studies.

Furthermore, we planned to use the longest time-point data where multiple time-points were reported for one category (e.g. two-week intervals for a period of eight weeks of treatment). This was not necessary as no multiple time-points were reported for any category.

We have presented the efficacy results as data for each of the listed primary and secondary outcomes separately for each condition identified. We have also presented the safety data separately for all conditions.

Assessment of risk of bias in included studies

The review authors (for the initial review: AS and JV; for the 2020 update: NR and AB) independently assessed each included study for risk of bias using the guidelines provided in the *Cochrane Handbook of Systematic Reviews of Interventions* ([Higgins 2011](#)). The components of the methodology that we assessed are sequence generation, allocation concealment, blinding performance, detection bias, incomplete outcome data, selective outcome reporting and other potential threats to validity. Blinding performance and detection bias were assessed separately in the update. We rated each included study as having a low risk of bias, a high risk of bias, or an unclear risk of bias for each of these seven domains. We resolved disagreements by consensus. For assessing the overall risk of bias per study we took into account the domains addressing allocation concealment, performance and detection bias.

Additionally, we assessed cross-over trials to determine:

1. whether the cross-over design was suitable;
2. whether there was a carry-over effect;
3. whether only first-period data are available;
4. whether a correct analysis (paired analysis) had been used; and
5. whether the results are comparable to those from parallel-group trials (Higgins 2019).

Measures of treatment effect

We used the latest version of the Review Manager software to conduct the analyses (Review Manager 2020). We calculated risk ratios (RRs) for dichotomous data and mean differences (MDs) for continuous data. Furthermore, for continuous data, where investigators reported data for an outcome across studies using different units, we calculated the standardised mean difference (SMD). We present all results with 95% confidence intervals (CIs) except where papers reported data as medians and ranges. Where investigators reported results insufficiently for analysis (e.g. where they did not provide the standard deviation (SD) of change and the contact authors of the studies have not yet responded to our requests), we presented the available results in an additional table.

Unit of analysis issues

We did not pool parallel-design studies and those of cross-over design as "it is generally advisable to meta-analyse parallel-group and cross-over trials in separate subgroups, irrespective of whether they are also combined" according to the current version of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2019).

We did not present two included cross-over studies in the [Data and analyses](#) section as the study authors did not report results for the placebo group or reported the results in sufficient detail (Hosseini 2001a; Hosseini 2001b).

One included study had three intervention groups (local application plus oral Pycnogenol®; oral Pycnogenol®; local Pycnogenol®) and one control group (no treatment). We calculated effect sizes for oral Pycnogenol® versus control, local Pycnogenol® versus control and the two versions of Pycnogenol® combined versus control (Belcaro 2006a).

One of the studies in the 2020 updated review made use of three treatment phases (Theadom 2013). One group received six weeks of placebo, followed by six weeks of intervention and then four weeks of placebo. The second group started off with six weeks of intervention, and then continued identically to the first group by receiving six weeks of intervention followed by four weeks of placebo. As this study does not conform to a cross-over design, we only extracted data from the first phase of the study (up until the first six weeks). As a result, we have analysed this study as a parallel-group design.

Dealing with missing data

We attempted to obtain essential missing data by contacting the original study authors wherever possible. In the presence of missing dichotomous data, we used the intention-to-treat principle but assumed that the missing participants did not experience the event. In the case of missing continuous data, we used the available-case analysis.

Assessment of heterogeneity

Where we could combine multiple studies for the same outcome and comparison (five meta-analyses), we assessed heterogeneity using visual inspection of the forest plots. If CIs for the results of individual studies had poor overlap, we took this as an indication of statistical heterogeneity. Furthermore, we used the Chi² test for heterogeneity (significance level $P < 0.1$) and quantified the degree of heterogeneity by means of the I² statistic (Higgins 2003). We used the following guidelines for the interpretation of the I² values (Higgins 2019):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

We defined substantial heterogeneity where I² values are 50% or more and the Chi² test's P value is < 0.1 (Higgins 2003). We did not pool data when heterogeneity between studies was substantial.

Assessment of reporting biases

We originally planned to assess funnel plots to explore the possibility of small study bias when we were able to combine more than 10 included studies. We planned to consider different explanations for funnel plot asymmetry such as publication bias, the effect of different study sizes and poor study design. However, it was not appropriate to use funnel plots as planned since the number of studies per comparison was insufficient. Therefore, we could not explore the possibility of small study bias.

Data synthesis

In the absence of substantial heterogeneity, we conducted meta-analyses in Review Manager using a fixed-effect model (Review Manager 2020). In the case of substantial heterogeneity, we used the random-effects model for meta-analysis.

We prioritised within-group change values for analyses where available, otherwise we used end of treatment values. Furthermore, we converted cardio-metabolic measurements to International System of Units (SI), such as mmol/L.

Subgroup analysis and investigation of heterogeneity

We planned to investigate substantial heterogeneity by conducting the following subgroup analyses:

- age: adults (over 16 years) versus children (16 years and younger);
- supplements where the pine bark extract is the main ingredient versus where it is not the main ingredient versus where it is unclear.

However, the data currently available were insufficient to allow us to undertake subgroup analysis.

Sensitivity analysis

We planned to perform a sensitivity analysis, if appropriate, in order to assess the influence of risk of bias (using adequacy of allocation concealment as a marker) and funding source on the findings. Due to insufficient data, this was not possible in this version of the review.

Summary of findings tables

In the 2020 review update, we have presented a 'Summary of findings' table for each chronic disorder addressed in the included studies. In each table, we reported a maximum of two participant- and three investigator-reported outcomes, all-cause mortality and serious adverse events ([Summary of findings 1](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#); [Summary of findings 5](#); [Summary of findings 6](#); [Summary of findings 7](#); [Summary of findings 8](#); [Summary of findings 9](#); [Summary of findings 10](#); [Summary of findings 11](#); [Summary of findings 12](#)).

We used the GRADE approach to determine the certainty of the evidence for five domains (risk of bias, indirectness, inconsistency, imprecision and other considerations) and for each outcome we considered these domains and downgraded the certainty of evidence, with reasons, where relevant ([GRADEPro GDT 2015](#)).

Figure 1. Search results.

Included studies

The 2020 updated review includes 27 RCTs (22 parallel and five cross-over design) with a total of 1641 participants. We have provided full details of these studies in the table '[Characteristics](#)

RESULTS

Description of studies

Results of the search

We have summarised the search results from the latest searches in a flow chart ([Figure 1](#)). In total for the 2020 update we screened 1352 records, of which we identified 87 records as potentially eligible and obtained the full-text articles of these for further assessment. We excluded 49 studies (54 records) with reasons ([Characteristics of excluded studies](#)) and included 12 studies (15 records) which were added to the 15 studies from the 2012 review bring the total to 27 included studies (34 records). We have also listed 17 ongoing studies ([Characteristics of ongoing studies](#)) and one study is awaiting classification ([Characteristics of studies awaiting classification](#)) (each with a single record).

of included studies'. The studies cover 10 different chronic conditions (asthma, ADHD, CVD and risk factors, chronic venous insufficiency (CVI), DM, erectile dysfunction (ED), female sexual dysfunction, osteoarthritis, osteopenia and traumatic brain injury (TBI)), with varied treatment duration and dosage across studies

and target conditions. We present details on the interventions (e.g. manufacturer, composition, dosage) as reported in the manuscripts for all included studies in the additional tables (Table 1). We present narrative summaries of the study characteristics by the condition investigated below.

Asthma

The review includes two studies (86 participants) of pine bark extract in asthma (Hosseini 2001a; Lau 2004). Both studies reported their funding sources.

Study design

The first study took place in Iran and had a cross-over design (Hosseini 2001a), while the second study was conducted in the USA and employed a parallel design (Lau 2004). The duration of the American study was three months after a one-week run-in period (Lau 2004); while in the Iranian cross-over study the treatment in each arm lasted four weeks, but with no washout period in between (Hosseini 2001a). The investigators conducted no follow-up of the participants beyond the completion of either study. Both studies had ethics approval.

Neither study reported a sample size calculation.

Participants

The American study enrolled 60 children with the mean age 14 years (range 6 to 16 years); 57% were male (Lau 2004). The Iranian study enrolled 26 adults with the mean age 32 years (range 18 to 50 years); 45.5% were male (Hosseini 2001a).

The children recruited to the American study had mild to moderate asthma as defined by the American Thoracic Society criteria, and a baseline forced expiratory volume in one second (FEV₁) of between 50% and 85% of the predicted normal value. Investigators excluded participants if they had had a severe asthma attack or lower respiratory tract infection in the month before commencement of the study (Lau 2004). The adult study recruited participants with asthma as defined according to the American Thoracic Society criteria and a baseline FEV₁ of between 30% and 75% of the predicted normal value; this study additionally reported that the mean duration of the disorder was eight years (range 1 to 16 years) (Hosseini 2001a).

Interventions

Both studies administered oral Pycnogenol® at a dose of 1 mg/lb body weight/day as the active treatment compared to placebo tablets. The adult study additionally specified that there was a maximum dose of 200 mg/day (Hosseini 2001a) while the paediatric study gave the daily treatment split into two doses over the day (Lau 2004). The latter study did not report whether specific concomitant medication was permitted during the study period: however, the study authors reported the change in use of rescue inhaler and oral medication as outcomes (Lau 2004). The Iranian study reported that usual medications could be used except for glucocorticoids, leukotriene antagonists, multivitamins, aspirin and any other non-steroidal anti-inflammatory drugs (NSAIDs) (Hosseini 2001a).

Outcomes measured

Both studies reported symptom scores, but used different scales (Hosseini 2001a; Lau 2004). The paediatric study used a scale from 0 to 4 where 0 = no symptoms, 1 = mild symptoms - not disturbing, 2 =

moderate symptoms - somewhat disturbing, 3 = severe symptoms - interfered with daily activities, 4 = very severe symptoms - could not go anywhere. This study also reported the number of participants with a decrease in symptom scores (Lau 2004). On the other hand, the adult study employed a symptom severity scale where 1 = mild intermittent, 2 = mild persistent, 3 = moderate persistent, and 4 = severe persistent (Hosseini 2001a).

Both studies also reported on lung function, but again the specific measures differed. The American study reported peak expiratory flow rate (PEF) as % predicted (Lau 2004), while the Iranian study reported FEV₁ % predicted and FEV₁/forced expiratory volume (FVC) (Hosseini 2001a).

The two studies reported laboratory measures of urinary leukotriene C4/D4/E4 levels (Lau 2004) and cysteinyl-leukotrienes C4, D4, and E4 levels, which are biomarkers of oxidative stress (Hosseini 2001a). Likewise, both studies reported any adverse events that manifested during the study.

The American study additionally reported on compliance and the use of additional medications (rescue inhaler and oral medication) (Lau 2004).

ADHD

One study in the review assessed 61 children with ADHD, and reported its funding source (Trebatická 2006).

Study design

This study used the parallel-group design and the treatment duration was one month. Participants were followed up at one and two months after the intervention was given. The study obtained ethics approval.

Investigators determined the sample size using a power of 80%, a type one error of 5% and 0.4 controls per participant. The resultant sample size was 41 participants for the intervention group and 16 participants for the placebo group; the study included 44 and 17 participants, respectively.

Participants

In the intervention group, 84% of participants were males, the mean age was 9.5 (range 6 to 14) years, the mean weight was 35.28 kg and the mean body mass index (BMI) was 17.41 kg/m². In the control group 76.5% of participants were males, the mean age was 8.8 (range 6 to 12) years, the mean weight was 34.80 kg and the mean BMI was 16.77 kg/m².

All participants were children with ADHD according to the International Statistical Classification of Diseases (ICD-10). Investigators excluded children with situational hyperactivity, pervasive developmental disorders, schizophrenia and other psychotic disorders. They also excluded participants who had personality changes due to medical conditions, mental retardation, living in under-stimulating environments, conduct disorders, tics, dyskinesias, acute inflammatory diseases, renal disorders, cardiovascular disorders and DM.

Interventions

The study investigators administered oral Pycnogenol® at a dose of 1 mg/kg body weight per day compared to placebo tablets.

No concomitant medication was allowed (including psychotropic drugs or vitamin E and C, as specified in the study report).

Outcomes measured

Teachers and parents measured inattention symptom scores and hyperactivity symptom scores using three different scales:

- Child attention problems Teacher Rating Scale;
- Conner's Teacher Rating Scale (CTRS); and
- Conner's Parent Rating Scale (CPRS) (where a lower score is beneficial).

The study also evaluated visual-motoric co-ordination and concentration. Psychologists evaluated "weight score" percentage; the score at baseline was put to 100% and is the sum of values of five subtests of the performance scale standardised for adequate age for each participant, where a higher score represents a better psychological state.

Investigators also measured urine catecholamine concentrations. The study investigators measured total glutathione concentration (GSH), oxidised glutathione (GSSG) and the ratio of GSH/GSSG levels. They determined total glutathione and GSSG from whole blood samples and calculated GSH using the following formula: $[GSH] = [total\ glutathione] - (2 \times [GSSG])$. The study also measured total antioxidant status (TAS) in plasma. Investigators evaluated the levels of oxidized purines, represented by 8-oxo-7,8-dihydroguanine (8-oxoG) in lymphocytes.

CVD and risk factors (post hoc change)

The review authors did not present this category in the original review, which included two studies on hypertension (Hosseini 2001b; Liu 2004c). These studies now fall under the CVD and risk factors category, which now includes seven studies with 338 participants, making it the condition with the most participants from included studies. The studies were conducted in the USA (Drieling 2010; Hosseini 2001b), China (Liu 2004c), Switzerland (Enseleit 2012), Germany (Reule 2017) and Spain (Valls 2016). All studies, except for one, reported their funding source; this study also does not report in which country it was conducted (Cesarone 2008).

Study design

Three studies used a parallel-group design (Cesarone 2008; Drieling 2010; Liu 2004c), while the remaining four studies used a cross-over design (Enseleit 2012; Hosseini 2001b; Reule 2017; Valls 2016). The treatment duration for two of the parallel group studies (Drieling 2010; Liu 2004c) was three months; and two months for the third study (Cesarone 2008). Two cross-over studies had an eight-week intervention period per arm, but one had no washout period (Hosseini 2001b), while the second study included a two-week washout period between crossing over of treatments (Enseleit 2012). A third cross-over study implemented a five-week intervention phase with a three-week washout period (Valls 2016). The final cross-over study had a four-week intervention phase with an eight-week washout period (Reule 2017). None of the studies followed up the participants past the end of the study and only three studies reported obtaining ethics approval (Cesarone 2008; Drieling 2010; Liu 2004c).

Participants

The seven studies enrolled a total of 338 participants, with the number of participants ranging from 11 (Hosseini 2001b) to 130 (Drieling 2010). All participants were adults and the mean age across six studies was 54 years (Cesarone 2008; Drieling 2010; Enseleit 2012; Hosseini 2001b; Reule 2017; Valls 2016). The remaining study reported age as median (interquartile range (IQR)) for the treatment group 56 (46 to 64) years and control group 69 (64 to 76) years (Liu 2004c). The gender split across studies varied; overall there were 72.6 % males and 27.4 % females. Generally each study enrolled more males than females and one study enrolled only males (Liu 2004c).

One study only included participants if their blood pressure (BP) was between 130 over 85 mm Hg and 140 over 95 mm Hg, if HDL cholesterol was below 40 mg/dL with a total cholesterol level between 200 mg/dL and 240 mg/dL and a pre-diabetic fasting blood glucose as defined by the American Diabetes Association of 100 mg/dL to 125 mg/dL (Cesarone 2008).

One study only included participants who were overweight or obese class I (BMI of 25.0 to 34.9 kg/m²), were pre-hypertensive or had a hypertensive systolic BP (125 mm Hg to 160 mm Hg) and were not taking diabetes medication, hypertension medication, or any dietary supplements within the past month aside from the recommended daily value of multivitamins (Drieling 2010).

One study only included participants aged 18 years and older with CVD documented by coronary angiography, nuclear imaging or a positive stress test and were on stable cardiovascular medication for at least one month (Enseleit 2012).

Inclusion criteria for a further study were non-smoking people with mild hypertension (stage I) who complied fully to take the provided placebo pills during the run-in period and who had a systolic BP of between 140 mm Hg and 159 mm Hg, or diastolic BP between 90 mm Hg and 99 mm Hg (or both) (Hosseini 2001b).

One study only included participants if they were diagnosed with hypertension according to the 1999 WHO International Society of Hypertension Guidelines for the Management of Hypertension (Liu 2004c).

Participants were included in one study if they were post-menopausal non-smokers between 40 and 65 years old, had a BMI between 20 and 32 kg/m², had homocysteine levels of at least 10 µmol/L, had an elevated systolic BP (mean of 130 mm Hg to 149 mm Hg measured during a period of seven days before visit 1) but without requiring medical therapy (Reule 2017).

One study only included participants if they were suffering from stage 1 hypertension (systolic BP $\geq$ 140 mm Hg and $\leq$ 159 mm Hg with a diastolic BP of $\geq$ 90 mm Hg and $\leq$ 99 mm Hg) and not receiving BP-lowering medication (Valls 2016).

Interventions

All studies used a placebo as the control intervention.

Three studies used oral Pycnogenol[®] tablets as the active intervention (Enseleit 2012; Hosseini 2001b; Liu 2004c). Doses ranged from 100 mg/day (frequency not stated) (Liu 2004c) to 200 mg/day (Enseleit 2012; Hosseini 2001b); one study additionally

recommended the full dose to be taken in the morning (Hosseini 2001b).

One study used OPC-3 as one 10 g pouch daily containing 400 mg flavonoids (consisting of equal amounts of Pycnogenol®, grape seed, bilberry, citrus, and red wine) as well as fructose, glucose, citric acid, potassium bicarbonate, silica, calcium sulfate, maltodextrin, pectin and colourants (Cesarone 2008). Participants took both placebo and control orally, following solubilization of sachet contents with 180 mL water resulting in an isotonic solution (Cesarone 2008).

A second study used Flavangenol® in the form of four 50 mg tablets daily every morning; these contained OPC extracted from *Pinus maritime* and *Pinus maritimus* compounded with excipients of palatinit sugar, caramel, sucrose, fatty acid ester, and calcium stearate (Drieling 2010). The four placebo capsules contained excipients of palatinit sugar, caramel, sucrose, fatty acid ester, and calcium stearate (Drieling 2010).

One study used verum (as stated on clinicaltrials.gov (NCT02392767)) which was described in the publication as AbMIP (marketed as vasologes® protect, Dr Loges & Co. GmbH) - participants took two capsules orally twice daily, together these contained 2400 mg L-arginine, 80 mg Pycnogenol®, 45 µg vitamin K2, 10 mg alpha lipoic acid, 8 mg vitamin B6, 500 µg vitamin B12 and 600 µg folic acid (Reule 2017). The placebo tablets contained maize starch similar to the intervention in taste, smell, and appearance, but with maize starch replacing the active compounds (Reule 2017).

In one study participants took one capsule of Oligopin® twice daily orally; one in the morning and one in the afternoon (Valls 2016). Each placebo capsule contained 280 mg of total content consisting of 250 mg maltodextrin and 30 mg magnesium stearate (Valls 2016).

Concomitant medication

Investigators on one study queried participants about their use of dietary supplements and medications at screening and asked them to report any changes. They also asked participants to refrain from changing their diet or losing weight. Participants completed three-day food records at baseline and at 12 weeks to monitor changes in diet, particularly intake of antioxidant-rich foods (Drieling 2010).

Investigators implemented optimal standard cardiovascular therapy as concomitant treatment in one study (Enseleit 2012).

In one study concomitant medication was permitted, but not specified. Investigators asked participants to exclude wine from their diets for the duration of the study (Hosseini 2001b).

One study implemented a two week run-in period on placebo where all participants took a calcium antagonist (nifedipine, sustained release tablets, 5 mg). The initial nifedipine dose was 20 mg (frequency not reported, assumed to be daily) which was then adjusted at two week intervals (either reduced or increased with 5 mg) as needed to sustain "stable blood pressure" (Liu 2004c).

A further study did not permit the consumption of alcohol 48 hours prior to and during the study visit. The meal before each visit was standardised as bread with low-fat cream cheese and tomatoes or cucumber. Before the postprandial endothelial function test participants received a high-fat meal consisting of 200 mL cream with 30% fat content (Reule 2017).

In the final study, investigators implemented a stabilisation diet containing 13% saturated fatty acids. They asked participants to follow the guidelines of the Adult treatment panel III and Dietary Approach to Stop Hypertension (DASH) diet during the intervention period (Valls 2016).

Outcomes measured

All trials reported on systolic and diastolic BP (Cesarone 2008; Drieling 2010; Enseleit 2012; Hosseini 2001b; Liu 2004c; Reule 2017; Valls 2016). All of them were at rest except one study which reported as 24-hour ambulatory BP (Enseleit 2012). Only one study measured heart rate (Cesarone 2008). One study assessed the dose of nifedipine needed to control BP. This outcome is dependent on the BP measurements during the treatment period since investigators adjusted the nifedipine dose every two weeks as needed to sustain "stable blood pressure" (Liu 2004c). One study measured the diastolic component of carotid artery flow and left ventricular ejection fraction (Cesarone 2008). One study reported flow-mediated dilatation-dependent vasodilation of the brachial artery (Enseleit 2012). One study reported flux, venoarteriolar response and transcutaneous partial O₂ and CO₂ pressures (Cesarone 2008).

Three studies measured total cholesterol, LDL, HDL and triglycerides (Drieling 2010; Enseleit 2012; Valls 2016) and one study measured total cholesterol, HDL and LDL but not triglycerides (Cesarone 2008). One study measured triglycerides on their own (Reule 2017). One study also measured apolipoprotein A-1, apolipoprotein B-1 and a ratio of apolipoprotein B-100/A-1 (Valls 2016). Another study also measured fasting lipoprotein(a), HDL and LDL particle size (Drieling 2010). Two studies measured oxidised LDL and soluble cell adhesion molecules (Enseleit 2012; Valls 2016).

Three studies reported fasting blood glucose levels (Cesarone 2008; Enseleit 2012; Valls 2016). Only one of these studies reported insulin levels and BMI (Valls 2016). One study measured HbA1c (Reule 2017).

Three studies reported high sensitivity CRP (Drieling 2010; Enseleit 2012; Valls 2016) and CRP was measured by one study (Cesarone 2008).

Three studies assessed endothelin-1 (Enseleit 2012; Liu 2004c; Valls 2016). Only one study each reported on the following outcomes: direct reactive oxygen metabolites (D-ROM) (Cesarone 2008), 15-F2t-Isoprostane (Enseleit 2012), total antioxidant capacity (Enseleit 2012), thromboxane B2 levels (Hosseini 2001b), 6-keto-prostaglandin-F1_α (Liu 2004c) which are all markers of oxidative stress.

Two studies measured reactive hyperaemia (lnRHI), the first expressed as percentage and the second as an index fasting and post fat meal respectively (Cesarone 2008; Reule 2017).

Two studies measured asymmetric dimethylarginine (ADMA) (Enseleit 2012; Reule 2017). One study additionally reported liver functions, symmetric dimethylarginine (SDMA), lipoproteins (Lp-PLA2) and blood chemistry (Na, K, Creatinine, Hb, Hk, ALT, AST) (Enseleit 2012).

Each of the following outcomes were reported by one study respectively: angiotensin II levels (Liu 2004c), nitrogen monoxide levels (Liu 2004c) and homocysteine (Reule 2017).

One study assessed nitrates, reduced GSH, GSSG, the ratio GSH/GSSG, E-selectin, human angiotensin converting enzyme and vascular endothelial growth factor (Valls 2016).

CVI

The review includes two studies on CVI comprising a total of 60 participants (Arcangeli 2000; Petrassi 2000). Both studies were conducted in Italy and funding sources were not reported in either study.

Trial design

Both studies used a parallel-group design and the treatment duration was two months. Both studies employed a run-in period of two weeks and undertook follow-up assessment at 30 and 60 days. Investigators did not follow up participants beyond the completion of the studies (Arcangeli 2000; Petrassi 2000). Only one study reported ethics approval (Arcangeli 2000) and neither study reported sample size.

Participants

The mean age of participants across both studies was 51 years, but this varied between groups and studies. Participants in one study were generally younger and within this study the placebo participants had a lower mean (SD) age (36.7 (3.66) years) than the intervention group (47.7 (3.65) years) (Petrassi 2000). In the second study, the mean (SD) age in the intervention group was lower (57.95 (12.78) years) than in the placebo group (61.4 (10.62) years) (Arcangeli 2000).

There were more females than males overall with 44 out of 60 participants (73%) being female. This was also reflected in the individual studies with 68% females in one study (Arcangeli 2000) and 85% females in the second study (Petrassi 2000),

One study recruited participants with clinically evident CVI as a result of deep venous thrombosis or idiopathic venous-lymphatic deficiency (Arcangeli 2000). The smaller study recruited participants with CVI symptoms such as heaviness and subcutaneous swelling, as well as a venous pressure above 40 mm Hg (Petrassi 2000).

Interventions

Both studies administered oral Pycnogenol® at a dose of 100 mg three times per day as the active treatment and its effects were compared to that of placebo tablets. During the run-in and treatment period participants were not allowed to take any medication which affects the cardiovascular system, as well as diuretics, analgesics or anti-inflammatory medication. Investigators also prescribed participants a standard diet according to their energy requirements.

Outcomes measured

Both studies measured outcomes using the same symptom scoring system where 0 = absent, 1 = light, 2 = moderate and 3 = severe. The larger study assessed heaviness, swelling and pain of legs (Arcangeli 2000). The smaller study assessed feeling of heaviness, swelling and evening oedema, localized or diffuse leg pain, night cramps and paraesthesia (Petrassi 2000). In both studies, investigators also calculated the proportion of participants whose symptoms disappeared.

One study assessed participants' venous blood flow measured with a hand-held Doppler ultrasound (Arcangeli 2000), while the second study assessed ambulatory venous pressure measured on each leg measured in mm Hg (Petrassi 2000).

In one study, the physician's judgement of efficacy and safety of the treatment was assessed by a "semi-quantitative 4-point scale" where 1 = poor, 2 = moderate, 3 = good, and 4 = very good. Investigators also assessed clinical tolerability, but did not report whether participants or investigators reported the "side effects" (Petrassi 2000).

The second study measured biochemical tolerability by means of blood samples including haematology, blood chemistry, liver functions and renal function (Arcangeli 2000). Investigators evaluated safety by means of biochemical tests which included haematology, blood chemistry as well as hepatic and renal functions. They assessed efficacy clinically with a semi-qualitative scale where 1 = poor, 2 = moderate, 3 = good and 4 = very good.

DM

The review includes six studies (336 participants) on DM (Belcaro 2006a; Chous 2016; Domanico 2015; Liu 2004a; Steigerwalt 2009; Zibadi 2008). Four studies included only participants with DM type II (Domanico 2015; Liu 2004a; Steigerwalt 2009; Zibadi 2008), one study was conducted in only DM type I participants (Belcaro 2006a) and one study assessed both DM type I and II (Chous 2016). Four studies reported where they were conducted; two were in Italy (Belcaro 2006a; Steigerwalt 2009), one in China (Liu 2004a) and one in the USA (Zibadi 2008). Two studies did not report their location and all studies reported their funding sources.

Study design

All six studies were of parallel group design. Two studies gave the intervention for six months (Chous 2016; Domanico 2015), two studies administered the intervention for three months (Liu 2004a; Zibadi 2008), one study for two months (Steigerwalt 2009) and one study for six weeks (Belcaro 2006a). Only one study followed participants up at one month and three months beyond the completion of the study period (Steigerwalt 2009). The remaining studies did not conduct any follow-up of participants after the intervention had finished. Only two of the studies reported receiving ethics approval (Domanico 2015; Zibadi 2008). No studies reported that a sample size calculation was performed.

Participants

The number of participants included in each study ranged from 30 (Belcaro 2006a) to 77 (Liu 2004a). Overall the studies included 172 (51.2%) males and 164 (48.8%) females spread evenly across all studies. The mean age of participants from five studies was 56 years (Belcaro 2006a; Chous 2016; Domanico 2015; Steigerwalt 2009; Zibadi 2008). The sixth study reported age as median (IQR) for the treatment group 54 (45 to 62) and control group 58 (47 to 66) separately (Liu 2004a). The mean duration of condition reported from five studies was 11.3 years ranging from 6.4 to 16.1 years (Belcaro 2006a; Chous 2016; Domanico 2015; Steigerwalt 2009; Zibadi 2008).

One study recruited people with insulin-dependent type I DM with foot ulcers which had appeared for the first time and were present for at least two months, and severe diabetic microangiopathy

based on blood flow in tibial arteries exceeding 60 mm Hg (Belcaro 2006a).

One study included participants who were diagnosed with DM – either type I or II – more than five years ago, had a best corrected visual acuity of greater than or equal to 20/30 in each eye and had no diabetic retinopathy, or mild to moderate non-proliferative diabetic retinopathy (NPDR). Investigators only included potential participants with diabetic macular oedema (DMO) as determined by spectral domain optical coherence tomography if they did not meet the diagnostic criteria for clinically significant DMO as specified in the Early Treatment Diabetic Retinopathy Study guidelines (Chous 2016).

Two studies assessed participants with diabetic retinopathy. However, investigators in one study only included participants if they had mild to moderate NPDR, absence of clinically significant macular oedema (CSME) according to Early Treatment Diabetic Retinopathy Study protocol, normal BP, normal blood lipids, normal HbA1c and had remained on the same anti-diabetic agents for six months prior to the start of the study (Domanico 2015). The second study only recruited participants with moderate diabetic retinopathy as judged by existence of DMO and retinal swelling and presence of minor exudates and haemorrhages, DM type II for at least four years and an HbA1c below 7% (Steigerwalt 2009).

The only inclusion criterion for one study was that participants had to have DM type II according to the WHO 1999 diagnostic criteria for diabetes (Liu 2004a).

Inclusion criteria for participants in the remaining study were type II DM, aged 40 to 75 years old with hypertension and taking angiotensin-converting enzyme (ACE) inhibitors for their hypertension (Zibadi 2008).

Interventions

Four studies administered Pycnogenol® at different dose regimens and routes of administration. The first study examined three different intervention groups and a control group over six weeks (Belcaro 2006a). The first treatment group (oral and local) received Pycnogenol® three 50 mg capsules per day orally together with 100 mg powder from two 50 mg capsules to be placed on the ulcerated area daily. In the second treatment group (local) 100 mg Pycnogenol® powder (from two 50 mg capsules) was placed on the ulcerated area daily. The third treatment group (oral) received three Pycnogenol® 50 mg capsules per day. The control group received no Pycnogenol® or other medication except standard ulcer care as received by the three active treatment groups (Belcaro 2006a).

The participants in the two-month study took three 50 mg Pycnogenol® tablets daily after breakfast and the control group took three placebo tablets according to the same regimen (Steigerwalt 2009).

In the first of two 12-week studies, the intervention group took Pycnogenol® 100 mg orally and the control group received an oral placebo. Investigators permitted conventional oral anti-diabetic medication as needed (Liu 2004a).

The participants in the second 12-week study took five 25 mg Pycnogenol® tablets per day orally. The control group took five placebo capsules orally. Additionally, investigators permitted

first-generation sulfonylureas, second-generation sulfonylureas, metformin, and thiazolidinediones for glucose control (Zibadi 2008).

One six-month study used a Diabetes Visual Function Supplement Study (DiVFuSS) formula comprising two capsules taken orally on a daily basis. Each capsule contained vitamins C, D3, and E (d-alpha-tocopherol), zinc oxide, eicosapentaenoic acid, docosahexaenoic acid, alpha-lipoic acid, co-enzyme Q10, mixed tocotrienols/tocopherols, zeaxanthin, lutein, benfotiamine, N-acetyl cysteine, grape seed extract, resveratrol, turmeric root extract, green tea leaf and Pycnogenol®. The control group received a placebo of two oral canola oil softgel capsules daily. In total, 26 participants consumed a single, daily multivitamin and mineral supplement. No participants consumed supplements that contained ingredients found in the DiVFuSS formula. Participants also refrained from eating foods that are high in xanthophyll or omega-3 fatty acids more than twice weekly (Chous 2016).

In the second six-month study all participants took a single type of oral metformin monotherapy at a dose of 1000 mg twice daily for the duration of the study and at least six months before enrolment. The intervention group additionally took one oral Diabere® capsule daily which contained 50 mg Pycnogenol®, 30 mg vitamin E, and 20 mg co-enzyme Q10. The control group received usual care only (Domanico 2015).

Outcomes measured

Three studies measured HbA1c (%) (Chous 2016; Liu 2004a; Zibadi 2008) and two of these measured the change in fasting blood glucose (Liu 2004a; Zibadi 2008). Two studies measured LDL cholesterol (Chous 2016; Zibadi 2008). Only one study measured the other lipid markers total cholesterol, HDL cholesterol and triglycerides (Chous 2016). This study was also the only study to measure contrast sensitivity measured for spatial frequencies of 1.5, 3, 6, 12 and 18 cycles per degree, macular pigment optical density, colour discrimination, 5-2 macular threshold perimetry, vitamin D and TNF-alpha levels (Chous 2016). Two studies reported endothelin-1 levels (Liu 2004a; Zibadi 2008).

One study measured microcirculation-related symptoms (e.g. pain) and using a clinical scale where 0 = absence of symptoms and 10 = very severe signs or symptoms (Belcaro 2006a). The same study was the only one to measure the area of ulceration (mm²) and to calculate the percentage of complete healing; investigators measured microcirculatory parameters including transcutaneous PO₂ and PCO₂, skin flux at rest and venoarteriolar response (Belcaro 2006a).

One study reported a free-oxygen radical-test to measure the levels of ROS and central macular thickness to determine structural changes over time (Domanico 2015).

One study measured 6-keto-prostaglandin F1a and reported the percentage decrease relative to pre-treatment levels; this was the only study to assess the change in nitrogen monoxide levels (Liu 2004a).

Only one study measured visual acuity using the standard Snellen Chart (Steigerwalt 2009). This was also the only study to report retinal blood flow and diastolic retinal blood flow relative to maximum systolic flow expressed as flow velocity, along with

retinal oedema score where a score of zero indicated no DMO and six indicated severe DMO and retinal thickness (Steigerwalt 2009).

One study reported change in ACE inhibitor dosage where dosage either remained unchanged (equal to baseline dose), reduced by 50% or brought back to the baseline dosage until a "stable blood pressure" was obtained (Zibadi 2008). This was also the only study to measure urinary albumin concentration (Zibadi 2008).

ED

The review includes three studies (277 participants) that assessed Pycnogenol® for use in men with ED (Cai 2013; Duracková 2003; Ledda 2010). One study was conducted in the Slovak Republic (Duracková 2003) and one study in Italy (Cai 2013). It is unclear from the study report where the third study was conducted (Ledda 2010). Two of the three studies reported their funding sources (Duracková 2003; Ledda 2010).

Study design

All three studies were of parallel-group design. The treatment duration was three months in two of the studies (Cai 2013; Duracková 2003) and six months in the third study (Ledda 2010). Participants were followed up one month after the end of treatment and at the end of the fourth month in one three-month study (Duracková 2003). In the second three-month study participants were assessed at baseline and at the end of the intervention period (Cai 2013); while the third study measured participants at baseline, three months and six months (Ledda 2010). Only one of the studies reported ethics approval (Duracková 2003). Only one study reported a sample size calculation, which resulted in a suggested sample size of 64 participants per group (Cai 2013).

Participants

The studies included 132, 21 and 124 males respectively (Cai 2013; Duracková 2003; Ledda 2010).

The mean age across all studies was 50 years. However, the mean age for the study conducted in Italy was 59 years as the minimum age for participants was 50 years (Cai 2013). The mean ages for the other two studies were 46.5 years (range 22 to 69 years) (Duracková 2003) and 44.25 years (range 30 to 50 years) (Ledda 2010).

The mean International Index of Erectile Function-5 (IIEF-5) score overall was 14 for participants, whereby the study conducted in the Slovak Republic had the lowest mean score of 11.95 (Duracková 2003) indicating more severe ED compared to the other two studies which reported mean scores of 15 (Cai 2013) and 15.15 (range ≥11 to 17) (Ledda 2010). Participants in the Italian study needed a IIEF-5 score less than 21 (Cai 2013).

The participants in the study conducted in the Slovak Republic had ED for a mean duration of 25.25 months (Duracková 2003).

Participants recruited to the Italian study had a mean BMI of 27 kg/m² (Cai 2013). Of the 21 participants recruited to the Slovak study, 14 had DM, 12 were at risk of atherogenetic hypertension, six had ischaemia and six were smokers (Duracková 2003). The third study reported mean total plasma testosterone levels of 16.4 nmol/L, mean total cholesterol levels of 208.5 mg/dL and a mean systolic BP of 138 mm Hg (Ledda 2010).

Participants in the Italian study were sexually active with a maximal urinary flow rate (Cmax) of less than 15 mL/s (Cai 2013). Participants in the Ledda study needed to be in a stable sexual partnership in the past six months (Ledda 2010).

Further inclusion criteria for the Italian study were a post-residual voided volume less than 100 cc, international prostate symptom score (IPSS) score of eight or greater, an IPSS quality of life (QoL) score of 2 or greater and a prostate specific antigen (PSA) less than 4 ng/mL, or higher if negative prostate biopsy. The IIEF-5 score had to be less than 21, participants had to be untreated for lower urinary tract symptoms (LUTS) or benign prostatic hyperplasia (BPH) with testosterone levels over 3 ng/dL (Cai 2013).

Intervention

One study administered one daily 950 mg capsule IDIProst® Gold orally which contained *Serenoa repens* (320 mg), *Crocus sativus* (100 mg) and *Pinus massoniana* (120 mg) (Cai 2013). The control group received one daily oral capsule of *Serenoa repens* (320 mg) which is a non-antioxidant supplement also known as saw palmetto extract.

One study administered Pycnogenol®: two 20 mg pills orally three times a day (total of 120 mg/day) for three months and compared this to a placebo which was also given as two pills orally three times per day for three months (Duracková 2003). Participants were not allowed to consume any concomitant medication.

In one study, participants in the intervention group took Prelox® at a dose of four oral tablets daily (two tablets in the morning after breakfast and another two after dinner) (Ledda 2010). Each tablet contained 20 mg Pycnogenol® and 700 mg L-arginine aspartate. Participants in the control arm took a placebo, with dicalcium phosphate replacing the active components. Investigators did not report the dose, route of administration or frequency of intake of the placebo group. No participants were on antihypertensives or cholesterol medication before the study commenced. Investigators provided standard dietary suggestions for weight loss, decreased sodium intake and moderate exercise.

Outcomes measured

All three studies measured ED symptom scores with the IIEF questionnaire. However, only two used the condensed IIEF-5 version containing five questions where normal function is represented by a score between 21 and 25 points, mild ED by 16 to 20 points, moderate ED by 10 to 15 points and severe ED by less than 10 points (Cai 2013; Duracková 2003). The third study used the IIEF questionnaire containing 15 questions across five domains (Ledda 2010).

The Italian study additionally measured IPSS to assess problems concerning urination, where the score can range from 0 to 35 (meaning asymptomatic to very symptomatic). The study also measured health-related quality of life by means of the 'Short-Form 36 questionnaire' (Cai 2013).

The second study additionally measured total cholesterol levels (mmol/L), LDL-cholesterol levels (mmol/L), HDL-cholesterol levels (mmol/L) and LDL/HDL ratio. The study measured triacylglycerols but investigators did not report any results. They measured antioxidant activity in the blood in mmol of Trolox/L and reported results as a percentage where 100% is the antioxidative activity of plasma before the trial (Duracková 2003).

The last study additionally measured systolic BP (mm Hg), diastolic BP (mm Hg) and total plasma testosterone (nmol/L) ([Ledda 2010](#)).

Female sexual dysfunction

The review includes one study (75 participants) on female sexual dysfunction; it was not reported in which country the study was conducted or whether it was funded ([Bottari 2012](#)).

Study design

The study was of parallel-group design and had a treatment duration of eight weeks, with follow-up assessments conducted at four and eight weeks. Investigators did not follow up participants beyond the completion of the intervention. The relevant ethics committee approved the study protocol. Investigators did not specify a sample size calculation, but indicated that at least 20 participants per group were necessary ([Bottari 2012](#)).

Participants

The mean (SD) age of the intervention group was 50.1 (3.1) years; the mean (SD) Female Sexual Function Index (FSFI) score was 44.6 (24.1) (with a lower score indicating more severe dysfunction). The placebo group had a mean (SD) age of 51.2 (2.3) years and a mean (SD) FSFI score of 44.1 (22.8).

The study recruited women between 45 and 55 years with previously defined menopause and moderate sexual function problems according to the FSFI scoring system and a maximum BMI of less than 24 kg/m².

Interventions

Participants in the intervention group took four tablets daily of Lady Prelox® (two tablets in the morning and two tablets in the evening); these contained a daily dose of 20 mg Pycnogenol®, 200 mg L-arginine, 200 mg L-citrulline, and 50 mg rose hip extract. Participants in the control group took a placebo; however, investigators did not specify the dose, frequency, duration and route of administration of the placebo. Investigators only permitted daily vitamins and minerals as concomitant treatment.

Outcomes measured

The FSFI score consists of six domains namely desire, arousal, lubrication, orgasm, satisfaction and pain. The study assessed the effect of Lady Prelox® on all six domains as well as on the total FSFI scores.

Osteoarthritis

The review includes three studies (294 participants) in this condition, all of which declared their funding source ([Belcaro 2008a](#); [Cisár 2008](#); [Farid 2007](#)).

Study design

All three studies used a parallel-group design and the treatment duration was three months. Investigators followed participants up at baseline and at three months in the first study ([Belcaro 2008a](#)). In the second study, investigators followed participants up every four weeks from baseline until four weeks after the completion of the intervention, which was 14 weeks after the baseline assessment ([Cisár 2008](#)). In the third study, follow-ups occurred at baseline, 30, 60 and 90 days ([Farid 2007](#)). All three studies obtained ethics approval ([Belcaro 2008a](#); [Cisár 2008](#); [Farid 2007](#)). Only one study

reported a sample size calculation and used 90% power, type-one error of 5% and one control per participant in the intervention group; thus recommending 35 participants per group ([Cisár 2008](#)).

Participants

The studies included 156 ([Belcaro 2008a](#)), 100 ([Cisár 2008](#)) and 38 participants ([Farid 2007](#)). Overall there were 113 (38.4%) male and 181 (61.6%) female participants, whereby two studies recruited predominantly females (68% ([Cisár 2008](#)) and 92% ([Farid 2007](#))). The mean age of all participants was 49.8 years, but one study only recruited participants between 25 and 65 years of age ([Cisár 2008](#)). The mean BMI reported from two studies was 25.2 kg/m² ([Cisár 2008](#); [Farid 2007](#)); in one study participants' mean BMI indicated they were overweight (27.3 kg/m²) ([Cisár 2008](#)) and in the second study showed normal weight (23.1 kg/m²) ([Farid 2007](#)).

All three studies included participants with grade 1 or 2 osteoarthritis but used different diagnostic criteria. The first study used X-ray investigation ([Belcaro 2008a](#)). Participants had mild to moderate pain, which was not adequately controlled with anti-inflammatory drugs; they had to be able to perform the treadmill test and understand all questions from the global Western Ontario and McMaster Universities (WOMAC) questionnaire. Participants' WOMAC index scores (24 visual analogue scales generating a score out of a maximum of 96, with 0 indicating no symptoms) were 79.2 and 76.9 for the intervention and placebo groups, respectively ([Belcaro 2008a](#)). The second study included participants over 25 years of age with primary osteoarthritis (stage 1 or 2 according to Kellgren-Lawrence in standard AP (anteroposterior) view X-rays) in at least one target knee, mild to moderate pain in the target knee for at least three months preceding the study, or morning knee stiffness or knee crepitus, or combinations of these ([Cisár 2008](#)). The remaining study recruited participants aged between 25 and 65 years with primary knee osteoarthritis (grade 1 or 2 according to the American College of Rheumatology criteria; 40% of participants had grade 1 knee osteoarthritis and 60% had grade 2 knee osteoarthritis), a WOMAC index score of at least 40 at baseline and pain in the target knee for at least 50% of the time in the last three months requiring medical treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors on most days ([Farid 2007](#)).

Interventions

All three studies compared Pycnogenol® to placebo for three months. In one study participants took two Pycnogenol® 50 mg oral capsules per day (after breakfast and dinner) and those in the control group took placebo capsules according to the same regimen. Participants documented any change in concomitant treatment. Following correspondence with the study authors it was discovered that concomitant medication included NSAIDs, paracetamol and ibuprofen ([Belcaro 2008a](#)). The remaining two studies administered Pycnogenol® but increased the dose to three 50 mg pills per day with meals. The control group received three placebo pills per day, also with meals. Participants in both studies were allowed to continue with pain medication prescribed prior to the study ([Cisár 2008](#); [Farid 2007](#)). However, in one study participants were allowed to change the dose and frequency of use, but had to report these changes to investigators at each visit ([Cisár 2008](#)).

Outcomes measured

All three studies evaluated the effect of Pycnogenol® on pain, stiffness, physical function (referred to as 'daily activities' by Cisár (Cisár 2008)) and overall effect by means of WOMAC scores. Additionally, investigators in one study also evaluated negative alterations in social functions and the sum of emotional parameters as osteoarthritis symptoms with the WOMAC instrument (Belcaro 2008b). The WOMAC instrument is available either in a Likert scale or in a visual analogue format (Bellamy 2001); Cisár used a Likert scale and Farid a visual analogue scale (VAS) (Cisár 2008; Farid 2007). Belcaro does not report the type of scale used, but does report the interpretation of the scale (see 'Characteristics of included studies'). Belcaro also assessed microcirculation-related symptoms (e.g. pain) by means of a clinical scale where 0 indicates the absence of symptoms and 10 indicates very severe signs or symptoms (Belcaro 2008a).

Two studies reported the change in analgesic use; one study reported this as a percentage reduction or increase (Cisár 2008), while the second reported the change in the number of pills (NSAIDs and COX-2 inhibitors) taken per month (Farid 2007).

All three studies reported adverse effects (Belcaro 2008a; Cisár 2008; Farid 2007). In two studies, investigators asked participants to report specific adverse or unusual events; these studies also measured safety by means of basic biochemical parameters (Cisár 2008; Farid 2007). The remaining study used direct questioning about tolerability and compliance - particularly gastrointestinal problems, systemic and local skin alterations, signs of allergic reaction and any other manifestation (Belcaro 2008a). One study measured participant compliance by pill counting in one study (Farid 2007).

Osteopenia

This review included one study (44 participants) from Iran which recruited participants with osteopenia and assessed them for up to 12 weeks (Panahande 2019).

Study design

The study was double-blind, placebo-controlled, of parallel design and received ethics approval and reported its funding source. The study authors reported using the 'Vanlint and Ried' sample size formula with C-terminal telopeptide of type 1 collagen (CTX1) as a key variable to calculate a sample size of 20 participants per group (Panahande 2019).

Participants

The intervention and control groups each consisted of 22 post-menopausal women between the ages of 50 and 65 years with osteopenia, defined as a bone mineral density (BMD) between -1 and -2.5 SDs. The mean (SD) age of participants was 57.38 (0.97) years in the intervention group and 56.47 (3.64) years in the placebo group. Participants in the intervention group had a menopause duration of mean (SD) 9.09 (4.89) years and 7.21 (3.45) years in the placebo group. The mean (SD) BMD T-score for the intervention group was -1.87 (0.41) and for the placebo group it was -1.94 (0.4). Participants had normal thyroid, liver and kidney function (Panahande 2019).

Interventions

The intervention group received five Oligopin® capsules per day, each containing 50 mg pine bark extract. The control group received five placebo capsules per day, each containing 50 mg medicinal starch. Investigators instructed participants to take two capsules after breakfast, two after lunch and one after dinner (Panahande 2019).

Outcomes measured

From fasting blood samples, the study reported on levels of serum calcium, magnesium, phosphorous, parathyroid hormone, bone alkaline phosphatase (BAP), C-terminal telopeptide of type I collagen (CTX1), ratio of CTX1/BAP, procollagen type 1 N-terminal propeptide (P1NP), receptor activator of nuclear factor k-B ligand (RANKL) and osteoprotegerin (OPG) to determine bone formation. Investigators assessed the usual dietary intake of participants, including calcium, energy and specific macro- and micronutrient levels, by 24-hour recall and using Nutritionist Software Version IV. They assessed physical activity levels using the International Physical Activity Questionnaire (Panahande 2019).

TBI

The review includes one study which recruited 60 participants with TBI (Theadom 2013). The study was conducted in Auckland, New Zealand and assessed participants for six weeks. The study authors reported that the study was partially funded by the pharmaceutical company.

Study design

The study was double-blind and placebo-controlled with three treatment phases. However, as stated above, the review authors have only extracted data from the first phase and treated this as a parallel-group design (see Unit of analysis issues). The study received ethics approval from the relevant ethics committee. Investigators did not undertake a sample size calculation, but did report using a convenience sample size of 60 participants because of financial constraints.

Participants

Participants were only recruited if they were aged 18 and 64 years, three to 12 months post-mild TBI (as defined by the Glasgow Coma Scale score of 13 to 15 and post-traumatic amnesia for less than 24 hours) and had persistent cognitive difficulties (as defined by a score above 38 on the Cognitive Failures Questionnaire).

The intervention group (n = 30) consisted of 12 males and 18 females with a median (IQR) age of 44 (28) years; the mean (SD) time since injury was 7.1 (2.66) months. The placebo group (n = 30) consisted of 14 males and 16 females with a median (IQR) age of 45 (27) years and a mean (SD) time since injury of 8.04 (2.46) months.

Interventions

The intervention group received Enzogenol® 100 mg given as two oral capsules 15 minutes before breakfast compared to placebo. Participants had to abstain from taking any other antioxidant supplements.

Outcomes measured

The study assessed cognitive functioning, post-concussion symptoms and mood by means of questionnaires. The Cognitive

Failure Questionnaire evaluated everyday memory, the California Verbal Learning Test evaluated episodic memory (and standardised results for age and gender) and the Wechsler Adult Intelligence Scale evaluated working memory. Participants also completed the Rivermead Post-Concussion Symptoms questionnaire and the Hospital Anxiety and Depression Scale questionnaire.

Excluded studies

We excluded 49 studies with reasons (see the table 'Characteristics of excluded studies'). In six studies the treated condition was not a chronic disorder (Kohama 2013; NCT03777683; Nishioka 2007; Ryan 2008; Suzuki 2008; Thom 2005) and one study investigated the use of pine bark extract as a prevention rather than treatment (Wilson 2010). Five studies used an inappropriate control group (Cesarone 2006a; Cesarone 2010; Furumura 2012; Koch 2002; Kohama 2007) and a further three studies were excluded as the intervention was not given for at least one month (Khurana 2013; Sedighiyan 2018; Tenenbaum 2002). The remaining 34 studies were not RCTs.

Studies awaiting classification

One study of parallel design comparing Pycnogenol® (120 mg daily) to placebo in people with diabetic nephropathy for three months is listed as awaiting classification (Muchova 2014). Investigators have recruited 20 participants with DM and will assess glucose levels, advanced glycation end-products (AGEs), malondialdehyde (MDA), 8-isoprostanes (8-Iso) as well as protein carbonyls. Currently the study is only available as an abstract; while we have requested the full text article from the author, we are still awaiting a response and the study is therefore listed as 'Awaiting classification' (Muchova 2014).

Ongoing studies

We identified 17 ongoing studies across different disorders (see Ongoing studies):

- pre-diabetes (ACTRN12615000233527);
- DM (IRCT20180718040512N1; IRCT20100408003664N21);
- CVD (ISRCTN22412590; ISRCTN44961472; NCT00952627);
- lymphoedema (NCT00064857; NCT00214032);
- osteoarthritis (NCT01321281; NCT03106584);
- osteopenia (IRCT2017060334308N1; NCT03260803);
- Gulf war illness (NCT02909686);
- cancer (NCT03704454);
- polycystic ovarian syndrome (PCOS) (IRCT20140406017139N3);
- and ADHD (NCT03368690; Verlaet 2017).

Study design

In total 13 studies are described as blinded, placebo-controlled, parallel-designed RCTs (ACTRN12615000233527; ISRCTN22412590; ISRCTN44961472; NCT00064857; NCT00214032; NCT00952627; NCT01321281; IRCT20100408003664N21; IRCT20140406017139N3; IRCT2017060334308N1; IRCT20180718040512N1; NCT03260803; Verlaet 2017). Four studies are described as blinded, cross-over RCTs (NCT02909686; NCT03106584; NCT03704454; NCT03368690), one of which is not placebo-controlled (NCT03106584). Nine studies do not report ethics approval (NCT00064857; NCT00214032; NCT00952627; NCT01321281; NCT02909686; NCT03106584; NCT03704454; NCT03368690; NCT03260803).

Participants

One study is recruiting children aged 6 to 12 years (Verlaet 2017), one study is recruiting participants aged from 7 to 64 years (NCT03368690), while all other studies planned to recruit adults. In seven studies only females are eligible for inclusion (IRCT2017060334308N1; NCT03260803; IRCT20140406017139N3; IRCT20180718040512N1; NCT03704454; NCT00214032; NCT01321281) and in one study only males are eligible for inclusion (NCT02909686).

Interventions

Seven studies plan to administer Pycnogenol® in doses ranging from 50 mg to 400 mg per day (NCT03704454; ISRCTN22412590; ISRCTN44961472; NCT00064857; NCT00214032; NCT00952627; NCT02909686). The single paediatric study intends to stratify dose according to weight: participants < 30 kg at Pycnogenol® 20 mg/day and participants > 30 kg at Pycnogenol® 30 mg/day (Verlaet 2017). One study states it will administer pine bark extract at 50 mL twice daily (ACTRN12615000233527), while the intervention in a further study is four capsules of AquaPT® daily (NCT01321281) and in another study is four Aquamin® capsules daily (NCT03106584). Six studies plan to compare Oligopin® in doses ranging from 25 mg per day for children to 150 mg per day for adults to control (IRCT20100408003664N21; IRCT20140406017139N3; IRCT2017060334308N1; IRCT20180718040512N1; NCT03260803; NCT03368690). Five studies do not indicate the intended duration of intervention (NCT00064857; NCT00214032; NCT00952627; NCT01321281; NCT02909686); for the remaining studies the duration of intervention is planned to range from one to three months.

Outcomes measured

The study with participants with pre-diabetes will assess blood glucose as a primary outcome (ACTRN12615000233527) and the two DM studies will assess blood glucose, blood lipids and BP (IRCT20100408003664N21; IRCT20180718040512N1). One CVD study plans to assess BP, lipids, blood glucose, endothelin and urinary albumin (ISRCTN44961472), a further CVD study will assess the maximum cardiac workload (ISRCTN22412590) and the third CVD study cardiac fibrosis and diastolic BP (NCT00952627). The two studies that are recruiting people with lymphoedema will report on a reduction in lymphoedema (NCT00064857; NCT00214032). One of the osteoarthritis studies will assess plasma cytokine levels as the primary outcome (NCT01321281) and the other participant-reported knee pain (NCT03106584). The study on Gulf war illness will assess the change in the severity of the condition (NCT02909686) and the two ADHD studies intend assessing behaviour rated by teachers and parents (NCT03368690; Verlaet 2017). The cancer study will use a menopause symptom rating scale as a primary outcome (NCT03704454). The two studies in osteopenia both would assess BAP and carboxyl terminal collagen type I in plasma as their primary outcomes (IRCT2017060334308N1; NCT03260803). Finally, the PCOS study will assess dehydroepiandrosterone sulphate (DHEA-S), blood glucose, follicle stimulating hormone (FSH), luteinising hormone (LH), sex hormone binding globulin and testosterone as its primary outcomes (IRCT20140406017139N3).

Risk of bias in included studies

The review authors have presented the judgements regarding the risk of bias for each of the included studies in the table 'Characteristics of included studies'. The overall risk of bias was low for four studies ([Chous 2016](#); [Drieling 2010](#); [Enseleit 2012](#); [Valls](#)

[2016](#)), high for one study ([Belcaro 2006a](#)), and unclear for the remaining 22 studies. For the five included cross-over trials, we have assessed the risk of bias for additional domains applicable for such type of studies ([Enseleit 2012](#); [Hosseini 2001a](#); [Hosseini 2001b](#); [Reule 2017](#); [Valls 2016](#)). Two figures provide a graphical summary of the risk of bias assessments, one per study ([Figure 2](#)) and one per assessment domain ([Figure 3](#)), .

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias	Was a paired analysis being used?	Is the cross-over design suitable?	Are data of both periods available?	Was there no carry-over effect?	Are the results comparable to those from parallel group trials?
Arcangeli 2000	?	?	?	?	?	?	?	+	+	+	+	+
Belcaro 2006a	?	?	+	+	+	+	?	+	+	+	+	+
Belcaro 2008a	+	?	+	+	+	+	?	+	+	+	+	+
Bottari 2012	?	?	+	+	+	?	?	+	+	+	+	+
Cai 2013	?	?	?	?	?	?	?	+	+	+	+	+
Cesarone 2008	?	?	+	+	+	+	?	+	+	?	?	?
Chous 2016	+	+	+	+	?	+	?	+	+	+	+	+
Cisár 2008	+	?	?	+	+	?	?	+	+	+	+	+
Domanico 2015	+	?	+	+	+	?	?	+	+	+	+	+
Drieling 2010	+	+	+	?	+	?	?	+	+	+	+	+
Duracková 2003	+	?	?	?	+	+	+	+	+	+	+	+
Enseleit 2012	?	?	+	+	+	+	?	?	?	?	+	+
Farid 2007	+	?	?	?	+	+	?	+	+	+	+	+
Hosseini 2001a	?	?	?	?	?	?	?	+	?	?	?	?
Hosseini 2001b	+	?	?	?	+	+	?	+	+	+	?	?
Lau 2004	?	?	+	?	+	+	?	+	+	+	+	+
Ledda 2010	+	?	+	+	?	?	?	+	+	+	+	+
Liu 2004a	?	?	?	?	+	+	?	+	+	+	+	+
Liu 2004c	?	?	?	?	+	+	?	+	+	+	+	+
Panahande 2019	?	?	+	+	+	+	?	+	+	+	+	+
Petrassi 2000	+	?	?	?	+	+	?	+	+	+	+	+
Reule 2017	+	?	+	+	+	?	?	+	+	?	+	+
Steigerwalt 2009	+	?	?	?	+	+	?	+	+	+	+	+

Figure 2. (Continued)

Reule 2017	+	?	+	+	+	?	?	+	+	?	+	+
Steigerwalt 2009	+	?	?	?	+	+	?	+	+	+	+	+
Theadom 2013	+	?	+	+	?	+	?	+	+	+	+	+
Trebatická 2006	+	+	?	?	+	+	?	+	+	?	?	?
Valls 2016	+	+	+	+	+	+	?	+	+	?	+	+
Zibadi 2008	+	?	?	?	+	+	?	+	+	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

We were not able to compare the results of the cross-over studies with other studies since either the same outcomes were not addressed (Hosseini 2001b) or the types of participants differed (Hosseini 2001a). One study did not report the SE (Hosseini 2001a; Table 2), so we could not add these data as a paediatric subgroup to the analysis with a second study (Lau 2004).

Allocation

Generation of the random allocation sequence

All included studies stated they were randomised, but the we judged the method used for generating the allocation sequence to have a low risk of bias in only 12 studies initially (Belcaro 2008a; Chous 2016; Domanico 2015; Drieling 2010; Hosseini 2001b; Ledda 2010; Petrassi 2000; Reule 2017; Steigerwalt 2009; Theadom 2013; Trebatická 2006; Valls 2016). However, after contact with the investigators, we obtained the randomisation methods of a further four studies and also rated these as having a low risk of bias (Cisár 2008; Duracková 2003; Farid 2007; Zibadi 2008). The remaining 11 studies provided insufficient information regarding this component of the study design and we judged these to have an unclear risk of bias (Arcangeli 2000; Belcaro 2006a; Bottari 2012; Cai 2013; Cesarone 2008; Enseleit 2012; Hosseini 2001a; Lau 2004; Liu 2004a; Liu 2004c; Panahande 2019).

Concealment of the allocation code

Five studies described the method used for concealing allocation (Chous 2016; Drieling 2010; Enseleit 2012; Lau 2004; Valls 2016). Three of these have a low risk of bias (Chous 2016; Drieling 2010; Valls 2016); two studies reported that the treatment was "identified by pre-assigned codes prepared by an independent laboratory" and we assessed these as having an unclear risk of bias (Enseleit 2012; Lau 2004). After contacting the corresponding authors of all studies, we learned that one study concealed allocation of participants and consequently changed our initial unclear judgement of this study to have a low risk of bias (Trebatická 2006). The remaining 21 studies provided either no or insufficient information and we judged these to have an unclear risk of allocation concealment (Arcangeli 2000; Belcaro 2006a; Belcaro 2008a; Bottari 2012; Cai 2013; Cesarone 2008; Cisár 2008; Domanico 2015; Duracková 2003; Farid 2007; Hosseini 2001a; Hosseini 2001b; Ledda 2010; Liu 2004a; Liu 2004c; Panahande 2019; Petrassi 2000; Reule 2017; Steigerwalt 2009; Theadom 2013; Zibadi 2008).

Blinding of participants and personnel (performance bias)

We judged 13 studies to have a low risk of performance bias. Investigators stated that 10 of the included studies were "double-blind"; nine of these mentioned which groups were blinded (e.g. participants, providers or outcome assessor), therefore, we judged these to have a low risk of bias (Chous 2016; Drieling 2010;

Enseleit 2012; Lau 2004; Ledda 2010; Panahande 2019; Reule 2017; Theadom 2013; Valls 2016). The remaining study described as "double-blind" did not provide any further detail, but we still judged this as having a low risk of bias as all outcomes were objective and the intervention was identical to placebo (Cesarone 2008). One further study only blinded participants; however, all outcomes were participant-reported and placebo and intervention were indistinguishable. Thus, we judged this as having a low risk of bias (Bottari 2012). We also judged a further study as having a low risk of bias for performance, since although the participants in the control arm of the study were untreated, the outcomes were assessed objectively by standardised scans and blood tests (Domanico 2015).

In one study, blinding did not occur because of the nature of the interventions (Belcaro 2006a). There were four groups in this study: oral Pycnogenol®; locally applied Pycnogenol® (on the ulcer); both oral and locally applied Pycnogenol®; and a control group with no medical treatment. We judged this study to have a high risk of bias (Belcaro 2006a).

The remaining 13 studies did not provide sufficient information and thus we judged them as having an unclear risk of bias (Arcangeli 2000; Cai 2013; Cisár 2008; Duracková 2003; Farid 2007; Hosseini 2001a; Hosseini 2001b; Liu 2004a; Liu 2004c; Petrassi 2000; Steigerwalt 2009; Trebatická 2006; Zibadi 2008).

Blinding of outcome assessment (detection bias)

We judged 14 studies to have a low risk of bias as the outcome assessors were blinded (Belcaro 2008a; Bottari 2012; Cesarone 2008; Chous 2016; Cisár 2008; Domanico 2015; Drieling 2010; Enseleit 2012; Lau 2004; Ledda 2010; Panahande 2019; Reule 2017; Theadom 2013; Valls 2016).

A further 12 studies provided insufficient information and we judged these to have an unclear risk of bias (Arcangeli 2000; Cai 2013; Duracková 2003; Farid 2007; Hosseini 2001a; Hosseini 2001b; Liu 2004a; Liu 2004c; Petrassi 2000; Steigerwalt 2009; Trebatická 2006; Zibadi 2008).

We judged one study to have a high risk of bias as there was no blinding of outcomes assessors (Belcaro 2006a).

Incomplete outcome data

We judged 11 of the 27 included studies to have a low risk of bias due to incomplete outcome data because no participants were lost to follow-up during the study period (Belcaro 2006a; Cesarone 2008; Domanico 2015; Duracková 2003; Hosseini 2001b; Liu 2004a; Liu 2004c; Panahande 2019; Petrassi 2000; Reule 2017; Steigerwalt 2009). We also judged seven further studies to have a low risk of bias since the number of participants who did not finish the study is small and balanced across the two groups (Belcaro 2008a; Bottari 2012; Enseleit 2012; Farid 2007; Trebatická 2006; Valls 2016; Zibadi 2008).

In one study, more than twice as many participants were lost to follow-up in the control group than in the group receiving the test drug; therefore, we judged this study to have a high risk of bias (Cisár 2008).

We judged the remaining eight studies to have an unclear risk of bias. One used a cross-over design, but does not report whether

investigators performed analyses with first- or second-period data or both, or how investigators dealt with participants who were lost to follow-up in the analysis (Hosseini 2001a). In the remaining two studies, investigators do not report whether all randomised participants completed the study and whether they performed analyses on data from all outcomes for all participants (Arcangeli 2000; Lau 2004). We judged five studies as having an unclear risk of bias since investigators did not report the reasons for exclusion from the studies sufficiently: it was unclear from which groups the participants were lost to follow-up or whether investigators excluded outcome data from the analysis or not (Cai 2013; Chous 2016; Drieling 2010; Ledda 2010; Theadom 2013). We could not obtain additional information from the corresponding authors.

Selective reporting

For each included study, we searched for a trial registry and protocol. Three studies had a protocol available and we judged these as having low risk of bias because all pre-specified outcomes were reported on (Chous 2016; Drieling 2010; Enseleit 2012).

Studies for which no protocol is available can at best be judged as having an unclear risk of bias with regards to selective reporting, provided that outcomes were pre-specified in the 'Methods' section of the paper and reported on in the 'Results' section; this was the case for six studies (Bottari 2012; Cisár 2008; Domanico 2015; Hosseini 2001a; Ledda 2010; Reule 2017).

We judged a total of 18 studies to have a high risk of selective reporting bias. For 12 studies, the trial registry entry or protocol is not available and not all outcomes were pre-specified in the 'Methods' section (Arcangeli 2000; Belcaro 2006a; Belcaro 2008a; Duracková 2003; Farid 2007; Hosseini 2001b; Lau 2004; Liu 2004a; Liu 2004c; Petrassi 2000; Steigerwalt 2009; Trebatická 2006). Investigators on one study registered its protocol retrospectively, with some outcomes stated in the protocol, but not reported in the article, and vice versa (Theadom 2013). A further three studies had a trial registry or protocol available, but outcomes are either pre-specified in the 'Methods' section but not reported in the 'Results', or results were reported for outcomes that were not pre-specified in the 'Methods' section (Panahande 2019; Valls 2016; Zibadi 2008). The remaining two studies did not have a protocol available and not all pre-specified outcomes stated in the 'Methods' section were reported in the 'Results' (Cai 2013; Cesarone 2008).

Other potential sources of bias

For the judgement of this domain, we focused on the source of funding and the reporting of baseline characteristics (except in the five cross-over studies where this is not relevant (Enseleit 2012; Hosseini 2001a; Hosseini 2001b; Reule 2017; Valls 2016)).

Horphag Research, the manufacturer and holder of the Pycnogenol® registered trademark, funded nine of the studies included in this review (Belcaro 2006a; Cisár 2008; Enseleit 2012; Farid 2007; Hosseini 2001b; Ledda 2010; Lau 2004; Trebatická 2006; Zibadi 2008). Cognis Corporation, a manufacturer of pharmaceuticals, as well as nutrition and health ingredients provided the intervention at no cost for one study in this review (Hosseini 2001a). We judged these 10 studies to have an unclear risk of bias. In 15 studies investigators did not report the source of funding or it was unclear if the study was funded by companies that manufacture supplements and therefore we also judged these studies as having an unclear risk of bias (Arcangeli 2000; Belcaro

2008a; Cai 2013; Cesarone 2008; Chous 2016; Domanico 2015; Drieling 2010; Liu 2004a; Liu 2004c; Panahande 2019; Petrassi 2000; Reule 2017; Steigerwalt 2009; Theadom 2013; Valls 2016). After contacting the study authors we learned that Horphag Research also funded four of these 15 studies; this did not change our judgement (Belcaro 2008a; Liu 2004a; Liu 2004c; Steigerwalt 2009).

One study was funded by an institution other than manufacturers, distributors or marketers of pine bark extract and we judged this to have a low risk of bias (Duracková 2003).

One study did not report its funding source; however, we judged it as having a high risk of bias as there is no clear indication what the cut-off values are for defining female sexual dysfunction (Bottari 2012). A score below 25.55 has been defined as sexual dysfunction (Wiegel 2005). In the Bottari study, investigators did not specify scores, but only stated they included participants with 'moderate sexual dysfunction' (Bottari 2012). However, the mean (SD) baseline FSFI scores were 44.6(24.1) and 44.1(22.8) for the intervention and control group respectively, which is far above the cut-off value for sexual dysfunction (Wiegel 2005).

Only one study did not report baseline characteristics separately for the treatment and control groups (Duracková 2003). We initially judged this study to have an unclear risk of bias because investigators did not report the age of the participants separately for the treatment and control groups (Duracková 2003). The authors subsequently provided additional information which allowed us to judge this study to have a low risk of bias.

Additional domains for cross-over trials

We judged the following categories as having a low risk of bias for the 21 studies with parallel-group design with the rationale for this judgement being 'not applicable' (Characteristics of included studies). We only report the following sections for the five cross-over trials included in the review (Enseleit 2012; Hosseini 2001a; Hosseini 2001b; Reule 2017; Valls 2016).

Use of paired analysis

We judged four studies as having a low risk of bias as they used a paired t-test (Hosseini 2001a; Hosseini 2001b; Reule 2017; Valls 2016). In the remaining study investigators used an unpaired Wilcoxon and Mann-Whitney U-test and as a result we judged this to have an unclear risk of bias (Enseleit 2012).

Suitability of cross-over design

The cross-over design was suitable for all five studies as they assessed stable conditions that do not require long-term follow-up and thus we judged them as having a low risk of bias.

Availability of data from both periods

We judged one study as having a low risk of bias as investigators analysed all 11 participants' data (from both the control and the intervention group) (Hosseini 2001b). We judged four studies as having an unclear risk of bias (Enseleit 2012; Hosseini 2001a; Reule 2017; Valls 2016). Three studies only reported limited summarized data of within-patient changes for the first and second phase of the trials (Enseleit 2012; Reule 2017; Valls 2016) and in the final study investigators did not report whether data from both phases were available (Hosseini 2001a).

Absence of carry-over effect

Two studies did not include a washout period between study arms and did not perform any tests to assess a carry-over effect (Hosseini 2001a; Hosseini 2001b). As a result, we judged both studies as having an unclear risk of bias. We judged the remaining three studies as having a low risk of bias (Enseleit 2012; Reule 2017; Valls 2016). One study excluded a carry-over effect by using the unpaired Wilcoxon test of within-patient change from baseline including only the first period of treatment (Enseleit 2012). A second study stated that a carry-over effect was checked for before analysis and no effect was detected (Reule 2017). The third study eliminated a carry-over effect was eliminated in the third study by implementing a three-week washout period between intervention periods (Valls 2016).

Results comparable to parallel group trials

We judged two studies as having an unclear risk of bias as there are no comparable parallel-design trials available that assessed the same outcomes (Hosseini 2001a; Hosseini 2001b). We judged the remaining three studies as having a low risk of bias as they all cited parallel-design trials where the results were comparable (Enseleit 2012; Reule 2017; Valls 2016).

Effects of interventions

See: **Summary of findings 1** Pine bark extract compared to placebo for the treatment of Asthma; **Summary of findings 2** Pine bark extract compared to placebo for the treatment of ADHD; **Summary of findings 3** Pine bark extract compared to placebo for the treatment of CVD; **Summary of findings 4** Pine bark extract compared to placebo for the treatment of CVI; **Summary of findings 5** Pine bark extract compared to control for the treatment of diabetes mellitus type I; **Summary of findings 6** Pine bark extract compared to placebo for the treatment of diabetes mellitus type II; **Summary of findings 7** Pine bark extract compared to placebo for the treatment of diabetes mellitus type I and II combined; **Summary of findings 8** Pine bark extract compared to placebo for the treatment of erectile dysfunction; **Summary of findings 9** Pine bark extract compared to control for the treatment of female sexual dysfunction; **Summary of findings 10** Pine bark extract compared to placebo for the treatment of osteoarthritis; **Summary of findings 11** Pine bark extract compared to control for osteopenia; **Summary of findings 12** Pine bark extract compared to placebo for the treatment of traumatic brain injury

We grouped the included studies according to the type of chronic disorders involved and reported findings for the outcomes as pre-specified in our review protocol, when available. No study addressed our primary outcome 'all-cause mortality'. While we would have preferred to report on the change in symptoms or signs from baseline for several outcomes, this was often not possible as studies did not provide the information required to calculate this (e.g. SD of change). In such cases we assessed the difference in outcomes at the end of treatment. This is not an ideal approach given that the studies are all small (ranging from 11 to 156 participants; median of 46).

Furthermore, in some studies key results were missing for some or all relevant outcomes, e.g. results were only available for the treatment group but not for the control group, or investigators did not report a measure of variation (or exact P value) to allow for the calculation of SDs. In the additional tables we present outcomes

for which results are in part missing and estimates of effect that we could not calculate; these tables show only the results as reported in the studies or obtained through correspondence with study authors.

EFFICACY

Asthma

Two studies examined the use of Pycnogenol® in people with asthma. One cross-over study (26 participants) conducted in Iran assessed the effect of four weeks of treatment with Pycnogenol® versus placebo in adults ([Hosseini 2001a](#)). Another study of parallel-group design (60 participants) in the USA, compared Pycnogenol® with placebo in children over a period of three months ([Lau 2004](#)).

Primary outcomes

1a. Participant-reported clinical outcomes

Both studies measured asthma symptom scores ([Hosseini 2001a](#); [Lau 2004](#)), but due to insufficient information we were not able to evaluate results ([Table 2](#)). We have contacted the study authors for additional information and still await a response from one ([Hosseini 2001a](#)). The authors of the second study have informed us that they can not provide the information as they no longer work at the university where the study was conducted ([Lau 2004](#)). We were able to calculate estimates of effects for other eligible outcomes for this study ([Lau 2004](#)). All 30 participants in the Pycnogenol® group reported a decrease in asthma symptoms at the end of the treatment period compared to 16 out of 30 in the control group (RR 1.85, 95% CI 1.32 to 2.58; very low-certainty evidence; [Summary of findings 1](#); [Analysis 1.1](#)). In the same study, the number of participants who stopped using their albuterol inhaler at the end of the treatment period was 18 out of 30 in the Pycnogenol® and three out of 30 in the control group (RR 6.00, 95% CI 1.97 to 18.25; very low-certainty evidence; [Summary of findings 1](#); [Analysis 1.2](#)). Lau also measured the mean number of albuterol inhaler puffs per 24 hours, but investigators did not provide the SD of change and we could not obtain it ([Lau 2004](#)). We could, however, compare the final values (at the end of the three-month treatment period) and found fewer puffs were needed per 24 hours with Pycnogenol® compared to placebo (mean difference (MD) -2.10, 95% CI -2.53 to -1.67; [Analysis 1.3](#)). The baseline values for this outcome were similar in the comparison groups ([Table 2](#)).

1b. Investigator-reported clinical outcomes

Lau measured peak expiratory flow, but only reported results in a figure; we contacted the authors for additional information but this was not available ([Lau 2004](#); [Table 2](#)). In the second study ([Hosseini 2001a](#)), there was a statistically significant improvement in pulmonary function at the end of the one-month treatment period for those receiving Pycnogenol® compared with placebo; for FEV₁ % predicted (MD 7.00%, 95% CI 0.10 to 13.90; very low-certainty evidence; [Summary of findings 1](#); [Analysis 1.4](#)) and for the ratio FEV₁ % predicted/FVC (MD 7.70, 95% CI 3.19 to 12.21; very low-certainty evidence; [Summary of findings 1](#); [Analysis 1.5](#)).

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

See below 'SAFETY'.

2. Biomarkers of oxidative stress

None of the studies addressed this outcome.

ADHD

In one placebo-controlled study (N = 61), conducted in Slovakia, children received Pycnogenol® for one month ([Trebatická 2006](#)).

Primary outcomes

1a. Participant-reported clinical outcomes

Parents and teachers evaluated hyperactivity and inattention; teachers applied the Child Attention Profile (CAP) Teacher Rating Scale and Conner's Teacher Rating Scale (CTRS) and parents used the Conner's Parent Rating Scale (CPRS). A decrease in all three measures represents an improvement in inattention and hyperactivity. Investigators only reported results in a figure together with most of the exact P values comparing final values (end of month one) of Pycnogenol® versus placebo. On request the study authors provided the means and exact P values comparing the change in each group which we used to calculate the SDs of change and effect sizes. The CAP scores showed that Pycnogenol® reduced inattention (MD -1.92, 95% CI -3.33 to -0.51; [Analysis 2.1](#)). However, the changes in levels of inattention were not statistically significant when measured by CTRS (MD -1.03, 95% CI -5.77 to 3.71; [Analysis 2.2](#)) and CPRS (MD 0.41, 95% CI -6.62 to 7.44; [Analysis 2.3](#)). Similarly, we found no evidence that Pycnogenol® reduced hyperactivity: CAP (MD -1.62, 95% CI -9.03 to 5.79; [Analysis 2.4](#)); CTRS (MD -0.69, 95% CI -2.51 to 1.13; [Analysis 2.5](#)); and CPRS (MD -1.85, 95% CI -3.91 to 0.21; [Analysis 2.6](#)). All participant-reported outcomes were of very low-certainty evidence ([Summary of findings 2](#)).

1b. Investigator-reported clinical outcomes

Visual-motoric co-ordination and concentration scores as assessed by a psychologist showed improvement with Pycnogenol® compared to placebo (MD 3.37, 95% CI 2.41 to 4.33; very low-certainty evidence; [Summary of findings 2](#); [Analysis 2.7](#)).

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

See below 'SAFETY'.

2. Biomarkers of oxidative stress

Glutathione formed from amino acids in human cells can occur either in a reduced (GSH) or oxidized form (GSSG). An increased GSH/GSSG ratio reflects a decrease in oxidative stress. The percentage change in GSH/GSSG was obtained from an additional paper to the main Trebatická study report ([Dvoráková 2007](#)). Results reported and presented in the tables were insufficient to calculate an effect size ([Table 3](#)); and we therefore contacted the study authors. However, as the results received (the change in the means from baseline to the end of month one in both groups) were not consistent with the results reported in the article, we decided not to use them. A second additional paper also reporting on the Trebatická study, presented the GSH and GSSG results separately ([Table 3](#); [Dvoráková 2006](#)). Since investigators did not report numeric results for the placebo group, we could not calculate effect sizes. The study authors provided results on request, but again we were not able to reconcile these with the published data.

A further paper evaluated 8-oxo-7,8-dihydroguanine (8-oxoG), a marker of oxidative DNA damage, and total antioxidant status (TAS) from the Trebatická study (Chovanová 2006). Investigators did not report the SD of change for either of the groups (Table 3) and we have contacted the study authors for additional information. Reported results in the paper by Chovanová et al allowed us to compare the final values for 8-oxoG levels after approximating the SE from the given exact P value (Chovanová 2006). This shows that Pycnogenol® treatment lowered the level of oxidative damage compared with placebo (MD -0.23, 95% CI -0.40 to -0.05; Analysis 2.8). Investigators did not report the baseline value for the placebo group and so we could not compare this with the Pycnogenol® group.

CVD and risk factors

A total of seven studies (338 adults) measured the effects of pine bark on CVD and its risk factors. Three studies investigated the treatment effect of Pycnogenol® versus placebo for a period of eight weeks in two studies (Enseleit 2012; Hosseini 2001b) and for 12 weeks in one study (Liu 2004c). The first study (N = 23) was of cross-over design and based in Switzerland (Enseleit 2012). The second study (N = 11) was also of cross-over design and based in the USA (Hosseini 2001b). The third study (N = 58) was of parallel design and based in China (Liu 2004c). One parallel-design study (N = 61) investigated the treatment of OPC-3 versus placebo for two months but the setting was not reported (Cesarone 2008). A further parallel-design study (N = 130) investigated the effects of Flavangenol® versus placebo for three months and was based in the USA (Drieling 2010). A cross-over study (N = 25) in Germany investigated the effects of L-arginine-based multi-ingredient product (verum, described in the paper as AbMIP and marketed as vasologes® protect) versus placebo for four weeks (Reule 2017). The remaining study (N = 21) was also of cross-over design and was the only one to compare Oligopin® to placebo for five weeks; it was based in Spain (Valls 2016).

Primary outcomes

1a. Participant-reported clinical outcomes

No participant-reported outcomes were assessed in all seven studies.

1b. Investigator-reported clinical outcomes

Only one study directly measured the change in BP, but did not report results for the placebo group (Hosseini 2001b; Table 4). We contacted the study authors for these data, but they have not responded to our request. In a second study, investigators indirectly evaluated BP changes by monitoring the nifedipine dose needed to control participants' BP (Liu 2004c). All participants received 20 mg nifedipine at the start of the study and investigators made dose adjustments as necessary at each visit. There was no difference between Pycnogenol® and placebo groups in the number of participants whose nifedipine dose had been reduced after three months (RR 1.12, 95% CI 0.83 to 1.52; Analysis 3.1). However, more participants in the Pycnogenol® group had their nifedipine dose reduced to 10 mg after three months (RR 4.29, 95% CI 1.63 to 11.27; Analysis 3.2).

Three studies measured systolic BP; one two-month study was of parallel design (Cesarone 2008) and the other two had a cross-over design (duration one month and five weeks) (Reule 2017;

Valls 2016). The parallel-designed trial reported that Pycnogenol® significantly reduced systolic BP (MD -4.00, 95% CI -5.77 to -2.23; Analysis 3.3). The two cross-over trials reported the change between intervention and placebo with relevant P values which were used to calculate the SE; when pooled results showed no difference between groups in the decrease of systolic BP (MD -1.53, 95% CI -4.96 to 1.91; fixed-effects analysis; heterogeneity: $\chi^2 = 0.20$; $I^2 = 0\%$; Analysis 3.4). We also applied this calculation to the other outcomes reported by these two cross-over studies (Reule 2017; Valls 2016).

One parallel study (Cesarone 2008) and two cross-over studies (Reule 2017; Valls 2016) reported diastolic BP. Results from the parallel study at two months showed Pycnogenol® significantly reduced diastolic BP compared to placebo (MD -3.00, 95% CI -4.51 to -1.49; very low-certainty evidence; Analysis 3.5). However, pooled data from the cross-over trials (at one month and five weeks) did not show any difference between groups (MD 0.16, 95% CI -2.07 to 2.39; fixed-effect model; heterogeneity: $\chi^2 = 0.14$; $I^2 = 0\%$; Analysis 3.6).

One parallel study reported fasting blood glucose (Cesarone 2008); after two months results showed that Pycnogenol® significantly reduced blood glucose levels (MD -109.01, 95% CI -111.88 to -106.14; Analysis 3.7). One cross-over study also reported on this outcome at five weeks (Valls 2016), but conversely showed no effect of the intervention on fasting blood glucose (MD -0.43, 95% CI -6.84 to 5.98; Analysis 3.8). This study also reported no effect on insulin levels (MD 4.24, 95% CI -4.38 to 12.86; Analysis 3.9). One cross-over trial reported HbA1c but only provided end values; we contacted the study authors for clarification, but have yet to receive a response (Reule 2017; Table 4).

The two-month parallel study (Cesarone 2008) and the five-week cross-over study (Valls 2016) also reported cholesterol (total, HDL and LDL) levels. The parallel study showed Pycnogenol® significantly reduced total cholesterol compared to placebo (MD -0.28 mmol/L, 95% CI -0.35 to -0.20; Analysis 3.10), but this was not true in the cross-over study (MD 0.07 mmol/L, 95% CI -0.32 to 0.46; Analysis 3.11). Conversely, the parallel study showed no effect of Pycnogenol® on HDL cholesterol levels (MD 0.05 mmol/L, 95% CI -0.01 to 0.11; very low-certainty evidence; Summary of findings 3; Analysis 3.12), but results from the cross-over study showed Pycnogenol® significantly increased HDL cholesterol (MD 0.22 mmol/L, 95% CI 0.06 to 0.38; Analysis 3.13). For LDL cholesterol, neither study showed any effect of the intervention; parallel study at two months (MD -0.03 mmol/L, 95% CI -0.05 to 0.00; very low-certainty evidence; Summary of findings 3; Analysis 3.14) or the cross-over study at five weeks (MD -0.08 mmol/L, 95% CI -0.33 to 0.17; Analysis 3.15).

Two cross-over studies measured triglyceride levels (Reule 2017; Valls 2016). However, results were not pooled due to substantial heterogeneity ($I^2 = 63\%$). Neither of these two studies favoured either the intervention or the control (Analysis 3.16).

Both the two-month parallel study (Cesarone 2008) and the five-week cross-over study (Valls 2016) reported on CRP. Neither study showed any effect of Pycnogenol® on this outcome: at two months (MD -5.00 mg/L, 95% CI -15.22 to 5.22; Analysis 3.17); and at five weeks (MD -0.91 mg/L, 95% CI -2.01 to 0.19; Analysis 3.18).

The five-week cross-over study reported on weight, BMI and waist circumference (Valls 2016). The MD between groups reported by Valls for weight was 0 which meant that the SE when calculated also equalled 0 (Analysis 3.19). There was no effect of the intervention seen on either BMI (MD -0.03, 95% CI -0.23 to 0.17; Analysis 3.20) or waist circumference (MD -0.14 cm, 95% CI -2.34 to 2.06; Analysis 3.21).

One cross-over study reported systolic BP, diastolic BP, fasting blood glucose, total cholesterol, HDL, LDL, triglycerides and high sensitivity CRP (Enseleit 2012). However, since the study does not provide the SE of change, we could not assess change in these outcomes (Table 4). We contacted the corresponding author of the Enseleit study, but have not yet received a response.

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

See below 'SAFETY'.

2. Biomarkers of oxidative stress

Liu measured the concentration of nitrogen monoxide and reported results as median (IQR) after three months (Liu 2004c). The study authors found no difference in the % change from baseline between the Pycnogenol® (median 11.75% (-1.44 to 32.08)) and placebo (median 10.50 (-2.07 to 29.11)) groups (P value not reported).

Valls found that Pycnogenol® did not reduce GSSG (MD -3.08 nmol/mL, 95% CI -10.72 to 4.56; Analysis 3.22) and did not increase GSH (MD 0.02 nmol/mL, 95% CI -3.10 to 3.14; Analysis 3.23) or the ratio GSH/GSSG (MD 0.02 nmol/mL, 95% CI -0.04 to 0.08; Analysis 3.24). Similarly, there was no effect seen on nitrates (MD 3.69 microM, 95% CI -8.74 to 16.12; Analysis 3.25). The two-month parallel study showed that Pycnogenol significantly reduced oxidative stress (D-ROM test) compared to placebo (MD -33.00 carr units (95% CI -40.41 to -25.59; Analysis 3.26).

One cross-over study measured 15-F2t-Isoprostane and total antioxidant capacity, but did not report the SE of change (Enseleit 2012; Table 4). We have contacted the study authors, but they have not responded to our request.

CVI

In two studies conducted in Italy, adults were treated with Pycnogenol® versus placebo for a period of two months (60 days) (Arcangeli 2000; Petrassi 2000). One study had 40 participants (Arcangeli 2000) and one had 20 participants (Petrassi 2000).

Primary outcomes

1a. Participant-reported clinical outcomes

Both studies evaluated the change in scores of leg heaviness, swelling and pain by using the same four-point symptom scale where 0 = symptom absent and 3 = symptom severe (see 'Characteristics of included studies'). Investigators in the Petrassi study stated in their 'Methods' section that they also evaluated the change in scores for night cramps and paraesthesiae, but did not report any results for these symptoms (Petrassi 2000). We contacted the study authors for this information, but have not received a response.

Since neither study provided the SD of change in symptoms from baseline, we could not assess change in leg heaviness, swelling or pain scores (Table 5). We contacted the corresponding author of the Petrassi study, but have not received a response (Petrassi 2000); we can not contact the author of the Arcangeli study (Arcangeli 2000). We compared the final symptom score (end of month two) in the treatment and control groups by pooling the results of the two studies (60 participants). Pycnogenol® was associated with a statistically significant reduced heaviness score (MD -0.72, 95% CI -0.91 to -0.54; fixed-effect analysis, heterogeneity: $\chi^2 = 0.00$; $I^2 = 0$; Analysis 4.1) and reduced swelling (MD -0.46, 95% CI -0.67 to -0.25; fixed-effect analysis, heterogeneity: $\chi^2 = 2.31$; $I^2 = 57\%$; Analysis 4.2).

Data for pain scores were available for analysis from one study (Arcangeli 2000) and were significantly lower with Pycnogenol® than with placebo (MD -0.59, 95% CI -1.02 to -0.16; very low-certainty evidence; Summary of findings 4; Analysis 4.3). Investigators in the Petrassi study reported that "the pain parameter could not be evaluated because of the small number of participants who showed a positive score" (Petrassi 2000). Since investigators report final values (rather than change in symptoms), it is important to note that baseline symptom scores were not balanced in either study (Arcangeli 2000; Petrassi 2000). In the first study, the mean heaviness score was 19.8% greater, legs were 12% more swollen and participants experienced 13.4% more pain at baseline in the Pycnogenol® group compared to placebo (Arcangeli 2000). In the second study, the mean heaviness score was 21.3% greater and there was 25% more leg swelling in the Pycnogenol® group compared to placebo; baseline values for pain were not reported in this study (Petrassi 2000).

Both studies reported the percentage of participants in whom the symptoms of heaviness and swelling disappeared at the end of the treatment period, and Arcangeli also reported on pain resolution (Arcangeli 2000). However, only effect sizes for the Arcangeli study could be calculated because the investigators in the Petrassi study did not report results for the placebo group. We contacted the study authors for this information and await their response. Arcangeli reported no significant difference between groups for the disappearance of heaviness (RR 15.00 (95% CI 0.91 to 246.20; very low-certainty evidence; Summary of findings 4; Analysis 4.4). However, results were statistically significantly in favour of Pycnogenol® for both the disappearance of swelling (RR 27.00, 95% CI 1.71 to 425.36; Analysis 4.5) and the disappearance of pain (RR 25.00, 95% CI 1.58 to 395.48; Analysis 4.6). These CIs are very wide because of the small sample size and zero events in the placebo group.

1b. Investigator-reported clinical outcomes

In the Arcangeli study, physicians judged the efficacy of the treatment according to a pre-specified scale where 1 = poor and 4 = very good (Arcangeli 2000). They judged Pycnogenol® significantly more efficacious than placebo (RR 4.75, 95% CI 1.97 to 11.48; very low-certainty evidence; Summary of findings 4; Analysis 4.7). Petrassi also assessed this outcome, but only reported the combined result of both the randomised and non-randomised arm of the study meaning we were not able to assess it (Petrassi 2000). This was also the case for change in ambulatory venous pressure. We have contacted the study authors for the disaggregated information, but we have not received their response. Investigators

in the Arcangeli study measured venous blood flow and reported simply that they found no difference in either of the groups at the end of the treatment period compared to baseline (Arcangeli 2000).

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

1. Adverse events

See below 'SAFETY'.

2. Biomarkers of oxidative stress

None of the studies addressed this outcome.

DM

Six studies (N = 336) enrolled adults with DM and each had different primary outcomes (Belcaro 2006a; Chous 2016; Domanico 2015; Liu 2004a; Steigerwalt 2009; Zibadi 2008). Only one six-week study (30 participants) enrolled people with type I (insulin-dependent) DM and evaluated the effect Pycnogenol® (oral, local or both) versus no medical treatment for healing foot ulcers in this population in the USA (Belcaro 2006a). Four studies enrolled participants with type II DM (Domanico 2015; Liu 2004a; Steigerwalt 2009; Zibadi 2008). One two-month study (46 participants) compared Pycnogenol® with placebo in people with retinopathy in Italy (Steigerwalt 2009). Two studies lasted three months; one study compared the effect Pycnogenol® versus placebo on blood glucose levels in 77 people with type II DM in China (Liu 2004a) and the second study (48 participants) compared Pycnogenol® to placebo for treating people with type II DM in the USA (Zibadi 2008). Two studies lasted six months; one study enrolled 68 participants with type II DM and compared Diabeter to no treatment (Domanico 2015) and the second enrolled 70 participants with type I and type II DM and compared a DiFuSS formula to placebo (Chous 2016).

DM type I

Primary outcomes

1a. Participant-reported clinical outcomes

The single study (30 participants) reported on the change in microcirculation symptoms where a score of 0 represents absence of symptoms and a score of 10 very severe symptoms (Belcaro 2006a). Investigators did not report the SD of the mean change (we contacted the study authors who responded that "the requested data is not available"), hence we used the final values (Table 6). There was no evidence that symptom scores were reduced with oral Pycnogenol® (MD -1.30, 95% CI -4.02 to 1.42; Analysis 5.1) or local Pycnogenol® (MD -1.10, 95% CI -3.60 to 1.40; Analysis 5.2); but combining the two formulations resulted in a significant difference between groups in favour of the intervention (MD -2.90, 95% CI -5.40 to -0.40; very low-certainty evidence; Summary of findings 5; Analysis 5.3).

1b. Investigator-reported clinical outcomes

The study (30 participants) showed that the final values for area of ulceration (mm²) for oral Pycnogenol® were no different from control (MD -4.00, 95% CI -9.92 to 1.92; Analysis 5.4; Belcaro 2006a). However, there was a statistically significant difference with local Pycnogenol® (MD -7.00, 95% CI -12.96 to -1.04; Analysis 5.5) and

with oral plus local Pycnogenol® (MD -23.00, 95% CI -27.44 to -18.56; very low-certainty evidence; Summary of findings 5; Analysis 5.6). The final transcutaneous pressure of oxygen (PO₂) values were higher in the oral Pycnogenol® group compared to the control group (MD 7.00 mm Hg, 95% CI 3.18 to 10.82; Analysis 5.7), but transcutaneous carbon dioxide partial pressure (PCO₂) showed no difference between the two groups (MD -1.00 mm Hg, 95% CI -3.79 to 1.79; Analysis 5.8). For the oral plus local Pycnogenol® group, transcutaneous PO₂ was better with Pycnogenol® (MD 10.00 mm Hg, 95% CI 7.06 to 12.94; Analysis 5.9), but not transcutaneous PCO₂ (MD -2.80 mm Hg (95% CI -5.89 to 0.29; Analysis 5.10). The study authors did not assess this outcome for the local Pycnogenol® group.

Belcaro reported veno-arteriolar response (laser Doppler flux (LDF) units) in median (IQR) values (Belcaro 2006a). Although both oral Pycnogenol® and combination oral and local Pycnogenol® improved from baseline (9 (0 to 21) units and 8 (0 to 20) units, respectively) to Week 6 (12 (4 to 32) units and 22 (5 to 38) units, respectively) compared to the control group which reported a reduction in veno-arteriolar response (9 (0 to 19) units at baseline and 8 (3 to 23) units at Week 6), the study authors reported no difference between the groups (P values not presented). Pycnogenol® improved the final values for skin flux at rest when compared to control for both the oral group (MD -1.70, 95% CI -2.67 to -0.73; Analysis 5.11) and for the local plus oral group (MD -1.80, 95% CI -2.54 to -1.06; Analysis 5.12). The study authors did not assess this outcome for the local Pycnogenol® group.

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

1. Adverse events

See below 'SAFETY'.

2. Biomarkers of oxidative stress

None of the studies addressed this outcome.

DM type II

Primary outcomes

1a. Participant-reported clinical outcomes

One study assessed the change in visual acuity as reported by participants (Steigerwalt 2009). Since there were no results for the placebo group in the published article, we contacted the study authors who responded that in the placebo group none of the participants perceived any improvement in their vision. Therefore 18 out of 24 participants in the Pycnogenol® group versus none of the 22 participants in the placebo group experienced "vision improvement" leading to an unusually strong result which remained unpublished in the original article (RR 34.04, 95% CI 2.17 to 533.19; low-certainty evidence; Summary of findings 6; Analysis 6.1). As a result of the small study size and no events in the placebo group the CI is very wide; and there is great uncertainty around the true effect size.

1.b. Investigator-reported clinical outcomes

One study measured the change in blood glucose (mmol/L) and plasma HbA1c (%) between baseline and week 12 and analysed it using the Mann-Whitney rank sum test (Liu 2004a). The results of this change were therefore reported as medians (IQRs) (Table 7). The study authors found improvement in blood glucose with Pycnogenol® ($P < 0.01$), but no difference in HbA1c levels ($P > 0.05$).

A second study also measured change in blood glucose (mmol/L) and HbA1c (%) (Table 8; Zibadi 2008), as well as a reduction in urinary albumin levels (mg/L). The investigators provided the SD of the change in glucose levels and we used this to calculate the effect size showing a significant decrease in favour of Pycnogenol® (MD 1.0 mmol/L, 95% CI 0.91 to 1.09; very low-certainty evidence; Summary of findings 6; Analysis 6.2). The study authors provided the SD of change for HbA1c levels for only one of the two groups and therefore we could not calculate an effect size for the change. We therefore used the final values to compare Pycnogenol® versus placebo at three months and this favoured the treatment group (MD -0.90% (95% CI -1.78 to -0.02; very low-certainty evidence; Summary of findings 6; Analysis 6.3). It should be noted that the mean HbA1c at baseline in the Pycnogenol® group was 2.5% less than that in the placebo group.

In the same way as described above, we obtained the SD of change for urinary albumin levels; results also showed a significant decrease with Pycnogenol® (MD 6.09 mg/L, 95% CI 3.23 to 8.95; Analysis 6.4).

In the Steigerwalt study investigators also evaluated the change in visual acuity using a Snellen chart (Steigerwalt 2009). However, they reported the results separately for participants with moderate and mild retinal edema (not pre-specified in the 'Methods' section), thereby making it impossible to compare Pycnogenol® and placebo for all randomised participants. For the same reason we could not analyse results for change in retinal blood flow, diastolic blood flow relative to maximum systolic blood flow, retinal edema score and retinal thickness. We contacted the study authors for the required information, but this has not yet been provided.

One study measured central macular thickness (Domanico 2015). There was no difference in results between the pine bark or control group (MD -8.94 μ m, 95% CI -35.85 to 17.97; Analysis 6.5; very low-certainty evidence; Summary of findings 6). The same study also assessed best corrected visual acuity, which again showed no difference between groups (MD -0.00 logMAR, 95% CI -0.02 to 0.01; Analysis 6.6).

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

1. Adverse effects

See below 'SAFETY'.

2. Biomarkers of oxidative stress

One study measured the concentration of nitrogen monoxide (nmol/L), a free radical; the study authors did not report results and only stated that the difference between Pycnogenol® and placebo was not statistically significant (Liu 2004a). After contacting the

study authors, we obtained the results which we present in the additional tables (Table 9). Since the authors did not provide the SD of change, we used the final values for calculating an effect size which shows no difference between groups (MD 5.09 nmol/L, 95% CI -3.03 to 13.21; Analysis 6.7). One study measured a free oxygen radical test at six months and significantly favours pine bark (MD -30.70 mg/L, 95% CI -41.91 to -19.49; Analysis 6.8; Domanico 2015).

DM type I and II combined

Primary outcomes

1a. Participant-reported clinical outcomes

One study assessed Diabetic Peripheral Neuropathy Symptom scores (DPNSS) where the maximum score was 4, with higher scores indicating increased severity of neuropathy symptoms. In the pine bark extract group 25 out of 39 participants and in the placebo group 23 out of 28 participants reported no change in symptoms (RR 0.78, 95% CI 0.58 to 1.04; very low-certainty evidence; Summary of findings 7; Analysis 7.1; Chous 2016). A total of 13 of 39 participants in the pine bark extract group and 1 of 28 in the placebo group reported a decrease in DPNS scores indicating an improvement in neuropathy symptoms significantly favouring pine bark (RR 9.33, 95% CI 1.29 to 67.27; Analysis 7.2). Correspondingly, the authors also reported an increase in DPNS scores indicating worsening of neuropathy symptoms in 1 of 39 participants in the pine bark group and 4 of 28 in the placebo group (RR 0.18, 95% CI 0.02 to 1.52; Analysis 7.3).

1b. Investigator-reported clinical outcomes

One study measured the change from baseline in HbA1c levels (%) and results showed no difference between groups (MD -0.20%, 95% CI -1.83 to 1.43; very low-certainty evidence; Summary of findings 7; Analysis 7.4; Chous 2016). The same study assessed total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels, which all significantly favoured pine bark: total cholesterol (MD -0.23 mmol/L, 95% CI -0.45 to 0.00; Analysis 7.5); LDL cholesterol (MD -0.22 mmol/L, 95% CI -0.38 to -0.06; Analysis 7.6); HDL cholesterol (MD 0.14 mmol/L, 95% CI 0.07 to 0.21; Analysis 7.7); and triglycerides (MD -0.15 mmol/L, 95% CI -0.26 to -0.03; Analysis 7.8). Finally, investigators also assessed high-sensitivity CRP (hsCRP) (mg/L) and results favoured pine bark extract (MD -1.86 mg/L, 95% CI -3.02 to -0.70; Analysis 7.9).

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

1. Adverse events

See below 'SAFETY'.

2. Biomarkers of oxidative stress

None of the studies addressed this outcome.

ED

We included three studies (258 adult participants) in this comparison (Cai 2013; Duracková 2003; Ledda 2010). The largest study (126 participants) evaluated the effects of IDiProst® versus *Serenoa Repens* for 90 days in Italy (Cai 2013). The smallest study (21 participants) assessed the effect of Pycnogenol® versus placebo over three months and was conducted in Slovakia (Duracková

2003). The third study (111 participants) evaluated the effects of Prelox[®] versus placebo for six months (location not reported) (Ledda 2010).

Primary outcomes

1a. Participant-reported clinical outcomes

Two studies measured symptom scores for ED using the IIEF-5 questionnaire (maximum score = 25; normal erectile function scores between 21 and 25) (Cai 2013; Duracková 2003), but we did not pool the scores due to substantial heterogeneity ($I^2 = 76\%$; very low-certainty evidence; [Summary of findings 8](#); [Analysis 8.1](#)). ED symptom scores in one study significantly favoured IDIProst[®] (MD 3.20, 95% CI 2.79 to 3.61; [Analysis 8.1](#); Cai 2013). Investigators of the second study did not report the SD of change, but we obtained this from them (Duracková 2003); an improvement in ED symptom scores significantly favoured of Pycnogenol[®] (MD 6.00 (95% CI 3.33 to 8.67; [Analysis 8.1](#)).

The third study implemented a more detailed version of the IIEF score and reported results for the five different domains of the score separately (where a lower score indicates dysfunction) (Ledda 2010). The erectile function domain of the score consists of questions one to five and 15 of the IIEF and was measured as a score from zero to 30. The scores for the erectile function domain were significantly increased by Prelox[®] (MD 8.10, 95% CI 7.12 to 9.08; very low-certainty evidence; [Summary of findings 8](#); [Analysis 8.2](#)). We could not obtain the SD for the remaining four domains (orgasmic function domain, sexual desire domain, intercourse satisfaction domain and the overall satisfaction domain) from the contact author.

One study evaluated the IPSS (Cai 2013). This is a questionnaire consisting of seven symptom questions and one quality of life (QoL) question; symptom scores range from zero to 35, with scores from zero to seven considered mild, eight to 19 moderate, and 20 to 35 severe. Results showed that IDIProst[®] significantly reduced symptom scores (MD -1.90, 95% CI -2.34 to -1.46; [Analysis 8.3](#)).

1b. Investigator-reported clinical outcomes

One study (111 participants) measured the change in total plasma testosterone levels, which were significantly raised by Prelox[®] at six months (MD 1.60 nmol/L, 95% CI 0.68 to 2.52; very low-certainty evidence; [Summary of findings 8](#); [Analysis 8.4](#); Ledda 2010). The changes in systolic and diastolic BP were also assessed after six months of supplementation and both were significantly reduced in the treatment group, (MD -3.90 mm Hg, 95% CI -6.44 to -1.36; very low-certainty evidence; [Summary of findings 8](#); [Analysis 8.5](#)) and (MD -3.40 mm Hg, 95% CI -5.36 to -1.44; very low-certainty evidence; [Summary of findings 8](#); [Analysis 8.6](#)) respectively.

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

1. Adverse effects

See below 'SAFETY'.

2. Biomarkers of oxidative stress

The investigators of one study provided the SD of change for the percentage of antioxidant activity in the blood (Duracková 2003); the effect size did not show any differences between Pycnogenol[®] and placebo (MD 0.06%, 95% CI -0.14 to 0.26; [Analysis 8.7](#)).

Female sexual dysfunction

One study treated 83 women with Lady Prelox[®] versus a placebo for eight weeks; investigators did not report where the study was conducted (Bottari 2012).

Primary outcomes

1a. Participant-reported clinical outcomes

The study evaluated the effects of Lady Prelox[®] using the FSFI score to assess six different domains (desire domain, arousal domain, lubrication domain, orgasm domain, satisfaction domain and pain domain). The FSFI score comprises 19 questions; the maximum score is 95 and a lower score indicates more severe sexual dysfunction.

All six domains significantly favoured pine bark (Bottari 2012): desire domain (MD 1.30, 95% CI 0.21 to 2.39; [Analysis 9.1](#)); arousal domain (MD 3.20, 95% CI 1.12 to 5.28; [Analysis 9.2](#)); lubrication domain (MD 5.30, 95% CI 3.11 to 7.49; [Analysis 9.3](#)); orgasm domain (MD 4.50, 95% CI 2.89 to 6.11; [Analysis 9.4](#)); satisfaction domain (MD 5.10, 95% CI 3.49 to 6.71; very low-certainty evidence; [Summary of findings 9](#); [Analysis 9.5](#)); and pain domain (MD 4.30, 95% CI 2.69 to 5.91; very low-certainty evidence; [Summary of findings 9](#); [Analysis 9.6](#)).

1b. Investigator-reported clinical outcomes

No investigator-reported outcomes were assessed in this study (Bottari 2012).

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

1. Adverse effects

See below 'SAFETY'.

2. Biomarkers of oxadative stress

None of the studies addressed this outcome.

Osteoarthritis

In three studies with a total of 293 adults, participants were treated with Pycnogenol[®] versus placebo for osteoarthritis of the knee over a period of three months (12 weeks or 90 days); the studies were conducted in Italy (156 participants) (Belcaro 2008a), Slovakia (100 participants) (Cisár 2008) and Iran (37 participants) (Farid 2007).

Primary outcomes

1a. Participant-reported clinical outcomes

All three studies used WOMAC scores to evaluate the effect of Pycnogenol[®] on pain, stiffness, physical function (referred to as 'daily activities' by one study (Cisár 2008)) and overall effect; additionally, one study used the WOMAC instrument to evaluate

negative alterations in social functions and the sum of emotional parameters as symptoms of osteoarthritis (Belcaro 2008a). The WOMAC instrument is available either in a Likert scale or in a visual analogue format (Bellamy 2001); one study used a Likert scale (Cisár 2008) and one study used a visual analogue scale (VAS) (Farid 2007) investigators on the third study did not report the type of scale they used, although they did report the interpretation of the scale as detailed in [Characteristics of included studies](#) (Belcaro 2008a).

Since we could not pool the results of the corresponding outcomes for these three studies, we contacted the study authors for the relevant information (e.g. SD of change); all of them responded. Belcaro indicated that they could not provide the SD at baseline and at month three or the SD of change for any of the outcomes we requested (Belcaro 2008a). Farid provided us with mean values of change and SD of change between baseline and month three for each group (Farid 2007). However, the mean changes obtained do not correspond to those reported in the paper and we did not use these in the analysis. We therefore only used the final values for this study (Farid 2007). We summarize the incomplete results from the Belcaro and Farid articles in the additional tables (Table 10). Cisár reported the medians with IQRs in the main paper (Cisár 2008), but in their response investigators provided the means and SD at baseline and month three allowing us to compare the final values for this study (Table 11).

We did not pool the pain scores for two studies due to considerable heterogeneity ($I^2 = 96\%$) (Cisár 2008; Farid 2007). Cisár found no difference between groups (MD 0.96, 95% CI -0.74 to 2.66; [Analysis 10.1](#)), but Farid reported that pain scores were lower with Pycnogenol® (MD -142.00, 95% CI -199.55 to -84.45; [Analysis 10.1](#)). Cisár additionally measured pain with VAS and found no difference between groups (MD -3.16, 95% CI -14.02 to 7.70; [Analysis 10.2](#)).

Heterogeneity for the outcome physical function was also considerable ($I^2 = 96\%$) and we again reported the results for each study separately. One study found no difference between groups (MD 3.36, 95% CI -2.43 to 9.15; [Analysis 10.3](#); Cisár 2008), but Farid found that physical function was significantly improved with Pycnogenol® (MD -529.00, 95% CI -741.59 to -316.41; [Analysis 10.3](#); Farid 2007).

For the outcome stiffness, heterogeneity was substantial ($I^2 = 71\%$) and thus we did not pool results. Neither study found a difference between the groups, SMD 0.16 (95% CI -0.27 to 0.59; $n = 84$) (Cisár 2008) and SMD -0.59 (95% CI -1.25 to 0.07; $n = 37$) (Farid 2007) ([Analysis 10.4](#)).

For total WOMAC scores, available data only allowed us to compare the final values (end of month three) of each group for the Farid study (Farid 2007). We present the results for the other two studies in the additional tables (Table 10; Table 11). The composite WOMAC scores were significantly lower in the Pycnogenol® group compared to the placebo (MD -730.0, 95% CI -1011.95 to -448.05; low-certainty evidence; [Summary of findings 10](#); [Analysis 10.5](#)).

Investigators in each of the three studies monitored any change in the use of concomitant medication (or specific concomitant medication such as NSAIDs and COX-2). In one study, investigators reported results for the reduction of NSAIDs use as 58% for the Pycnogenol® and 1% for the placebo group (Belcaro 2008a). We contacted the study authors for clarification and interpretation of

this outcome and they responded: "NSAIDs were indeed the only concomitant medications used for osteoarthritis. The reduction of NSAIDs medication was calculated on the basis of the number of tablets an individual took. These were noted by themselves in a diary. Of course the medication varied in a way that one patient took e.g. paracetamol while another took ibuprofen, and also the dosage may have varied. They had to stay with their preferred medication brand throughout the study. A decrease by the average 58% means that patients in average required a little less than half of their preferred analgesic product". We unfortunately still do not have the corresponding numbers to which these percentages refer. Cisár reported that 38% of participants in the Pycnogenol® and 8% in the placebo group (50 participants in both groups) decreased their analgesic dosage by the end of the three-month treatment period compared to the start (Cisár 2008). This translates into a significant difference of 19 out of 50 versus 4 out of 50 events (RR 4.75, 95% CI 1.74 to 12.97; [Analysis 10.6](#)). Farid reported on the change in frequency and dosage of NSAIDs and COX-2 inhibitor usage during the treatment period, but only reported results in a figure from which we could not extract data accurately (Farid 2007). We contacted the study authors who sent us the requested results. The change in the number of NSAIDs and COX-2 inhibitor usage between the first and the third month was reduced with Pycnogenol® compared to placebo (MD -18.30 mean number of pills per month, 95% CI -25.14 to -11.46; very low-certainty evidence; [Summary of findings 10](#); [Analysis 10.7](#)). Similarly, there was a decrease in the number of days taking pain relief when participants took NSAIDs and COX-2 inhibitor with Pycnogenol® (MD -11.80 days, 95% CI -16.00 to -7.60; [Analysis 10.8](#)).

1b. Investigator-reported clinical outcomes

In one study, investigators evaluated physical performance on a treadmill at baseline and after three months of treatment (Belcaro 2008a).

In the Pycnogenol® group the mean (range) distance walked increased from 68 m (0 to 133) at baseline to 198 m (55 to 374) at three months; this compared to a smaller increase in the placebo group from 65 m (12 to 98) to 88 m (25 to 102). At baseline the groups were similar, but the difference was significant at three months ($P < 0.05$) (Belcaro 2008a).

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

1. Adverse effects

See below 'SAFETY'.

2. Biomarkers of oxidative stress

None of the studies addressed this outcome.

Osteopenia

In one study conducted in Tehran (Iran), compared Oligopin® to placebo in 44 participants for 12 weeks (Panahande 2019).

Primary outcomes

1a. Participant-reported clinical outcomes

No participant-reported outcomes were reported in this study.

1b. Investigator-reported clinical outcomes

Investigators measured BAP, P1NP and the ratio of BAP/CTx1 as markers of bone formation. All three outcomes increased significantly after pine bark supplementation compared to placebo: BAP (MD 2.21 ug/L, 95% CI 0.58 to 3.84; [Analysis 11.1](#); very low-certainty evidence); P1NP (MD 73.00 ng/mL, 95% CI 17.03 to 128.97; very low-certainty evidence; [Summary of findings 11](#); [Analysis 11.2](#)); and BAP/CTx1 (MD 38.19, 95% CI 3.09 to 73.29; [Analysis 11.4](#)).

Investigators also measured markers of bone resorption markers, none of these results were statistically significant: CTx1 (MD -0.08 ng/mL, 95% CI -0.19 to 0.03; very low-certainty evidence; [Summary of findings 11](#); [Analysis 11.3](#)); RANKL (MD -54.43 ng/mL, 95% CI -133.33 to 24.47; [Analysis 11.5](#)); and OPG (MD 0.14 ng/mL, 95% CI -1.82 to 2.10; [Analysis 11.6](#)).

Investigators also assessed markers in serum ([Panahande 2019](#)), none of these outcomes differed significantly: parathyroid hormone (MD -1.86 pg/mL, 95% CI -10.67 to 6.95; [Analysis 11.7](#)); calcium (MD 0.02 mg/dL, 95% CI -1.98 to 2.02; [Analysis 11.8](#)); magnesium (MD 0.04 mg/dL, 95% CI -1.90 to 1.98; [Analysis 11.9](#)); and phosphorus (MD -0.10 mg/dL, 95% CI -2.17 to 1.97; [Analysis 11.10](#)).

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

1. Adverse effects

See below 'SAFETY'.

2. Biomarkers of oxidative stress

None of the studies addressed this outcome.

TBI

In one study based in Auckland (New Zealand), investigators treated 56 adults with Enzogenol® versus placebo for six weeks ([Theadom 2013](#)).

Primary outcomes

1a. Participant-reported clinical outcomes

Investigators assessed everyday memory using the Cognitive Failure Questionnaire (CFQ), where a score above 38 indicates persistent cognitive difficulties. There was no difference between Enzogenol® and placebo (MD -2.24, 95% CI -11.17 to 6.69; [Analysis 12.1](#)). They assessed symptom severity using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ). Participants reported the first three questions and the first 13 questions of the RPQ separately; however, there were no significant difference in either score between groups either for the first three questions (MD -0.25, 95% CI -1.66 to 1.16; [Analysis 12.2](#)) or for the first 13 questions (MD -0.76, 95% CI -5.39 to 3.87; [Analysis 12.3](#)). The Hospital Anxiety and Depression Scale assesses anxiety and depression separately; there was no difference between groups for either anxiety (MD -1.77, 95% CI -4.07 to 0.53; [Analysis 12.4](#)) or depression (MD -1.17, 95% CI -2.90 to 0.56; [Analysis 12.5](#)).

1b. Investigator-reported clinical outcomes

The California Verbal Learning Test consists of four different tests namely: short-delay free recall, long-delay free recall, recognition and mean total accuracy as percentage. Investigators implemented the short-delay free recall test to evaluate episodic memory through free recall following a short-delay; results showed no statistical significance between the intervention and control (MD 0.26, (95% CI -0.30 to 0.82; [Analysis 12.6](#)). Similarly the long-delay free recall test showed no difference between Enzogenol® and placebo (MD 0.28, 95% CI -0.26 to 0.82; very low-certainty evidence; [Summary of findings 12](#); [Analysis 12.7](#)). The recognition test assesses episodic memory through discerning target and distractor words in a 44-word list; again investigators saw no difference between groups (MD 0.24 (95% CI -0.46 to 0.94; [Analysis 12.8](#)). The final test evaluated episodic memory through percentage mean total accuracy of recall and found no difference in participants' scores between the Enzogenol® group and the placebo group (MD 2.04%, 95% CI -4.37 to 8.45; very low-certainty evidence; [Summary of findings 12](#); [Analysis 12.9](#)).

The Wechsler Adult Intelligence Scale (WAIS) consists of three different assessments namely: digit span, letter number sequencing and arithmetic. The digit span measures working memory by determining the longest sequence of read or heard numbers an individual can recall; there was no difference in span between treatment and placebo groups (MD -1.02 (95% CI -2.47 to 0.43; [Analysis 12.10](#)). The scale also measured working memory by asking participants to order a random sequence of letters and numbers; numbers in ascending order first, then letters alphabetically. No difference was identified in the letter number sequencing section of the WAIS (MD -0.39 (95% CI -1.49 to 0.71; very low-certainty evidence; [Summary of findings 12](#); [Analysis 12.11](#)). Lastly in the arithmetic section of the WAIS, participants' working memory was evaluated by asking them to solve 22 timed arithmetic problems without a pencil and paper. Again, no significant difference was identified between groups (MD -0.01, 95% CI -1.41 to 1.39; [Analysis 12.12](#)).

2. All-cause mortality

None of the studies addressed this outcome.

Secondary outcomes

1. Adverse effects

See below 'SAFETY'.

2. Biomarkers of oxidative stress

None of the studies addressed this outcome.

SAFETY

We present results for safety of the treatment across all 10 chronic disorders, stratified as serious and non-serious, in the additional tables ([Table 12](#)). None of the 27 included studies assessed safety as a main outcome. Only two studies did not evaluate safety of the treatment by asking participants to report on adverse events they experienced during the treatment period, or by reports from the caregiver (if participants were children) or investigator or both, and by analysing the levels of various biochemical parameters in order to assess whether or not the levels stayed within the range of physiological values during the treatment period ([Belcaro 2008a](#); [Duracková 2003](#)).

We classified cessation of treatment as a serious adverse event. Only one study clearly reported that the reason for withdrawal from the study was related to the received treatment, but found no difference between the groups (Cisár 2008). In this study in adults with osteoarthritis of the knee, investigators withdrew two out of 50 participants from the Pycnogenol® group compared to five out of 50 from the placebo group (RR 0.40 (95% CI 0.08 to 1.97; Analysis 13.1).

Hospitalisation of one participant from the pine bark extract group occurred in each of two studies in participants with CVD and risk factors (Drieling 2010; Enseleit 2012). In the parallel group design study (130 participants) results showed no difference between groups (RR 3.09, 95% CI 0.13 to 74.54; Analysis 13.2; Drieling 2010); this was also true in the cross-over study (23 participants), which we were only able to analyse as a parallel study (RR 3.0, 95% CI 0.13 to 70.02; Analysis 13.2; Enseleit 2012). Therefore, pine bark extract supplements probably make little or no difference to hospitalisation (narrative synthesis; very low-certainty evidence; Summary of findings 3). In addition, the Drieling study reported two emergency department visits by participants taking placebo (RR 0.19, 95% CI 0.01 to 3.96; Analysis 13.3; Drieling 2010).

Seven studies reported non-serious adverse events (Cai 2013; Drieling 2010; Hosseini 2001a; Liu 2004a; Liu 2004c; Theadom 2013; Trebatická 2006); we present these in the additional tables (Table 12).

DISCUSSION

Summary of main results

Our review aimed to assess the efficacy and safety of pine bark extract for the treatment of chronic disorders. We identified 27 studies, with a total of 1641 participants, which addressed 10 different disorders.

Two of the studies were conducted exclusively in children; the remainder recruited adults. Participants ranged in age from six to 74 years, with the majority of participants aged between 40 to 60 years. Across all studies, the intervention lasted between one and six months. The control group was placebo for 24 studies. When considering allocation concealment as well as performance and detection biases as key domains, we judged the overall risk of bias to be low for four studies, unclear for 22 studies, and high for one study.

In adults with asthma, we do not know whether pine bark extract increases change in FEV₁ % predicted/FVC (MD 7.70, 95% CI 3.19 to 12.21; one study; 44 participants; very low-certainty evidence); increases change in FEV₁ % predicted (MD 7.00, 95% CI 0.10 to 13.90; one study; 44 participants; very low-certainty evidence); improves asthma symptoms (RR 1.85, 95% CI 1.32 to 2.58; one study; 60 participants; very low-certainty evidence); or increases the number of people able to stop using albuterol inhalers (RR 6.00, 95% CI 1.97 to 18.25; one study; 60 participants; very low-certainty evidence).

In children with ADHD, we do not know whether pine bark extract decreases inattention and hyperactivity assessed by parent- and teacher-rating scales (narrative synthesis; one study; 57 participants; very low-certainty evidence), and increases the change in visual-motoric coordination and concentration (MD 3.37, 95% CI 2.41 to 4.33; one study; 57 participants; very low-certainty evidence).

In participants with CVD, we do not know whether pine bark extract decreases diastolic blood pressure (MD -3.00 mm Hg, 95% CI -4.51 to -1.49; one study; 61 participants; very low-certainty evidence), increases HDL (MD 0.05 mmol/L, 95% CI -0.01 to 0.11; one study; 61 participants; very low-certainty evidence) or decreases LDL cholesterol (MD -0.03 mmol/L, 95% CI -0.05 to 0.00; one study; 61 participants; very low-certainty evidence).

In participants with CVI, we do not know whether pine bark extract decreases pain scores (MD -0.59, 95% CI -1.02 to -0.16; one study; 40 participants; very low-certainty evidence), increases the disappearance of pain (RR 25.0, 95% CI 1.58 to 395.48; one study; 40 participants; very low-certainty evidence) or increases physician-judged treatment efficacy (RR 4.75, 95% CI 1.97 to 11.48; 1 study; 40 participants; very low-certainty evidence).

In type 2 DM, we do not know whether pine bark extract leads to a greater reduction in fasting blood glucose (MD 1.0 mmol/L, 95% CI 0.91 to 1.09; one study; 48 participants; very low-certainty evidence) and decreases HbA1c (MD -0.90 %, 95% CI -1.78 to -0.02; 1 study; 48 participants; very low-certainty evidence). In a mixed group of participants with type 1 and type 2 DM it is also not known whether pine bark extract decreases HbA1c (MD -0.20 %, 95% CI -1.83 to 1.43; one study; 67 participants; very low-certainty evidence).

In men with ED, we do not know whether pine bark extract supplements increase International IIEF-5 scores (MD 4.28, 95% CI 1.61 to 6.95; two studies; 147 participants; very low-certainty evidence). In participants with female sexual dysfunction, we do not know whether pine bark extract increases satisfaction as measured by the FSFI (MD 5.10, 95% CI 3.49 to 6.71; one study; 75 participants; very low-certainty evidence) and leads to a slightly greater reduction of pain scores (MD 4.30, 95% CI 2.69 to 5.91; one study; 75 participants; very low-certainty evidence).

In adults with osteoarthritis, we do not know whether pine bark extract decreases composite WOMAC osteoarthritis index scores (MD -730.00, 95% CI -1011.95 to -448.05; one study; 37 participants; very low-certainty evidence) and whether it decreases the use of NSAIDs (MD -18.30, 95% CI -25.14 to -11.46; one study; 35 participants; very low-certainty evidence). We do not know whether pine bark extract increases bone alkaline phosphatase in postmenopausal women with osteopenia (MD 1.16 ug/L, 95% CI -2.37 to 4.69; one study; 40 participants; very low-certainty evidence).

Lastly in individuals with TBI, we do not know whether pine bark extract decreases cognitive failure scores (MD -2.24, 95% CI -11.17 to 6.69; one study; 56 participants; very low-certainty evidence) and post-concussion symptoms (MD -0.76, 95% CI -5.39 to 3.87; one study; 56 participants; very low-certainty evidence).

Two studies reported the hospitalisation of two participants, both from the pine bark extract groups; and seven studies reported non-serious adverse events.

Overall completeness and applicability of evidence

The included studies comprising 10 different chronic disorders are fairly representative of the variety of chronic conditions that pine bark extract supplements are marketed for. An important chronic condition that we did not find an included study for, is cancer. However, among the ongoing studies identified for this review update, three are assessing the effects of pine bark extract

supplements on breast cancer ([NCT00064857](#); [NCT00214032](#); [NCT03704454](#)).

The included studies used a variety of brand names from different manufacturers ([Table 1](#)). Dosage of pine bark extract supplements varied from 50 mg to 250 mg, which is in line with advertised products' dosage instructions, and doses were given either in capsule, tablet or powder form orally, or in powder form locally to ulcerated areas in one study. Four studies explicitly stated that they did not permit participants to also take other antioxidant supplements ([Duracková 2003](#); [Hosseini 2001a](#); [Hosseini 2001b](#); [Trebatická 2006](#)), while two studies allowed this ([Bottari 2012](#); [Chous 2016](#)), which may have influenced the results. The duration of use ranged from four weeks to six months; however, most studies tested pine bark extract supplements for three months or less. It can be argued that this is fair for a RCT, but considering that people with chronic disorders take medication and often also supplements chronically, this may have limited generalisability.

It is unclear from the reporting in the included studies to what extent good manufacturing practice standards were adhered to in the manufacturing of the supplements. For example, Pycnogenol® was the intervention in many of the included studies, but the tablets or capsules were manufactured by different companies and the comparability of the interventions, in terms of quantity and quality of active ingredients, is unknown. This highlights the importance of the international regulation of dietary supplements (e.g. that the individual ingredients meet accepted standards, purity and quantities as per the product label).

None of the studies considered safety as an important concern and the duration of most of the included studies was insufficient to adequately detect adverse events that may occur from taking the supplement chronically.

All-cause mortality is a primary outcome in this review, because chronic disorders are a leading cause of death globally. However, none of the included studies were adequately powered to detect a difference in mortality between groups, and none of the studies reported on this.

A challenge in this review is the heterogeneity in outcomes reported across studies. With the exception of participant-reported symptom scores, the outcomes per disorder varied widely across the different studies making it impossible to pool results from different studies. In some cases, investigators did not measure outcomes in an optimal manner. For example, in one study of hypertension, investigators did not report systolic and diastolic blood pressure directly, but by the change in drug (nifedipine) dosage at the end of the treatment period ([Liu 2004c](#)). A lack of consistency in how outcomes are measured hampered our ability to present a complete picture of the evidence. Attention has previously been drawn to the importance of standardising outcomes in trials that evaluate the same intervention for the same condition ([Clarke 2007](#)). Core outcome sets for conditions such as asthma, CVD, DM, female sexual dysfunction, osteoarthritis and TBI have been developed or are underway ([COMET Initiative](#)).

In the nutrition profession, generally, it is common practice to optimise dietary intake first to meet nutritional requirements, before resorting to supplementation. There are many dietary sources of proanthocyanidins, e.g. berries, apples, nuts, cinnamon, cocoa beans and red wine. Excessive amounts of antioxidants

(which include proanthocyanidins) may negatively affect the physiological functions of ROS ([Bjelakovic 2007](#)). Such excessive amounts are difficult to ingest through dietary sources, but can be attained easily in supplement form. Given the body of evidence synthesised in this review does not provide definitive conclusions regarding the efficacy or safety of pine bark extract supplements for chronic disorders, the routine use of these supplements for a specific chronic condition is not supported.

Quality of the evidence

A major limitation of the current evidence with regards to supplements of pine bark extract is the small sample sizes of the included studies. Small studies can sometimes provide definitive answers to questions about efficacy when outcomes are dichotomous and the number of events is large ([Sackett 1993](#)). However, in general, the findings of small studies can be misleading due to the play of chance. It has been demonstrated that for results to be statistically robust and clinically useful 500 participants per comparison group are needed ([Moore 1998](#)), which can be achieved either by conducting a large trial or by pooling results from multiple studies of small size. None of the included studies in this review update met this guideline.

The overall quality of reporting of studies included in this review was generally poor when compared to that of the CONSORT reporting guideline ([Schulz 2011](#)). This made judgements about risk of bias within studies difficult. We contacted authors of the included studies by email to ask for additional information and received responses to 14 of the 22 email enquiries sent. Lack of allocation concealment, incomplete blinding and selective outcome reporting were the main quality issues we identified. A further concern was that the manufacturer of the test drug funded 20 of the 27 studies, and we are unsure to what extent this could have influenced the studies.

Applying the GRADE tool we downgraded the certainty of evidence in the presence of a high risk of bias in two outcomes, indirectness of the evidence in 38 outcomes, unexplained heterogeneity or inconsistency in one outcome and imprecision of results in 38 outcomes. The certainty of evidence for all outcomes across all the summary of findings tables was very low. We did not downgrade any outcomes for publication bias as we were unable to generate funnel plots.

Potential biases in the review process

It is unlikely that we missed any relevant RCTs that have assessed the clinical efficacy or safety of supplements of pine bark extract since, apart from our electronic and manual searches, for this review update we contacted various manufacturers of pine bark extract supplements. We requested information regarding additional published or unpublished studies, but did not receive a response. We did not apply any language restrictions to studies considered for our review. We included adults and children with any chronic disorder and used wide criteria for interventions and outcomes.

Our review highlights the inadequate reporting of study details by authors which makes judgements of study quality challenging. Reporting standards, e.g. CONSORT Guidelines, have been established for reporting trials and journal editors should ensure that these are applied as a condition for publishing.

We were unable to formally assess the likelihood of publication bias (selective reporting of positive findings) in this review due to the small number of studies per condition. However, as publication bias is more likely with small studies, this could be a possible explanation of the positive findings seen in the studies we identified.

Agreements and disagreements with other studies or reviews

The initial version of this review was the first systematic review that specifically focused on the efficacy and safety of Pycnogenol® for the treatment of chronic disorders. However, we are currently aware of five systematic reviews that evaluated the effects of a variety of supplements for chronic conditions which included Pycnogenol® (Bartlett 2008; Clark 2010; Hadi 2019; Henrotin 2011; Zhang 2018).

Bartlett examined the effects of nutritional supplementation for the treatment of type II DM (Bartlett 2008). Of the three studies included in this review focusing on Pycnogenol®, we only include the study by Liu in our Cochrane Review (Liu 2004a). Another study by Spadea did not meet our eligibility criteria because the results for randomised participants were not reported separately from non-randomised participants (Spadea 2001) (see 'Characteristics of excluded studies'). An additional article by Leydhecker seems to have been an unpublished study from the University Clinic of Wurzburg, Germany; while we did not identify this study in our search, on closer inspection we would have excluded it since the control treatment (Dexium) has antioxidant properties (Leydhecker 1986). Bartlett presented the findings as reported in these studies and did not attempt to recalculate the estimates or synthesise the results quantitatively (Bartlett 2008).

Clark assessed the efficacy of herb and plant extracts, including Pycnogenol®, in the management of asthma (Clark 2010); and included two studies of Pycnogenol®, both of which we included in our review (Hosseini 2001b; Lau 2004). Clark also noted the problem of the use of different outcome measures across different studies, e.g. they pointed out that FEV₁ was measured in five different ways across 17 of their included studies (Clark 2010). In the two Pycnogenol® studies, Clark calculated an effect size for the use of albuterol inhaler by measuring the number of puffs needed per 24 hours at the end of the treatment period and obtained the same results as in this Cochrane Review (Clark 2010). Regarding the risk of bias assessments, Clark assessed only sequence generation, allocation concealment and blinding (Clark 2010). For the study by Hosseini, their judgements matched ours (Hosseini 2001b), but for the study by Lau, they judged allocation concealment as adequate compared to ours which was 'unclear' (Lau 2004).

Hadi and colleagues examined the effects of Pycnogenol® supplementation on plasma lipids (Hadi 2019). They included 14 clinical trials of Pycnogenol®, four of which we include in our review (Drieling 2010; Duracková 2003; Enseleit 2012; Zibadi 2008). Hadi reported a significant increase in HDL levels after Pycnogenol® supplementation; however, our analysis did not (Analysis 3.12). Regarding the risk of bias, our review differentiated between performance and detection bias. Hadi judged random sequence allocation for Enseleit as low, while we assessed it as unclear (Enseleit 2012; Hadi 2019). We assessed two studies as having a high risk of bias for selective outcome reporting (Duracková 2003;

Zibadi 2008), while Hadi and team assessed it as unclear (Duracková 2003; Hadi 2019; Zibadi 2008). We excluded the eight studies which Hadi included (Hadi 2019); the reasons for this were as follows: two were not RCTs (Belcaro 2013; Yang 2007), five enrolled participants who did not have a chronic disorder (Kohama 2013; Luzzi 2017; Nishioka 2007; Ryan 2008; Sedighiyan 2018) and one study had an inappropriate control (Koch 2002).

The Henrotin review aimed to "synthesize and evaluate scientific relevant data" on nutraceuticals that can "support health and physiological or functional benefit on osteoarthritis" (Henrotin 2011); the review included four clinical trials of Pycnogenol®, three of which have been included in our review (Belcaro 2008a; Cisár 2008; Farid 2007). Henrotin presented only the results as reported in the various studies (Henrotin 2011). In contrast with the risk of bias judgements in our review (Figure 2), Henrotin judged three studies to be of good to very good quality using a different instrument to ours (Belcaro 2008a; Cisár 2008, Farid 2007). We present further details of the instrument used by Henrotin in the additional tables (Table 13 (point 7)).

Zhang assessed the effects of Pycnogenol® on blood pressure (Zhang 2018); including nine studies of Pycnogenol®, three of which we included in our review (Drieling 2010; Enseleit 2012; Hosseini 2001b).

We assessed the methodological quality of the above-mentioned systematic reviews with the validated AMSTAR tool (Shea 2007) and present our findings in the additional tables (Table 13). The quality was poor, with the exception of the review by Clark (Clark 2010). Our updated Cochrane Review is the only systematic review to use GRADE to assess quality of studies per outcome.

AUTHORS' CONCLUSIONS

Implications for practice

Pine bark extract supplements are marketed worldwide as a treatment for a wide variety of chronic disorders (American Botanical Council 2010). Our review shows that currently available evidence is not sufficient to support claims regarding its benefit or to assure its safety in the chronic conditions we came across. It is important for users or potential users to be cognisant of this. Furthermore, healthcare professionals need to be aware of the diverse range of chronic conditions for which pine bark extract supplements are promoted, and the lack of evidence for efficacy and safety aspects, so that they are better equipped to guide individuals in deciding whether or not to include pine bark extract supplements as part of the management of their condition.

Implications for research

Despite the inclusion of 27 randomised controlled trials (RCTs) that assessed the efficacy of pine bark supplements for treating a variety of chronic disorders, the certainty of evidence is very low. Well-designed, adequately powered and well-reported RCTs of pine bark extract supplements are lacking. However, as meaningful amounts of proanthocyanidins and antioxidants can be obtained from a healthy diet (Benzie 2014), this raises the question whether it is worth spending further research funds on more RCTs, and whether it is fair to expose more individuals to research that is not making a meaningful contribution to the overall body of evidence. However, should future trials be conducted, careful attention should be given

to the outcomes to ensure that selected outcomes are clinically relevant to people and are measured in a standardised manner.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arcangeli 2000

Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: Italy; clinical centre.</p> <p>Ethics approval by the 'Ministry of Health'.</p> <p>Treatment duration: 2 months after a 2-week run-in period during which neither drugs acting on the cardiovascular system nor diuretics, analgesics or anti-inflammatory compounds were allowed.</p> <p>No follow-up after end of treatment.</p>
Participants	<p>Total participants: 40 (20 in each group).</p> <p><u>Inclusion criteria</u>: adults with CVI as a result of deep vein thrombosis or idiopathic venous lymphatic deficiency. Diagnosis was based on clinical judgement.</p> <p><u>Exclusion criteria</u>: not reported.</p> <p><u>Baseline characteristics</u>:</p> <p>Pycnogenol® group: 25% males; age, mean (SD) 57.95 (12.78) years (range 34 to 74 years).</p>

Pine bark (*Pinus* spp.) extract for treating chronic disorders (Review)

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Arcangeli 2000 (Continued)

Control group: 40% males; age, mean (SD) 61.40 (10.62) years (range 30 to 70 years).

Interventions	<p><u>Treatment:</u> Pycnogenol® 100 mg 3x per day for 2 months.</p> <p><u>Control:</u> "visually matched" placebo; 3x per day for 2 months.</p> <p>Route of administration: not reported; assumed to be oral.</p> <p>Concomitant medication: participants were not allowed to take drugs which act upon the cardiovascular system, diuretics, or analgesic and anti-inflammatory combinations during the treatment period.</p> <p>Diet: a standard diet determined according to participants' energy requirements had to be followed.</p>
Outcomes	<ul style="list-style-type: none"> Symptom scores (heaviness; swelling; pain of legs): collected at baseline, after 30 days and after 60 days of treatment; assessed by a clinical symptomatology score system where 0 = absent, 1 = light, 2 = moderate and 3 = severe; the percentage of participants who had disappearance of each symptom was also calculated. Venous blood flow: collected at baseline, after 30 and after 60 days of treatment; measured with a hand-held Doppler ultrasound. Clinical assessment of efficacy: collected at 60 days after treatment; assessed by a semi-qualitative scale where 1 = poor, 2 = moderate, 3 = good and 4 = very good. Clinical tolerability: participants were asked to report "adverse effects" anytime during treatment. Biochemical tolerability: blood samples were collected at baseline and after 60 days of treatment for blood tests (haematology, blood chemistry, liver functions, renal function); the unit of measurement for each blood test is specified in the article.
Notes	<p>Funding source: not reported.</p> <p>Study date: 1989.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...patients were randomly divided". However, the randomisation method is not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported whether all randomised participants completed the study, i.e. whether data from all participants for all outcomes were collected.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were pre-specified in the 'Methods' section outcomes reported in the Results section were not pre-specified in the Methods section.
Other bias	Unclear risk	Funding source not reported.

Arcangeli 2000 (Continued)

Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Belcaro 2006a

Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: Italy; setting not reported.</p> <p>Ethics approval: not reported.</p> <p>Treatment duration: 6 weeks.</p> <p>No follow-up after end of treatment.</p>
Participants	<p>Total participants: 30 (divided into 3 treatment groups and 1 control group).</p> <p><u>Inclusion criteria:</u> insulin-dependent diabetics with foot ulcers appearing for the first time and had been present for at least 2 months; severe diabetic microangiopathy based on blood flow in tibial arteries exceeding 60 mm Hg as measured by Laser Doppler skin perfusion pressure.</p> <p><u>Exclusion criteria:</u> severe stenosis or obstruction at the femoral or iliac artery level or recent venous thrombosis as indicated by colour duplex imaging; any clinical disease requiring treatment; severe bone or joint problems or limited mobility; uncontrolled diabetes; severe hypertension; signs of systemic infections; obesity; recent thrombosis (less than 6 months); and the presence of aneurysms or thrombi.</p> <p><u>Baseline characteristics</u></p> <p>Pycnogenol® oral and local treatment group: 37.5% males; mean (SD) age 54.3 (4.4) years; mean (SD) duration of disorder 11.3 (2.6) years.</p> <p>Pycnogenol® local treatment group: 37.5% males; mean (SD) age 55.0 (5.0) years; mean (SD) duration of disorder 11.0 (2.4) years.</p> <p>Pycnogenol® oral treatment group: 66.7% males; mean (SD) age 55.0 (3.0) years; mean (SD) duration of disorder 11.2 (4.0) years.</p> <p>Control group: 50% males; mean (SD) age 52.4 (6.1) years; mean (SD) duration of disorder 12.0 (3.0) years.</p>

Belcaro 2006a (Continued)

Interventions

Treatment Group 1 (oral and local): Pycnogenol® 50 mg capsule 3x per day orally for 6 weeks together with 100 mg powder from 2x 50 mg capsules placed on ulcerated area daily for 6 weeks.

Treatment Group 2 (local): Pycnogenol® 100 mg powder from 2x 50 mg capsules placed on ulcerated area daily for 6 weeks.

Treatment Group 3 (oral): Pycnogenol® 50 mg capsule 3x per day for 6 weeks.

Control: no Pycnogenol® or other medication, standard ulcer care only as received by the 3 active treatment groups for 6 weeks.

Concomitant treatment: all participants received general ulcer care daily that included washing and cleaning in water and a mild disinfectant (Citrosil, Italy), drying with soft paper tissue and dressed with nonallergic paper and a elastic-adhesive bandage (Tensoplast, South Africa).

Exercise: an exercise plan that included an educational video explaining foot protection for diabetics during exercise was given to all participants. Friction-free socks were provided that also kept the medication in place during the study period.

Outcomes

- Microcirculation-related symptoms (e.g. pain): collected at baseline and after 6 weeks of treatment; signs and symptoms were measured by means of a clinical scale where 0 = absence of symptoms and 10 = very severe signs or symptoms.
- Area of ulceration: collected at baseline and after 6 weeks of treatment; the area of ulceration was copied on a transparent plastic sheet and the relative integral of the area recorded in a computerized Logitech (Palo, Alto, Calif) system; measured in mm².
- % complete healing: collected after 6 weeks of treatment; individuals could have had varying numbers of ulcers.
- Microcirculatory parameters (transcutaneous PO₂ and PCO₂; skin flux at rest; veno-arteriolar response): collected at baseline and after 6 weeks of treatment; transcutaneous PO₂ and PCO₂ were measured in mm Hg with a combined measurement (CombiuSensor Kontron, United Kingdom) after heating the skin to 44°C, the measurements were recorded after a period of 20 minutes of stabilization and capillarization of the area, and it was made at 1 cm away from the ulcer edge in non-inflamed or infected area where the skin was intact; skin flux at rest was measured by a Laser Doppler in LDF units; veno-arteriolar response was also measured by a Laser Doppler. Because of high cost these parameters were only measured in the group receiving both the oral and local Pycnogenol® treatment, the group receiving only the oral Pycnogenol® as well as the control group.
- Side effects: reported during the 6-week intervention period; measured by direct questioning about tolerability and compliance - particularly gastrointestinal problems, systemic and local skin alterations, signs of allergic reaction and any other manifestation.

Notes

Funding source: "The study was not sponsored by companies producing materials and products quoted in the article. The compound was supplied, without conditions, by Horphag Research Management SA, Geneva, Switzerland."

% complete healing: there could have been more than 1 ulcer per participant. It is not clear whether all ulcers of a participant were completely healed in order to be counted as 'complete healed', or whether 1 ulcer healed was counted. The unit of randomisation was participants, not ulcers.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to four groups." However, the randomisation method is not reported. After contacting the study authors we learned that "comparative groups [were] set up for this pilot trial". This may mean that this study was not truly randomised. We have contacted the contact author again and are waiting for their response.

Belcaro 2006a (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding (the control group received no treatment or placebo while the three treatment groups got capsules for treatment used orally, locally or both). It is unclear who was caring for the ulcers daily, and who the outcome assessors were. It is plausible that participants and/or outcome assessors were influenced in caring for the ulcers differently between groups.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patient-reported subjective outcome of pain is likely to have been influenced by lack of blinding. It is unclear who measured the area of ulceration, but lack of blinding also could have influenced their assessment to a lesser extent, depending in their involvement in wound care.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were pre-specified in the 'Methods' section.
Other bias	Unclear risk	The study was funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Belcaro 2008a
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: Italy; community setting</p> <p>Ethics approval by the ethical committee of the University of Pescara.</p> <p>Treatment duration: 3 months.</p> <p>No follow-up after end of treatment.</p>
Participants	Total participants: 156 (77 in the treatment group and 79 in the control group).

Pine bark (*Pinus spp.*) extract for treating chronic disorders (Review)

Belcaro 2008a (Continued)

Inclusion criteria: people with grade I or II osteoarthritis of one or both knees (classified by the American Rheumatism Association system), confirmed by X-ray performed by a qualified orthopaedist (Belcaro 2008b); WOMAC pain sub-scale index of at least 10 out of 20 (Belcaro 2008b); intermittent or constant pain in the target knee for at least 50% of the time during the last 3 months which required medical treatment with selective COX-2 inhibitors or other NSAIDs (Belcaro 2008b); able to perform the treadmill test; understand all questions from the WOMAC questionnaire.

Exclusion criteria: secondary osteoarthritis due to a known disorder (Belcaro 2008b); joint injection of the target knee within the last 6 months (Belcaro 2008b); cardiovascular disease requiring drug treatment; diabetes; overweight; severe metabolic disorders; surgery or arthroscopy 3 months before inclusion; radiotherapy or chemotherapy; pregnant, breastfeeding or planned conception.

Baseline characteristics:

Treatment group: 50.6% males; mean (SD) age 48.6 (8.0) years; mean global WOMAC score 79.2; mean of treadmill test 68 m; distance (range) achieved with treadmill test 0 - 133 m.

Control group: 49.4% males; mean (SD) age 47.8 (7.7) years; mean global WOMAC score 76.9; mean of treadmill test 65 m; distance (range) achieved with treadmill test 12 - 98 m.

Interventions

Treatment: Pycnogenol® 50 mg capsule 2x per day (after breakfast and dinner) for 3 months.

Control: placebo that matched the test drug by appearance, size and shape; 2 capsules daily (after breakfast and dinner) for 3 months.

Route of administration: orally.

Concomitant medication: associated treatments prescribed by the participant's general practitioner were to be reported in a diary. After contacting the study authors we learned that NSAIDs, paracetamol and ibuprofen was allowed during the study.

Outcomes

- Symptom scores (pain; stiffness; physical function; global score (sum of previous 3 scores); negative alterations in social functions; sum of emotional parameters): collected at baseline and after 3 months of treatment; measured by the WOMAC index. The interpretation of the WOMAC scores: total score ranges from 0 (no symptoms) to 96; pain score ranges from 0 (no symptoms) to 20; stiffness score ranges from 0 (no symptoms) to 8; and physical function score ranges from 0 (no symptoms) to 68.
- Use of concomitant medication: participants kept a diary of medication prescribed by their general practitioner during the treatment period; expressed in percentage reduction at the end of the 3-month treatment period. After contacting the study authors we learned that NSAIDs use was noted by participants in a diary. "Of course the medication varied in a way that one patient took e.g. paracetamol while another took ibuprofen, and also the dosage may have varied."
- Physical performance: collected at baseline and after 3 months of treatment; measured as the total distance (m) on the treadmill that could be covered at 3 km/hour with an inclination of 10% without pain.
- Vascular problems (clinical assessment of ankle and foot oedema; ankle and foot oedema measured by foot volumetry on randomly selected subsample): data for the clinical assessment was collected at baseline and after 3 months of treatment, whereas data on ankle and foot oedema measured by foot volumetry was only collected after 3 months of treatment; oedema was scored by the investigator as 0 = not visible, 1 = only visible after standing for a "long" time or in the evening, 2 = visible during the day but resolves overnight, 3 = visible during the day but only partially resolves overnight, 4 = present all the time; the actual foot volume at inclusion was defined as 100%.
- Reduction in health care costs (drugs and treatments besides NSAIDs; average management; hospital admissions; days hospitalised; indirect costs): information was recorded in a specific costing file during the treatment period; expressed in percentage reduction at the end of the 3-month treatment period.
- "Unwanted effects": reported by participants in diaries during the treatment period.

Notes

Funding source: Horphag Research.

Risk of bias

Belcaro 2008a (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated blocked randomisation.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo were identical in appearance and labelled as either A or B.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were measured by blood specimens.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 out of 77 participants were lost to follow-up from the treatment group and 5 out of 79 from the control group.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were pre-specified in the 'Methods' section.
Other bias	Unclear risk	The study was funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Bottari 2012

Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: not reported.</p> <p>Ethics approval: protocol received approval from the ethical committee of the University of Pescara.</p> <p>Treatment duration: 8 weeks.</p>
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Bottari 2012 (Continued)

Follow-up after the treatment period? No.

Method of diagnosis: The FSFI questionnaire total score and its 6 individual domain (desire, arousal, lubrication, orgasm, satisfaction, and pain) scores were used to determine sexual function.

Sample size calculation: "It was concluded that at least 20 subjects completing the study/observation period in each group were necessary to obtain statistically meaningful information."

Participants

Total number of participants randomised: 83. Initially 40 participants in intervention group with 4 loss to follow-up. Initially 43 participants in placebo group with 4 loss to follow-up.

Inclusion criteria: healthy women aged 45 - 55 years of age; moderate sexual function problems; satisfactory educational and cultural-social status; defined previous menopause; BMI < 24 kg/m².

Exclusion criteria: Inclusion in previous studies; clinically significant cardiovascular disease; surgery or hormonal treatment within the past 12 months prior to inclusion.

Baseline characteristics:

Treatment group:

Gender: 100% females.

Age, mean (SD), range: 50.1 (3.1) years (45 - 55 years).

Condition indicators, mean (SD) FSFI score: 44.6 (24.1).

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Control group:

Gender: 100% females.

Age, mean (SD), range: 51.2 (2.3) years (46 - 55 years).

Condition indicators, mean (SD) FSFI score: 44.1 (22.8).

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported

Socio-economic status: not reported.

Overall:

Gender: 100% females.

Age: not reported.

Condition indicators, FSFI score: described as moderate sexual dysfunction, but exact scoring not indicated.

Bottari 2012 (Continued)

Condition duration: not reported.

Nutritional status: BMI < 24kg/m².

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Interventions

Treatment: Lady Prelox® 2x capsules in morning and 2x in evening containing 20 mg Pycnogenol®, 200 mg L-arginine, 200 mg L-citrulline, 50 mg Rosvita rose hip extract.

Control: Placebo, 2x capsules in morning and 2x in evening.

Route of administration: orally.

Concomitant treatment: "No medications or other supplements were permitted during the trial period, with the exception of daily vitamins and minerals."

Diet: not reported.

Monitoring: not reported.

Outcomes

The FSFI questionnaire collected at baseline, 4 and 8 weeks, consists of the following domains where a lower score indicates dysfunction:

- Desire domain: consists of the first 2 questions of the questionnaire; the score ranges from 2 - 10.
- Arousal domain: consists of questions 3 to 6; the scores ranges from 0 - 20.
- Lubrication domain: consists of questions 7 - 10; the score also ranges from 0 - 20.
- Orgasm domain: consists of question 11 till 13; the score ranges from 0-15.
- Satisfaction domain: consists of questions 14 - 16; the score ranges from 2 - 15.
- Pain domain: consists of questions 17 - 19; the score ranges from 0-15.

Notes

Funding Source: not reported.

Date of study: not reported.

Authors' conflict of interest declarations: "The Authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. All the Authors contributed equally to this work."

Protocol or trial registry entry? Protocol was approved by ethics committee of Chieti-Pescara University but not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It is stated that women were randomly assigned to the experimental or control group, but no detail is given on how the randomisation was performed.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A control group of comparable women...were given placebo tablets of similar colour, shape, weight and appearance in a single blinded fashion." Only participants were blinded, however, all outcomes were participant-reported.

Bottari 2012 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were participant-reported and participants were blinded as described above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"These drop outs resulted from non-medical reasons, due to failure to attend the check-ups in timely fashion." These reasons are unlikely to be related to the true outcome. The attrition is approximately the same across groups (10.0% in experimental and 9.3% in control group) further indicating that it is unlikely to be associated with the intervention.
Selective reporting (reporting bias)	Unclear risk	There is no mention or availability of a trial registry entry or protocol, but the specified outcomes in the 'Methods' section were addressed in the 'Results' section.
Other bias	High risk	A paper by Wiegel, Meston & Rosen entitled 'The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores' (Journal of Sex and Marital Therapy 2005; 31(1): 1-20) defined the optimal total FSFI score for differentiating between women with and without sexual dysfunction as 26.55. This score is far below the mean score at baseline for both the experimental and control group. Funding source not reported.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Cai 2013
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: Italy; clinical, urological institutions.</p> <p>Ethics approval: not reported.</p> <p>Treatment duration: 3 months.</p> <p>Follow-up after the treatment period? No.</p> <p>Sample size calculation: "The sample size was calculated prospectively under the following conditions: difference between the groups = 10%, Alpha Error Level = 0.05 two-sided, statistical power = 80% and anticipated effect size (Cohen's d = 0.5)."</p>
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Cai 2013 (Continued)

Method of diagnosis: "...clinical and instrumental diagnosis of LUTS due to BPH and ED."

Participants

Total number of participants randomised: 132 participants were randomised, 85 were allocated to IDIProst® Gold and 47 to Serenoa repens. 2 were lost to follow-up in group A (IDIProst® Gold) and 1 lost to follow-up in group B (Serenoa repens).

Inclusion criteria: aged 50 years or older; sexually active; maximal urinary flow rate (Cmax) of less than 15 mL/s, post-residual voided volume less than 100 cc; IPSS score ≥ 8 ; IPSS QoL ≥ 2 ; PSA < 4 ng/mL, or higher if negative prostate biopsy; IIEF-5 score < 21 ; untreated for LUTS/BPH; testosterone level > 3 ng/dL

Exclusion criteria: affected by major concomitant diseases such as diabetes, liver and/or renal failure; known anatomical abnormalities or malignancies of the urinary tract or bladder; upper tract stones; diverticula; foreign bodies; prostatitis; active urinary tract infection; chronic retention; polycystic kidney disease; urethral stenosis interfering with voiding function; a history of transurethral resections of the prostate, laser therapy, or thermotherapy; testing positive for sexually transmitted diseases such as *Chlamydia trachomatis*, *Ureaplasma urealyticum*, or *Neisseria gonorrhoeae*; allergy to 1 or more compounds of IDIProst® Gold; treated with phosphodiesterase type 5 inhibitors.

Baseline characteristics:

Treatment group:

Gender: 100% male.

Age, mean (SD): 58.9 (3.56) years.

Condition indicators, mean (SD): IPSS score: 17.1 (5.9); IIEF-5 score: 14.9 (3.5); SF-36 score: 96.4 (1.1); PSA total: 2.02 (1.45) ng/mL; post-void residual urine: 29.9 (28.8) mL; uroflowmetry data Qmax: 11.7 (2.2) mL/sec; prostate volume: 43.9 (21.1) mL.

Condition duration: not reported.

Nutritional status: BMI, mean (SD): 26.9 (1.3) kg/m².

Comorbidities: Comorbidity Charlson Index, mean (SD): 1.9 (0.8).

Lifestyle factors, n (%): married: 53 (63.8%); unmarried: 20 (24%); divorced: 10 (12.2%); smoker: 28 (33.8%); non-smokers 55 (66.2%)

Family history: not reported.

Socio-economic status, n (%): primary school qualification: 30 (36.2%); high school qualification: 29 (35.0%); university qualification: 24 (28.8%).

Control group:

Gender: 100% male.

Age, mean (SD): 59.1 (3.68) years.

Condition indicators, mean (SD): IPSS score: 16.9 (5.8); IIEF-5 score: 15.1 (3.7); SF-36 score: 96.9 (1.2); PSA total: 2.08 (1.59) ng/mL; post-void residual urine: 32.8 (29.9) mL; uroflowmetry data Qmax: 11.9 (2.1) mL/sec; prostate volume: 41.4 (17.2) mL.

Condition duration: not reported.

Nutritional status: BMI, mean (SD): 27.1 (1.1) kg/m².

Comorbidities: Comorbidity Charlson Index, mean (SD): 2.0 (0.9).

Lifestyle factors, n (%): married: 30 (65.3%); unmarried: 11 (23.9%); divorced: 5 (10.8%); smoker: 16 (34.7%); non-smokers: 30 (65.3%).

Family history: not reported.

Cai 2013 (Continued)

Socio-economic status, n (%): primary school qualification: 18 (39.1%); high school qualification: 15 (32.7%); university qualification: 13 (28.2%).

Overall:

Gender: 100% male.

Age: no statistically significant differences between groups.

Condition indicators, mean (SD): IPSS score 17.1(6.4); IIEF-5 score 14.9 (3.7); SF-36 score 96.3 (1.2); no statistically significant differences between groups.

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: no statistically significant differences between groups.

Lifestyle factors: no statistically significant differences between groups.

Family history: not reported.

Socio-economic status: no statistically significant differences between groups.

Interventions	<p><u>Treatment:</u> IDIProst® Gold, 1x 950 mg capsule containing <i>Serenoa repens</i> (320 mg), <i>Crocus sativus</i> (100 mg), and <i>Pinus massoniana</i> (120 mg) per day.</p> <p><u>Control:</u> <i>Serenoa repens</i>, one capsule daily containing 320 mg <i>Serenoa repens</i> per day.</p> <p>Route of administration: oral.</p> <p>Concomitant treatment: none.</p> <p>Diet: none.</p> <p>Monitoring: "All patients were contacted by telephone on day 30 of the therapy to ensure correct timing and dose treatment."</p>
Outcomes	<ul style="list-style-type: none"> IIEF-5: participant-reported questionnaire with a maximum score out of 25 where normal function = 21 - 25 points, mild ED = 16 - 20 points, moderate ED = 10 - 15 points and severe ED ≤ 10 points; collected at baseline and at 3 months. IPSS: participant-reported questionnaire with a maximum score out of 35 where 1 - 7 = mild, 8 - 19 = moderate and 20 - 35 = severe urinary symptoms; collected at baseline and at 3 months. SF-36: participant-reported questionnaire with a maximum score out of 100 where the lower the score the more severe the disability; includes questions on 8 sections namely vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health; collected at baseline and at 3 months. Adverse events: only reported 1 participant in intervention group and 1 participant in placebo group reported 'mild adverse effects that did not require treatment suspension'.
Notes	<p>Sponsorship source: not reported.</p> <p>Date of study: enrolment from May to December 2012</p> <p>Authors' conflict of interest declarations: "No conflict of interest declared."</p> <p>Protocol or trial registry entry? Not reported.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Cai 2013 (Continued)

Random sequence generation (selection bias)	Unclear risk	"All patients who met the inclusion criteria were assigned to groups according to a 1:1 randomisation..."
Allocation concealment (selection bias)	Unclear risk	There is insufficient information on the allocation concealment to make a judgment of low or high risk, as the procedure is not described but only referred to.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There is no information available on whether blinding of either participants or personnel were done. No description of how the two interventions were made to look and taste similar is available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no information available on the blinding of outcome assessors. As the participants are the predominant outcome assessors (the primary outcome is participant-reported), the lack of description on whether the 2 interventions were made to look and taste similar makes it unclear whether blinding of outcome assessors was achieved.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	While the number of participants lost to follow-up is reported per group; there is no explicit reason for the attrition. It is stated that a participant in each group developed mild adverse effects, but that only the <i>Serenoa repens</i> participant was lost to follow-up. Therefore, the reasons for losing 2 participants from the IDiProst® Gold group is unknown.
Selective reporting (reporting bias)	High risk	The study protocol with a priori outcomes is not readily available online, but main outcomes are listed as "...improvement of quality of life at the end of the whole study period, in terms of changes in IPSS, IPSS-QOL, Cmax, PVR, SF-36 and the IIEF-5..." Only total IPSS, IIEF-5 and SF-36 outcomes are reported at 3 months. No laboratory clinical outcomes are reported.
Other bias	Unclear risk	As by the admission of the authors themselves, the lack of a placebo arm is a limitation of the study. The findings should be interpreted as the improvement of sexual function and QoL with IDiProst® Gold when compared to <i>Serenoa repens</i> alone. This comparison, however, would likely diminish any effect size rather than over-estimate it and does not increase inherent bias. Funding source not reported.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Cesarone 2008

Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and Setting: not reported.</p> <p>Ethics approval: not reported.</p> <p>Treatment duration: 2 months.</p> <p>Follow-up after the treatment period?: No.</p> <p>Method of diagnosis: metabolic syndrome including borderline cardiovascular health risks, blood pressure, lipid profile and fasting glucose.</p> <p>Sample size calculation: not reported.</p>
Participants	<p>Total number of participants randomised: 61 participants, 31 lost to follow-up in treatment group and 30 lost to follow-up in placebo group.</p> <p><u>Inclusion criteria:</u> blood pressure between 130/85 and 140/95 mm Hg; HDL cholesterol < 40 mg/dL; total cholesterol between 200 and 240 mg/dL; and a prediabetic fasting blood glucose as defined by the American Diabetes Association (100 to 125 mg/dL).</p> <p><u>Exclusion criteria:</u> any metabolic conditions or any other clinical conditions requiring drug treatment; severely handicapped people; pregnant or nursing women.</p> <p><u>Baseline characteristics:</u></p> <p>Treatment group:</p> <p>Gender: 12 females (38.7%); 19 males (61.3%).</p> <p>Age, mean: 49.7 years.</p> <p>Condition indicators, mean (SD): oxidative stress D-ROM test 428 (24) Carr units; fasting blood glucose 118 (9) mg/dL; total cholesterol 233 (11) mg/dL; HDL cholesterol 37 (3) mg/dL; LDL cholesterol 41 (3.1) mg/dL; C-reactive protein 238 (23) ug/L; systolic blood pressure 135 (5) mm Hg; diastolic blood pressure 92 (4) mm Hg; heart rate 78 (7) beats per minute; diastolic carotid artery flow 16 (IQR 11 to 26)%; reactive hyperaemia: 25 (IQR 11 to 69)%; left ventricular ejection fraction: 100%; flux at rest 1.1 (0.1) flux units; flux on standing 0.9 (0.1) flux units; venoarteriolar response: 34; transcutaneous partial O₂ pressure 52 (8) mm Hg; transcutaneous partial CO₂ pressure 29 (3) mm Hg.</p> <p>Condition duration: not reported.</p> <p>Nutritional status: not reported.</p> <p>Comorbidities: not reported.</p> <p>Lifestyle factors: Not reported.</p> <p>Family history: not reported.</p> <p>Socio-economic status: not reported.</p> <p>Control group:.</p> <p>Gender: 9 females (30.0%); 21 males (70.0%)</p> <p>Age, mean: 48.3 years.</p> <p>Condition indicators, mean (SD): oxidative stress D-ROM test 429 (22) Carr units; fasting blood glucose 119 (8) mg/dL; total cholesterol 228 (12) mg/dL; HDL cholesterol 38 (4) mg/dL; LDL cholesterol 38.1</p>

Cesarone 2008 (Continued)

(2.2) mg/dL; C-reactive protein 228 (29) ug/L; systolic blood pressure 134 (4) mm Hg; diastolic blood pressure 93 (3) mm Hg; heart rate 79 (6) beats per minute; diastolic carotid artery flow 16 (IQR 12 to 27)%; reactive hyperaemia 24 (IQR 12 to 74)%; left ventricular ejection fraction 100%; flux at rest 1.12 (0.1) flux units; flux on standing 1.0 (0.15) flux units; venoarteriolar response 36; transcutaneous partial O₂ pressure 51 (8) mm Hg; transcutaneous partial CO₂ pressure 28 (4) mm Hg.

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Overall:

Gender: 21 females (34.4%); 40 males (65.6%).

Age, mean: 49.0 years.

Condition indicators: not reported.

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Interventions

Treatment: OPC-3, 1x 10 g pouch daily containing 400 mg flavonoids (consisting of equal amounts of Pycnogenol®, grape seed, bilberry, citrus, and red wine); as well as fructose, glucose, citric acid, potassium bicarbonate, silica, calcium sulfate, and pectin.

Control: placebo, 1x 10 g pouch daily containing fructose, citric acid, potassium bicarbonate, maltodextrin, silica, calcium sulfate, apple fibre, FD Red #40, and FD Blue #1.

Route of administration: orally, following solubilization of sachet contents with 180 mL water resulting in an isotonic solution

Concomitant treatment: "...none of the subjects was on a medical intervention..."

Diet: "...none of the subjects was on a medical intervention, and only a risk management program, including diet and an exercise..."

Monitoring: not reported.

Outcomes

Outcomes measured at baseline and at 2 months.

- D-ROM measured using the Free Radical Analytical System in which the assay estimates hydrogen peroxides in blood after incubation in a buffer solution with a chromogenic agent; measured in Carr units where 1 Carr unit corresponds to 80 microgram H₂O₂/dL.
- Fasting blood glucose determined by 'routine chemical methods'.
- Total cholesterol determined by 'routine chemical methods'.
- HDL cholesterol determined by 'routine chemical methods'.
- LDL cholesterol determined by 'routine chemical methods'.

Cesarone 2008 (Continued)

- CRP measured using an automated analysis system CRP 200 (Roche, Switzerland).
- Systolic blood pressure measured in mm Hg.
- Diastolic blood pressure measured in mm Hg.
- Heart rate measured in beats per minute.
- Diastolic component of carotid artery flow measured as % using high-resolution duplex ultrasonography scanning with an ATL 5000 HDL (Advanced Technology Laboratories, Seattle, WA).
- Reactive hyperaemia measured as % using strain-gauge plethysmography to test for endothelium-dependent vasodilatation; forearm blood flow was measured with a mercury-filled Silastic strain-gauge plethysmograph.
- Left ventricular ejection fraction measured as % by cardiac ultrasound using a modified Simpson rule as described in the standards of the American Society of Cardiac Ultrasound and the American Heart Association.
- Flux at rest, laser Doppler measured in flux units; Laser Doppler flowmetry measurements were carried out with a TSI Vasamedics instrument.
- Flux on standing, laser Doppler measured in flux units; Laser Doppler flowmetry measurements were carried out with a TSI Vasamedics instrument.
- Venoarteriolar response measured as % as skin flux at perimalleolar region.
- Transcutaneous partial O₂ pressure measured in mm Hg by using a Kontron pO₂-pCO₂ analyser following adaptation of the skin at 42°C for 20 minutes.
- Transcutaneous partial CO₂ pressure measured in mm Hg by using a Kontron pO₂-pCO₂ analyser following adaptation of the skin at 42°C for 20 minutes.
- Tolerance and safety: liver enzymes, kidney function, white blood cells, red blood cells, clotting factors.
- Participants were interviewed for possible adverse events but none were reported by all participants.

Notes

Sponsorship source: not reported.

Date of study: not reported.

Authors' conflict of interest declarations: not reported however the contact author is employed by NutraMetrix who manufactures OPC-3®.

Protocol or trial registry entry? Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors state that randomisation took place, but there is no information on the procedure which was followed.
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment is not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The experimental and control powders were in matching foil pouches; and the placebo powder had "equivalent taste and colour". The base of inactive ingredients in the experimental powder "covers the bitter and astringent tastes of the extracts". Only reports double-blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No specific mention is made of the blinding of outcome assessors, but outcomes were objective and analytical/laboratory-based.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The paper states that all participants who were recruited also completed the study.

Cesarone 2008 (Continued)

Selective reporting (re-reporting bias)	High risk	Neither trial registry nor study protocol were mentioned or are available. Some outcomes, such as systolic blood flow component, were mentioned in the 'Methods' section; but not in the 'Results' section.
Other bias	Unclear risk	Funding source not reported.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Unclear risk	Not applicable.
Was there no carry-over effect?	Unclear risk	Not applicable.
Are the results comparable to those from parallel group trials?	Unclear risk	Not applicable.

Chous 2016
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: not reported; optometric practice focused on diabetic eye care.</p> <p>Ethics approval: not reported. Informed consent and study protocol approved by the Western Institutional Review Board.</p> <p>Treatment duration: 6 months.</p> <p>Follow-up after the treatment period? No.</p> <p>Method of diagnosis: diagnosed by ophthalmoscopy which determines deficits in contrast, visual field and colour vision sensitivity; patients with type 1 or 2 diabetes with no retinopathy or mild to moderate non-proliferative retinopathy.</p> <p>Sample size calculation: "Sample size was based on previous published trials and differences in key visual function variables."</p>
Participants	<p>Total number of participants randomised: 70 participants; 39 allocated to DiVFuSS supplement and 28 to placebo; 3 lost to follow-up and excluded from initial and final analysis.</p> <p><u>Inclusion criteria:</u> diabetes diagnosis for 5 years or more; best corrected visual acuity $\geq 20/30$ in each eye; no diabetic retinopathy or mild to moderate NPDR; potential participants with DMO as determined by spectral domain optical coherence tomography could be included if they did not meet the diagnostic criteria for clinically significant DMO as specified in the Early Treatment Diabetic Retinopathy Study guidelines.</p> <p><u>Exclusion criteria:</u> known sensitivity to any of the test ingredients; renal impairment; minors; non-English speaking/reading.</p> <p><u>Baseline characteristics</u></p>

Pine bark (*Pinus spp.*) extract for treating chronic disorders (Review)

Chous 2016 (Continued)

Treatment group:

Gender: 26 female (66.7%); 13 male (33.3%).

Age, mean (SD): 53.5 (14.6) years.

Condition indicators: HbA1c mean (SD) 7.1 (1.0%); 16 (41.0%) with type 1 diabetes, 23 (59.0%) with type 2 diabetes; 24 (61.5%) with no DR, 10 (25.6%) with mild NPDR, 5 (12.8%) with moderate NPDR.

Condition duration: diabetes duration mean (SD) 16 (12.2) years

Nutritional status: 15 (38.5%) used multivitamins; 24 (61.5%) did not.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Control group:

Gender: 16 female (57.1%); 12 male (42.9%).

Age, mean (SD): 59.7 (10.3) years.

Condition indicators: HbA1c: mean (SD) 7.3 (1.1%); 11 (39.3%) with type 1 diabetes, 17 (60.7%) with type 2 diabetes; 13 (46.4%) with no DR, 14 (50.0%) with mild NPDR, 1 (3.6%) with moderate NPDR

Condition duration: DM duration mean (SD) 16.1 (9.9) years

Nutritional status: 8 (28.6%) used multivitamins; 20 (71.4%) did not.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Overall:

Gender: 42 female (62.7%); 25 male (37.3%); "No statistically significant differences...based on...gender..."

Age, mean (SD): 56.1 (13.2) years; "No statistically significant differences...based on age..."

Condition indicators: HbA1c: mean (SD) 7.2 (1.1%); 27 (40.3%) with type 1 diabetes, 40 (59.7%) with type 2 diabetes; 37 (55.2%) with no DR, 24 (35.8%) with mild NPDR, 6 (9.0%) with moderate NPDR; "No statistically significant differences...based on diabetes duration...diabetes subtype, DR status..." "However, a higher percentage of placebo subjects (54%) had some degree of DR versus those receiving the DiVFuSS supplement (38%) post randomisation (Fisher's exact test=0.12)." "Baseline visual function (contrast sensitivity, colour error score and visual field mean sensitivity), MPOD, mean foveal and RN-FL thickness and serum laboratory values (glycohaemoglobin (HbA1c), serum lipids, 25-OH-vitamin D3, hsCRP and TNF-a) were all without significant difference." "...borderline significantly better mean contrast sensitivity...in the right eyes of subjects randomised to placebo (p=0.05)."

Condition duration: not reported.

Nutritional status: 23 (34.3%) used multivitamins; 44 (65.7%) did not.

Comorbidities: not reported.

Lifestyle factors: not reported.

Chous 2016 (Continued)

Family history: not reported.

Socio-economic status: not reported.

Interventions

Treatment: DiVFuSS formula 2x capsules daily; each capsule containing vitamins C, D3, and E (d-alpha-tocopherol), zinc oxide, eicosapentaenoic acid, docosahexaenoic acid, alpha-lipoic acid (racemic mixture), coenzyme Q10, mixed tocotrienols/tocopherols, zeaxanthin, lutein, benfotiamine, N-acetyl cysteine, grape seed extract, resveratrol, turmeric root extract, green tea leaf, and Pycnogenol®.

Control group: placebo 2x canola oil soft gel capsules daily identical in appearance to the DiVFuSS formula

Route of administration: Oral

Concomitant treatment: With the exception of a single, daily multivitamin and mineral supplement (23 of 67 subjects), no subjects were currently using dietary supplements containing ingredients found in the test formula.

Diet: participants also agreed to refrain from consuming xanthophyll-rich or omega-3 fatty acid-rich foodstuffs (spinach, kale, collard greens and cold water fatty fish) more than twice per week during the study period

Monitoring: "Subjects returned for a pill count at 10-12 weeks after initiation to help ensure adherence."

Outcomes

Data collected at baseline and 6 months.

- Contrast sensitivity for spatial frequencies of 1.5, 3, 6, 12 and 18 cycles per degree.
- Total colour error score.
- 5 to 2 threshold visual field mean deviation.
- Macular pigment optical density using heterochromatic flicker photometry (QuantifEye, ZeaVision, LLC, Chesterfield, Missouri, USA).
- Foveal thickness measured using Spectral domain optical coherence tomography (Cirrus-SDOCT, Carl Zeiss, Peabody, Massachusetts, USA).
- Retinal nerve fibre layer thickness: measured using Spectral domain optical coherence tomography (Cirrus-SDOCT, Carl Zeiss, Peabody, Massachusetts, USA).
- Blood chemistry (HbA1C, total cholesterol, LDL, HDL, triglycerides, HsCRP, vitamin D, TNF-alpha).
- Diabetic Peripheral Neuropathy symptom score: participant-reported with a maximum score of 4; reported as 'one-point decrease' indicating an improvement in symptoms, 'no change' in scores or 'one-point increase' indicating worsening in symptoms.

Notes

Sponsorship source: ZeaVision, LLC, Chesterfield, Missouri, USA.

Date of study: enrolment dates April 2012 until February 2014.

Authors' conflict of interest declarations: Dr Chous is a consultant to ZeaVision, LLC

Protocol or trial registry entry? www.ClinicalTrials.gov identifier: NCT01646047

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A block randomised list was created using predetermined ratios for participants with and without diabetic retinopathy (2:1 for participants without diabetic retinopathy at baseline, and 1:1 for participants with diabetic retinopathy at baseline).
Allocation concealment (selection bias)	Low risk	Sequentially numbered vials with formula and placebo of identical appearance were distributed by a masked investigator.

Chous 2016 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Investigators and subjects alike were blinded to subjects' supplement status." Capsules were identical in appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators...were blinded to subjects' supplement status." Outcomes were objective, laboratory-based outcomes with lower risk of information bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reason for the attrition is provided, and it is unclear whether the loss to follow-up was in the experimental or control group. 3 lost to follow-up however they were excluded from initial and final analysis.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported and corresponded with the trial registry outcomes.
Other bias	Unclear risk	The study was funded by ZeaVision® LLC, which sells vision supplements under its parent company EyePromise®.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Cisár 2008

Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: Slovakia; outpatients attending the Orthopaedics Department of the University Hospital Ružinov in Bratislava.</p> <p>Ethics approval by the Local Ethical Committee of the University Hospital in Bratislava, Slovakia.</p> <p>Treatment duration: 12 weeks.</p> <p>Follow-up: 2 weeks after end of treatment, at week 14.</p>
Participants	<p>Total participants: 100 (50 in each group).</p> <p><u>Inclusion criteria:</u> adults (> 25 years) with stage I or II osteoarthritis according to Kellgren-Lawrence in standard AP X-ray view in at least 1 target knee; mild to moderate pain in the target knee for at least 3 months preceding the study, and/or morning knee stiffness and/or knee crepitus; females must con-</p>

Cisár 2008 (Continued)

firm that they are not presently pregnant and do not plan to get pregnant for at least 1 year after the end of the trial; post-menopausal women must have been amenorrhoeic for at least 1 year.

Exclusion criteria: participation in another study less than 30 days before the start of the study; moderate or severe osteoarthritis (Kellgren-Lawrence stage III or IV); rheumatoid arthritis or other chronic inflammatory disease affecting the target joint; secondary osteoarthritis; arthroscopic surgery or other major surgery of the target knee; major trauma of the target knee; intra articular injection of corticosteroids or symptomatic slow acting drugs of osteoarthritis (SYSADOA) in target knee in the past 3 months prior to the study; acute infection of the target knee in the last 6 months, or if the participants started any form of physiotherapy in the 3 weeks prior to the study; having a significant psychiatric disorder (including depression) or receiving antipsychotic medication; breastfeeding.

Baseline characteristics

Treatment group: 28% males; "average" age 54 (range 25 to 65) years; "average" BMI 27.3 (range 16.9 to 35.4) kg/m².

Control group: 36% males; "average" age 54 (range 30 to 65) years; "average" BMI 27.2 (range 20.7 to 37.2) kg/m².

Interventions	<p>Treatment: Pycnogenol® 50 mg pills 3x per day with meals for 12 weeks.</p> <p>Control: placebo that matched the test drug in terms of appearance; 3 pills per day with meals for 12 weeks.</p> <p>Route of administration: orally.</p> <p>Concomitant medication: participants could use NSAIDs or other analgesics prescribed prior to the start of the study and could change the dose and frequency of drug intake, but they had to report changes at each visit.</p>
Outcomes	<ul style="list-style-type: none"> • Symptom scores (pain; stiffness; ability to perform daily activity; total WOMAC score): collected at baseline and then every 2 weeks of treatment until the end of the study at week 14; measured by the WOMAC questionnaire (in Slovakian language) that rates pain, stiffness and ability to perform daily activity on a 5-point Likert scale. • Pain measured with a VAS "filled in by the patients each week during the whole study (14 weeks)"; where intensity of pain is rated where 0 = no pain and 100 = very severe pain. • Change in analgesic use: collected at baseline and then "at each visit" (assumed to be every 4 weeks); reported in % reduction or % increase. • Adverse effects: "Patients were asked every 2 weeks to report any unwanted or unusual effects". • Safety by means of basic biochemical parameters (glucose; uric acid; total cholesterol; HDL cholesterol; LDL cholesterol; triacylglycerol; high sensitivity CRP; gamma-glutamyl transferase; alkaline phosphatase; aspartate aminotransferase; alanine aminotransferase); collected at baseline, after three months of treatment and at the end of the study (week 14); fasting venous blood were drawn in the mornings and the serum were analysed by "standard biochemical procedures using the Hitachi 911 automatic analyser and kits, Roche, Switzerland".
Notes	<p>Funding source: "This study was supported by Horphag Research Ltd, partly by VEGA Grant No. 1/2294/05, 1/1157/04 and 1/3037/06 of Ministry of Education of Slovakia and Mind and Health, civil association."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The subjects were randomly allocated..." However, the randomisation method is not reported. After contacting the study authors we learned that "randomisation was done with the StatDirect program as 'allocate unpaired intervention control group' procedure".

Cisár 2008 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not enough information provided, simply states that intervention and placebo looked identical.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators involved in measuring clinical outcomes did not know the allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Data of all patients were evaluated in the intention-to-treat analysis." However, it is not described what the primary study authors mean with the term "intention-to-treat analysis" and how they handled the missing data from participants who were lost to follow-up. 6/50 participants were lost to follow-up from the treatment group and 13/50 from the control group - a big difference.
Selective reporting (reporting bias)	Unclear risk	Protocol not available. The study authors pre-specified study outcomes in the 'Methods' section and addressed these in the 'Results' section.
Other bias	Unclear risk	The study was, amongst others, funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Domanico 2015
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and Setting: not reported.</p> <p>Treatment duration: 6 months.</p> <p>Follow-up after the treatment period? None.</p> <p>Date of study: not reported.</p>
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Domanico 2015 (Continued)

Ethics approval: Institutional board approval was obtained from ethics committee of our institution. All procedures adhered to the tenets of the declaration of Helsinki.

Sample size calculation: not reported.

Method of diagnosis: people with type 2 diabetes suffering from mild to moderate NPDR.

Participants

Total number of participants randomised: 68 randomised; 34 allocated to antioxidant supplementation (Group A) and 34 to control (Group B)

Inclusion criteria: mild to moderate NPDR; absence of clinically significant DMO according to Early Treatment Diabetic Retinopathy Study protocol; HbA1c levels in the normal range ($\leq 6.0\%$); normal lifestyle based on the Mediterranean diet; mild to moderate physical exercise; abstinence from alcohol and tobacco; no systemic hypertension or dyslipidaemia; no excessive exposure to ultraviolet rays; treatment with 1000 mg metformin monotherapy 2x daily; and treatment with the same oral hypoglycaemic medication for at least 6 months prior to enrolment.

Exclusion criteria: coronary artery disease or family history of coronary artery disease, prior treatment with vitamin C or any other antioxidant dietary supplements, steroid or NSAIDs, history of acute or chronic infections, fever, cancer or organ failure, peripheral vascular disease, thrombotic events, urinary micro-albumin > 300 mg/day, other ocular pathologies, dioptric media opacities, history of intravitreal injection therapies and previous laser treatment, and a history of intraocular or vitreoretinal surgery within 6 months.

Baseline characteristics
Treatment group:

Gender: 19 (55.9%) female; 15 (44.1%) male.

Age, mean (SD): total group 58.29 (12.37) years; DRT subgroup 54.00 (9.68) years; wDRT subgroup 54.24 (14.72) years.

Condition indicators, mean (SD): HbA1c total group 5.8 (1.21)%; FORT-UF total group 349.88 (131.72) units; FORT-UF DRT subgroup 336.11 (112.97) units; FORT-UF wDRT subgroup 354.84 (139.66) units; FORT total group 2.64 (0.99) mmol/L peroxide; FORT DRT subgroup 2.55 (0.85) mmol/L peroxide; FORT wDRT subgroup 2.68 (1.05) mmol/L peroxide; CMT total group 223.97 (73.95) μ m; CMT DRT subgroup 323.33 (75.52) μ m; CMT wDRT subgroup 188.00 (24.14) μ m; mean BCVA total group 0.026 (0.032) log-MAR.

Condition duration, mean (SD): 9.2 (2.3) years.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Control group:

Gender: 16 (47.1%) female; 18 (52.9%) male.

Age, mean (SD): total group 62.29 (11.54) years; DRT subgroup 64.28 (8.07) years; wDRT subgroup 61.77 (12.36) years

Condition indicators, mean (SD): HbA1c total group 5.6 (1.13)%; FORT-UF total group 330.41 (119.44) units; FORT-UF DRT subgroup 295.71 (139.28) units; FORT-UF wDRT subgroup 339.40 (114.99) units; FORT total group 2.50 (0.91) mmol/L peroxide; FORT DRT subgroup 2.24 (1.05) mmol/L peroxide; FORT wDRT subgroup 2.57 (0.87) mmol/L peroxide; CMT total group 209.35 (56.97) μ m; CMT DRT subgroup 301.57 (63.32) μ m; CRT wDRT subgroup 185.44 (17.66) μ m; mean BCVA total group 0.030 (0.036) log-MAR.

Domanico 2015 (Continued)

Condition duration, mean (SD): 8.9 (2.5) years.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Overall:

Gender: difference between groups $P = 0.47$ with χ^2 test, males: 33, females: 35.

Age: range 40 to 79 years; difference between total groups $P = 0.08$ with an unpaired Student's t-test.

Condition indicators: HbA1c difference between groups $P = 0.42$ with Mann-Whitney test.

Condition duration: difference between groups $P = 0.38$ with Mann-Whitney test.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: normal lifestyle based on Mediterranean diet, no smoking, no alcohol, mild-moderate physical activity.

Family history: not reported.

Socio-economic status: not reported.

Interventions

Treatment: Diabereet 1x daily containing 50 mg Pycnogenol®; 30 mg vitamin E; and 20 mg Coenzyme Q.

Control: no treatment.

Route of administration: oral.

Concomitant treatment: single type of oral metformin monotherapy at a dose of 1000 mg 2x daily for the duration of the study and at least 6 months before enrolment.

Diet: Mediterranean diet.

Monitoring: "HbA1c was periodically monitored as an index of glycaemic control." Adherence monitoring not reported.

Outcomes

Data collected at baseline, 3 and 6 months.

- FORT to measure blood levels of reactive oxygen species with free oxygen radicals monitoring (FORM) and kit which is a colorimetric test which produces different degrees of colours directly related to the quantity of radical compounds and oxidative status of the blood sample; expressed in UF where 1 UF = 0.26mg/L.
- CMT "Spectral domain optical coherence tomography scans were performed with the Spectralis® HRA +OCT (software version 5.4.7.0, Heidelberg Engineering, Heidelberg, Germany), in a pattern of $20^\circ \times 15^\circ$ (5.8 mm $\times$ 4.3 mm) raster scans consisting of 19 high-resolution line scans, each composed of 50 averaged frame" where CMT was measured and expressed in μm .
- BCVA expressed in logMAR units.

Notes

Sponsorship source: none.

Authors' conflict of interest declarations: none declared.

Protocol or trial registry entry? not reported.

Domanico 2015 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised allocation was done with software. Baseline characteristics reported and appears similar across groups.
Allocation concealment (selection bias)	Unclear risk	No information is provided on measures taken to protect the randomisation sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	There was no blinding as the intervention group received Diaberet and the control group was untreated (no placebo). All outcomes were however assessed by objective scans/blood tests. Testing methods and standardisation is stated.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	While no explicit mention is made of blinding of outcome assessors the outcomes were objective and laboratory-based, minimising the risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up or discontinued the intervention during the study.
Selective reporting (reporting bias)	Unclear risk	No protocol available, but all pre-specified outcomes stated in the 'Methods' section was reported on in the 'Results' section.
Other bias	Unclear risk	Funding source not reported.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Drieling 2010
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and Setting: California; Stanford Prevention Research Center.</p> <p>Ethics approval: The study protocol was approved by the Stanford University Institutional Review Board, Stanford, California.</p>
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Drieling 2010 (Continued)

Treatment duration: 3 months

Follow-up after the treatment period? Not reported.

Method of diagnosis: Systolic blood pressure between 125 and 160 mm Hg.

Sample size calculation: After projecting 10% participant attrition over 12 weeks, a sample size of 130 participants (65 per study group) was calculated to provide 75% power for detecting an effect size of 0.5 (mean divided by standard deviation) at $\alpha=0.05$.

Participants

Total number of participants randomised: 130 participants; 64 participants in intervention group and 66 participants in the placebo group. 4 lost to follow-up from intervention group, 5 lost to follow-up from placebo group.

Inclusion criteria: overweight or obesity class I (BMI (calculated as weight in kg divided by height in m²) 25.0 - 34.9) and pre-hypertensive or hypertensive systolic blood pressure (125 - 160 mm Hg); not taking diabetes medication, hypertension medication, or any dietary supplements within the past month aside from the recommended daily value of multivitamins.

Exclusion criteria: fasting levels exceeding the following: 450 mg/dL for triglycerides, 126 mg/dL for blood glucose, or 200 mg/dL for LDL.

Baseline characteristics

Treatment group

Gender, n: females 25, males 39.

Age: mean (SD): 56.9 (9.8) years.

Condition indicators, mean (SD): systolic blood pressure 132.6 (10.9) mm Hg, diastolic blood pressure 78.6 (7.9) mm Hg.

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history, n (%): white 50 (78.1%); African American 2 (3.1%); Asian 7 (10.9%); Hispanic 5 (7.8%); other 0.

Socio-economic status, n (%): Grade 12 2 (3.1%); college 1 - 3 years 10 (15.6%); college 4 years or more 20 (31.3%); postgraduate 32 (50%).

Control group

Gender, n: females 23, males 43.

Age, mean (SD): 53.9 (12.0) years.

Condition indicators, mean (SD): systolic blood pressure 133.2 (10.9) mm Hg, diastolic blood pressure 79.9 (7.7) mm Hg.

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history, n (%): white 46 (69.7%); African American 2 (3.0%); Asian 14 (21.2%); Hispanic 3 (4.5%); other 1 (1.5%).

Drieling 2010 (Continued)

Socio-economic status, n (%): Grade 12 0; college 1 - 3 years 17 (25.8%); college 4 years or more 25 (37.9%); postgraduate 24 (36.4%).

Overall

No overall details were reported.

Interventions

Treatment: Flavangenol 50 mg 4x daily every morning containing OPC extracted from *Pinus maritime* and *Pinus maritimus* compounded with excipients of palatinit sugar, caramel, sucrose, fatty acid ester, and calcium stearate.

Control: placebo 4x daily every morning containing excipients of palatinit sugar, caramel, sucrose, fatty acid ester, and calcium stearate.

Route of administration: oral.

Concomitant treatment: participants were queried about their use of dietary supplements and medications at screening and were asked to report any changes.

Diet: participants were asked to refrain from changing their diet or losing weight; 3-day food records were administered at baseline and at 12 weeks to monitor changes in diet, particularly intake of antioxidant-rich foods.

Monitoring: adherence was tracked by counting returned tablets at 3, 6, and 12 weeks; tablet counting was conducted by pharmacy staff.

Outcomes

- Change in combined systolic and diastolic blood pressure: measured at rest in mm Hg where participants were seated for 5 minutes with their feet and ankles uncrossed before blood pressure was measured on their right arm; 3 measurements were taken with at least 1 minute elapsing between the 1st and 2nd and at least 3 minutes between the 2nd and 3rd.
- Change in systolic blood pressure: measured at rest in mm Hg where participants were seated for 5 minutes with their feet and ankles uncrossed before blood pressure was measured on their right arm; 3 measurements were taken with at least 1 minute elapsing between the 1st and 2nd and at least 3 minutes between the 2nd and 3rd.
- Change in diastolic blood pressure: measured at rest in mm Hg where participants were seated for 5 minutes with their feet and ankles uncrossed before blood pressure was measured on their right arm; 3 measurements were taken with at least 1 minute elapsing between the 1st and 2nd and at least 3 minutes between the 2nd and 3rd.
- High-sensitivity CRP: measured in nmol/L and used as an indication of systemic inflammation.
- Total cholesterol: fasting values measured in mg/dL.
- HDL cholesterol: fasting values measured in mg/dL.
- HDL cholesterol particle size: fasting values measured in nm.
- Lipoprotein(a): fasting values measured in nmol/L.
- LDL cholesterol: fasting values measured in mg/dL.
- LDL cholesterol particle size: fasting values measured in nm.
- Triglycerides: fasting values measured in mg/dL.
- BMI: measured in kg/m²; height measured to the nearest 10th of an inch using a wall-mounted stadiometer as baseline only; weight measured to the nearest 10th of a pound using a calibrated balance scale.
- Weight: measured to the nearest 10th of a pound using a calibrated balance scale.
- Fasting plasma glucose: fasting values measured in mg/dL.
- Insulin levels: fasting values measured in µU/mL.
- HbA1C: fasting values measured as %.
- Safety: liver function tests ALT and AST measured in U/L.
- Adverse events

All outcomes measured at baseline, 6 and 12 weeks, except adverse events which were reported at 6 and 12 weeks.

Driling 2010 (Continued)

Notes

Sponsorship source: this research was supported by a research grant from Toyo Shinyaku Co, Ltd, Saga, Japan. Toyo Shinyaku Co, Ltd provided study tablets (Toyo-FVG pine bark extract and placebo).

Authors' conflict of interest declarations: not reported.

Protocol or trial registry entry? clinicaltrials.gov Identifier: NCT00425945

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated, sex-stratified, block permutation lists were generated by the research analyst..."
Allocation concealment (selection bias)	Low risk	Randomisation lists were generated by the research analyst and provided to pharmacy staff, who dispensed study tablet A or study tablet B according to this list. "Pharmacy staff had no role in subject recruitment, assessment, or follow-up."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants and all study staff (including clinicians) were blinded until study completion." The placebo tablets contained exactly the same excipients as the experimental tablets, with the exception of the active ingredients of interest.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study staff, including clinicians, were blinded for the duration of the study. Outcomes were highly objective.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	While the loss to follow-up was approximately equal across study groups, half of the dropouts from the experimental arm left because of concerns related to the supplement, while none in the control arm left explicitly for that reason. The other participants in the experimental arm left for medical reasons which may or may not have been related to the intervention. Reason for loss to follow-up accounted for. Outcome data exclusion unclear. Smoking history not reported.
Selective reporting (reporting bias)	Low risk	Mention a pre-specified analysis plan in the study report. All outcomes as stated in the 'Methods' section were reported on in the 'Results'. Trial registry available and all primary and secondary outcomes were reported.
Other bias	Unclear risk	Study tablets were provided by Toyo Shinyaku Co, Ltd, a pharmaceutical company.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Duracková 2003

Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design</p> <p>Country and setting: Bratislava, Slovak Republic; outpatients of Department of Urology, Comenius University Hospital.</p> <p>Ethics approval by the Ethical Committee of the Comenius University Hospital, Slovak Republic.</p> <p>Treatment duration: 3 months.</p> <p>Follow-up: 1 month after end of treatment, at the end of month 4.</p>
Participants	<p>Total participants: 21 (13 in the treatment and 8 in the control group).</p> <p><u>Inclusion criteria</u>: men with ED as determined by IIEF-5 which consists of a questionnaire of 5 questions where 25 points is the maximum score.</p> <p><u>Exclusion criteria</u>: acute inflammatory cardiovascular disease; renal failure; hepatic insufficiency; endocrine abnormalities (testosterone deficit); psychiatric disorders; no concomitant use of other therapies for ED.</p> <p><u>Baseline characteristics</u></p> <p>Treatment group</p> <p>Age, "average" (SD): 47.8 (15.6) years.</p> <p>Condition indicators, "average" (SD): ED score (as measured by IIEF-5) 12.6 (1.1); duration of ED 22.75 (13.5) months.</p> <p>Condition indicators, n: diabetes mellitus, 9 out of 13; at risk for atherogenetic hypertension, 5 out of 13; ischaemia, 1 out of 13; smokers, 3 out of 13; stress, 8 out of 13.</p> <p>Control group</p> <p>Age, "average" (SD): 46.0 (13.8) years.</p> <p>Condition indicators, "average" (SD): ED score (as measured by IIEF-5) 11.3 (1.3); duration of ED 27.75 (21.0) months.</p> <p>Condition indicators, n: diabetes mellitus, 5 out of 8; at risk for atherogenetic hypertension, 7 out of 8; ischaemia, 5 out of 8; smokers, 3 out of 8; stress, 5 out of 8.</p>
Interventions	<p><u>Treatment</u>: Pycnogenol® 2x 20 mg pills 3x per day (total of 120 mg/day) for 3 months.</p> <p><u>Control</u>: placebo 2x pills 3x per day for 3 months.</p> <p>Route of administration: oral.</p> <p>Concomitant medication: none permitted (also no vitamin C and E supplements).</p>
Outcomes	<ul style="list-style-type: none"> Symptom scores: assessed using IIEF-5 questionnaire where normal function = 21 to 25 points, mild ED = 16 to 20 points, moderate ED = 10 to 15 points and severe ED = < 10 points". Total cholesterol levels: analysed by standard biochemical procedures using a Hitachi 911 automatic analyser (Roche, Switzerland); measured in mmol/L. LDL-cholesterol levels: analysed by standard biochemical procedures using a Hitachi 911 automatic analyser (Roche, Switzerland); measured in mmol/L.

Duracková 2003 (Continued)

- HDL-cholesterol levels: analysed by standard biochemical procedures using a Hitachi 911 automatic analyser (Roche, Switzerland); measured in mmol/L.
- LDL/HDL ratio.
- TAG levels: no detail reported.
- Antioxidant activity in the blood: determined by the FRAP method; measured in mmol of trolox/L; reported in percentage where 100% is the antioxidative activity of plasma before the trial.

Outcome data collected at baseline, at the end of the 1st and 3rd month as well as at the end of month 4 (1 month after end of treatment).

Notes

Funding source: "This study was supported partly by VEGA grants No. 1/8303/01, 1/9243/02 of Ministry of Education of the Slovak Republic and by Drug Research Institute, Modra, Slovak Republic."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Selection to the different groups was randomised." The randomisation method is not reported, but after contacting the study authors we learned that "selection into the Pyc or PL group was carefully randomised with help of Stat-Direct programme as 'allocate unpaired intervention-control groups' analysis".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were specified in the 'Methods' section.
Other bias	Low risk	Incomplete baseline characteristics, i.e. unclear whether the participants of the treatment and control groups were similar with respect to various important baseline characteristics. Through contacting the study authors we received the baseline characteristics for both groups. The study is unlikely to have been influenced by the reported funder.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.

Duracková 2003 (Continued)

Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Enseleit 2012

Study characteristics

Methods	<p>RCT.</p> <p>Design: Cross-over design.</p> <p>Country and setting: Clinic of Cardiology, CardiovascularCenter, University Hospital Zurich, Switzerland.</p> <p>Ethics approval: protocol approved by the Institutional Review Board (Ethics Committee of the Canton Zurich) and the Swiss Agency for Therapeutic Products (Swissmedic, Bern, Switzerland).</p> <p>Treatment duration: 8 weeks with a 2-week washout period.</p> <p>Follow-up: not reported.</p> <p>Method of diagnosis: people with CAD, documented by coronary angiography, nuclear imaging, or a positive stress test, on stable cardiovascular medication for at least 1 month.</p> <p>Sample size calculation: not reported.</p>
Participants	<p>Total number of participants randomised: 28 participants were randomised. 5 participants discontinued prematurely. 3 withdrew consent (unknown from which group). 1 participant from intervention group was hospitalized for acute decompensated heart failure and 1 participant in the placebo group was excluded after development of an itching rash.</p> <p><u>Inclusion criteria:</u> people with CAD, diagnosed as above and ≥ 18 years of age; written informed consent; recruited at the Clinic of Cardiology, Cardiovascular Center, University Hospital Zurich, Switzerland.</p> <p><u>Exclusion criteria:</u> acute myocardial infarction, unstable angina, stroke, or coronary intervention/revascularization procedure within 3 months prior to study entry; uncontrolled symptomatic congestive heart failure (New York Heart Association functional class $> II$) in the last 4 weeks prior to study entry; smoking, alcohol, or illicit substance abuse; uncontrolled blood pressure despite adequate therapy ($\geq 160/100$ mm Hg); symptomatic hypotension; ventricular tachyarrhythmias; any cardiomyopathy, untreated thyroid dysfunction, or adrenal insufficiency; renal failure (creatinine clearance using the Modification of Diet in Renal Disease formula $12,50$ mL/min); liver disease; chronic use of long-acting nitrates; oral or intravenous steroid therapy; insulin-dependent diabetes mellitus; anaemia (Hb < 10 g/dL); known hypersensitivity to Pycnogenol®; systemic inflammatory diseases (e.g. rheumatoid arthritis, Crohn's disease); known human immunodeficiency virus infection or active virus hepatitis; pregnancy or breast-feeding, women with childbearing potential without adequate contraception; malignancy (unless healed or in remission > 5 years); recipient of any major organ transplant (e.g. lung, liver, heart) or renal replacement therapy and the participation in another study within the last month.</p> <p><u>Baseline characteristics</u></p> <p>Treatment</p> <p>Gender: not reported.</p>

Enseleit 2012 (Continued)

Age: not reported.

Condition indicators, mean (SD): fibromuscular dysplasia 5.3 (2.6)%; glyceryl trinitrate 18.4 (5.4)%; 24h systolic blood pressure 125.8 (8.7) mm Hg; 24h diastolic blood pressure 75.0 (7.0) mm Hg; office systolic blood pressure 129.9 (12.5) mm Hg; office diastolic blood pressure 77.4 (6.8) mm Hg; office heart rate 58.3 (8.3) bpm; CRP 1.52 (1.37) mg/L; lipoprotein-associated phospholipase A2 315.89 (23.5) ng/mL; asymmetric dimethylarginine 0.47 (0.11) uM; symmetric dimethylarginine 0.47 (0.13) uM; endothelin-1 1.20 (0.36) ng/L; platelet adhesion 3.84 (2.0)%; soluble vascular cell adhesion molecule 869 (232) ng/mL; soluble intercellular adhesion molecule 284 (90) ng/mL; CD40 ligand 0.54 (1.11) ng/mL; total antioxidant capacity 10.12 (1.65) uM; oxidised LDL 77.9 (119.0) ng/mL; 15-F2t-isoprostane 0.71 (0.09) pg/mL

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Control

Gender: not reported.

Age: not reported.

Condition indicators, mean (SD): fibromuscular dysplasia 5.4 (2.4)%; glyceryl trinitrate 19.5 (5.4)%; 24h systolic blood pressure 124.8 (9.7) mm Hg; 24h diastolic blood pressure 73.9 (7.5) mm Hg; office systolic blood pressure 130.1 (12.1) mm Hg; office diastolic blood pressure 78.9 (7.5) mm Hg; office heart rate 60.3 (12.3) bpm; CRP 1.63 (1.71) mg/L; lipoprotein-associated phospholipase A2 279.4 (20.4) ng/mL; asymmetric dimethylarginine 0.45 (0.12) uM; symmetric dimethylarginine 0.45 (0.12) uM; endothelin-1 1.23 (0.27) ng/L; platelet adhesion 3.2 (1.6)%; soluble vascular cell adhesion molecule 824 (265) ng/mL; soluble intercellular adhesion molecule 277 (91) ng/mL; CD40 ligand 0.54 (1.10) ng/mL; total antioxidant capacity 9.65 (2.72) uM; oxidised LDL 85.8 (155.4) ng/mL; 15-F2t-isoprostane 0.72 (0.09) pg/mL

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Overall

Gender, n (%): 19/23 (82.6%) male; 4/23 (17.4%) female.

Age, mean (SD): 63.1 (7.1) years, range 49 - 73 years.

Condition indicators, mean (SD): left ventricular ejection fraction 62 (10)%; all participants had stable CAD, 11 participants with one-vessel disease, 1 participant with 2 disease, and 11 participants with 3-vessel disease.

Condition duration: at least 1 month.

Nutritional status, mean (SD): BMI 27.3 (3.3) kg/m².

Comorbidities: not reported.

Enseleit 2012 (Continued)

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Interventions

Treatment: Pycnogenol® 200 mg daily.

Control: placebo, dose and frequency of use not reported.

Route of administration: not reported.

Concomitant treatment: optimal standard cardiovascular therapy "The patients were advised not to take their usual drugs in the morning of the examination day...medical therapy was unchanged throughout the study."; participants on concomitant medication were as follows: aspirin 100%; statin 87%; ACE-inhibitor/ARB 78%; beta blocker 74%; diuretics 35%; calcium-antagonist 17%; clopidogrel 17%; ezetimibe 17%; oral anti-diabetics 17%; marcoumar 4%; alpha-antagonist 4%.

Diet: not reported.

Monitoring: not reported.

Outcomes

- Flow-mediated dilatation-dependent vasodilation of the brachial artery: measured as % and calculated as maximal % increase in diameter from baseline by high resolution 10 MHz linear array transducer and a high resolution ultrasound system Siemens X300 (Siemens Switzerland).
- Flow-mediated dilatation-independent vasodilation of the brachial artery: measured as % and calculated as the % increase in vessel size from baseline after administering sublingual glycerol trinitrate (0.4 mg nitrolingual spray, Pohl-Boskamp, Germany).
- High-sensitivity CRP: analysed by using a Imulite 2002 high-sensitive immunoluminometric assay; measured in mg/L.
- Systolic ambulatory blood pressure: measured for 24 h while the participant is moving around and going about his/her normal routine; the 'Tracker NIBP 2' instrument was used and took readings every 15 minutes during the day and every 30 minutes during the night; participants asked to keep their arm still when the cuff was inflating, and to avoid physical exertion for the duration of the monitoring; measured in mm Hg.
- Diastolic ambulatory blood pressure: measured for 24 h while the participant is moving around and going about his/her normal routine; the 'Tracker NIBP 2' instrument was used and took readings every 15 minutes during the day and every 30 minutes during the night; participants asked to keep their arm still when the cuff was inflating, and to avoid physical exertion for the duration of the monitoring; measured in mm Hg.
- 15-F2t-Isoprostane: analysed from plasma using an Express EIA Kit 8-isoprostane enzyme immunoassay; measured in pg/mL.
- Total antioxidant capacity: analysed from plasma using the Abcam total antioxidant capacity kit, Cu ++ was reduced by plasma for 1.5h at room temperature before reduced Cu+ was chelated with a colorimetric probe and absorbance measured was at 570 nm; results are expressed as trolox equivalent according to a trolox standard curve; measured in µM.
- Glucose: measured in mmol/L.
- Total cholesterol: measured in mmol/L.
- HDL cholesterol: measured in mmol/L.
- LDL cholesterol: measured in mmol/L.
- Oxadised LDL cholesterol: quantitative detection of oxLDL from plasma using Bender Med Systems ELISA; measured in ng/mL.
- Triglycerides: collected at baseline, 8, 10 and 18 weeks; measured in mmol/L.
- Soluble cell adhesion molecules (soluble vascular cell adhesion molecule, soluble intercellular adhesion molecule, soluble CD40 ligand, endothelin-1): collected at baseline, 8, 10 and 18 weeks; quantitative detection from plasma using Bender Med Systems ELISA; measured in ng/mL.
- Liver functions (asymmetric dimethylarginine, symmetric dimethylarginine).
- Lipoprotein-associated phospholipase A2.
- Blood chemistry (Na, K, creatinine, Hb, Hk, ALT, AST)

Enseleit 2012 (Continued)

Outcome data collected at baseline, 8, 10 and 18 weeks.

Notes

Funding source: supported by an unrestricted grant of Horphag Research (UK) Ltd, London, UK.

Study date: not reported.

Authors' conflict of interest declarations: none declared.

Protocol or trial registry entry? ClinicalTrials.gov identifier: NCT00641758

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It is stated that participants were randomly assigned into 2 groups, but no detail is given on how the randomisation was performed.
Allocation concealment (selection bias)	Unclear risk	"For randomisation, an unpredictable allocation sequence was provided by external institutions, which were responsible for the blinding and labelling of the drugs." It is not clear whether the coding was sufficient to protect sequence generation and whether this above quote refers to blinding rather than allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study drug and placebo were prepared in identical capsules to ensure uniform appearance..." Blinding of patients and investigators. Blinding was ensured by packaging and labelling at an external institution (InterCoreNet, Zurich, Switzerland). Placebo and intervention was produced at Horphag Research (UK).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All investigators including ultrasonographers were unaware of the allocation procedure at any time."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data and reasons for attrition are provided. The reasons for attrition are judged unlikely to be related to the true outcome. No information on when participants dropped out, and whether participants who did not receive both treatments were excluded from analysis.
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes as stated in trial registry (NCT00641758) were reported on in the 'Results'.
Other bias	Unclear risk	Unsure what standard cardiovascular therapy entails; standard therapy might vary or include therapy that could influence/interact with effects of Pycnogenol®. The study was funded by Horphag Research (the manufacturer and holder of the Pycnogenol® registered trademark).
Was a paired analysis being used?	Unclear risk	Not sure whether paired analyses were performed.
Is the cross-over design suitable?	Low risk	Stable condition where no long-term follow-up is required. The cross-over design is suitable, given the low persistence of Pycnogenol® in the human body as well as the rapid consumption thereof in the presence of oxidants coupled with a 2-week washout period.
Are data of both periods available?	Unclear risk	Data for both periods are not available, but only the summarised data of within-patient changes between period 1 and period 2.
Was there no carry-over effect?	Low risk	"The carry-over effect was excluded using an unpaired Wilcoxon test of within-patient change from baseline including only the first period of treatment."

Enseleit 2012 (Continued)

Are the results comparable to those from parallel group trials?

Low risk

The authors cite a study by Araghi-Niknam et al. which demonstrated that Pycnogenol® had a positive effect on platelet function, as well as a study by Liu 2004c which found that the dosage of calcium channel blockers could be reduced in hypertensive patients using Pycnogenol®. Therefore, the results appear comparable with previous parallel group trials.

Farid 2007

Study characteristics

Methods

RCT.

Design: parallel group design.

Country and setting: Iran; Rheumatology Department of Mashhad Medical University.

Ethics approval by the ethical committee of Mashhad Medical University.

Treatment duration: 3 months.

No follow-up after end of treatment.

Participants

Total participants: 37 (19 in the treatment group and 18 in the control group).

Inclusion criteria: adults (25 - 65 years) with primary osteoarthritis in the knee (according to the American College Rheumatology criteria grade I or II); WOMAC pain subscale index of at least 40 at baseline; intermittent or constant pain in the target knee for at least 50% of the time in the last 3 months that required medical treatment in the form of COX-2 inhibitors or other NSAIDs on most days.

Exclusion criteria: secondary osteoarthritis; arthroscopy, surgery, or a joint injection of the target knee within the previous 6 months; prior history of knee joint replacement; any serious systemic disease; any other chronic inflammatory disease; use of any supplement apart from a multivitamin daily.

Baseline characteristics

Treatment group:

Gender: 11.1% males.

Age, mean (SD): 47.5 (7.4) years.

Condition indicators, mean (SD): BMI 22.7 (3.2) kg/m²; 38.9% participants had knee osteoarthritis grade I; NSAIDs or COX-2 inhibitors use 15.6 (4.3) days per month; pain WOMAC score 292 (101); stiffness WOMAC score 110 (66); physical function WOMAC score 997 (352); composite WOMAC score 1400 (482).

Condition duration, mean (SD): duration of disorder symptoms 3.8 (5.1) years.

Control group

Gender: 5.9% males.

Age, mean (SD): 48.9 (9.6) years.

Condition indicators, mean (SD): BMI 23.5 (2.8) kg/m²; 41.2% participants had knee osteoarthritis grade I; NSAIDs or COX-2 inhibitors use 14.8 (5.6) days per month; pain WOMAC score 301 (119); stiffness WOMAC score 120 (63); physical function WOMAC score 1042 (420); composite WOMAC score 1463 (552).

Condition duration, mean (SD): duration of disorder symptoms 4.5 (4.7) years;

Interventions

Treatment: Pycnogenol® 50 mg pills 3x per day for 3 months.

Farid 2007 (Continued)

Control: placebo-matched the test drug in terms of appearance 3x per day for 3 months.

Route of administration: oral.

Concomitant medication: COX-2 and other NSAIDs as medical treatment for pain in the target knee.

Outcomes	<ul style="list-style-type: none"> • Symptom scores (pain; stiffness; physical function; composite WOMAC score): collected at baseline and then after 30, 60 and 90 days of treatment; measured by the WOMAC index which consists of a total of 24 visual analogue scales. • Use of concomitant medication (NSAIDs and COX-2): collected after 30, 60 and 90 days of treatment; participants were asked to keep a diary of medication usage (frequency and dose); data are reported as change in the number of pills per participant per month. • Participants' treatment compliance: collected after 30, 60, and 90 days of treatment; measured by means of pill counting. • Clinical adverse events: collected after 30, 60 and 90 days of treatment; volunteered reporting by participants or data are extracted by questioning. • Safety by means of biochemical parameters (fasting blood glucose; ALT; AST; urea; creatinine; complete blood count; haemoglobin levels; hematocrit levels): collected at baseline and after 90 days of treatment; assessed by the clinical laboratory of Mashhad Medical School.
Notes	<p>Funding source: "This research was supported by Horphag Research, Inc which also provided the supplement and placebo pills."</p> <p>Title: the claim made about stiffness in the title of this study is not reflected in the results.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...patients...were allocated randomly to either..." However, the randomisation method is not reported. After contacting the study authors we learned that "patients eligible for the study were numbered from 1 to 40. These numbers were divided to Group A and B according to random numbers table by statistician."
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not enough information reported. Just states intervention and placebo were identical in appearance.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 out of 19 participants lost to follow-up from the treatment group and 1 out of 18 from the control group.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were specified in the 'Methods' section
Other bias	Unclear risk	<p>The study was funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.</p> <p>It is reported in the article that "analysis was performed according to the intention-to-treat principle. A per protocol analysis was also conducted". After</p>

Farid 2007 (Continued)

asking the study authors how they handled the data of the 2 missing participants and how they dealt with the intention-to-treat principle they responded: "As we didn't analyse this study according to the intention to treat principle, so we can't report something more". This is confusing and we judged the risk of bias to be unclear.

Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Hosseini 2001a

Study characteristics

Methods	<p>RCT.</p> <p>Design: cross-over design (no washout period).</p> <p>Country and setting: Iran; Allergy Clinic of Mashhad University of Medical Sciences</p> <p>Ethics approval by the Human Subjects Committee of Mashhad University of Medical Sciences, Mashhad, Iran.</p> <p>Treatment duration: 4 weeks per arm.</p> <p>No follow-up after end of treatment.</p> <p>Sample size calculation: not reported.</p>
Participants	<p>Total participants: 26 enrolled; 22 completed the 1st period and 19 completed the 2nd period.</p> <p><u>Inclusion criteria</u>: adults (18 - 60 years old) with asthma according to the American Thoracic Society criteria; baseline FEV₁ should be 30 to 75% of predicted normal value, with an increase in FEV₁ of > 15% of pretreatment value after 2 puffs of a beta-adrenergic agonist.</p> <p><u>Exclusion criteria</u>: emphysema, bronchitis, renal, hepatic, cardiac, or endocrine disease; pregnant women and women of childbearing potential; NSAIDs use (including aspirin); vitamin supplement use; unwilling to exclude wine from their diet during the study period.</p> <p><u>Baseline characteristics</u></p> <p>Gender, n (%): 10 out of 22 males (45.5%).</p> <p>Age, mean (range): 32 (18 - 50) years.</p> <p>Duration of disorder, mean (range): 8 (1 - 16) years.</p>

Hosseini 2001a (Continued)

Interventions	<p><u>Treatment</u>: Pycnogenol® 1 mg/lb body weight/day (maximum 200 mg/day) for 4 weeks.</p> <p><u>Control</u>: placebo pills for 4 weeks.</p> <p>Route of administration: oral.</p> <p>Concomitant medication: usual medications could be used except for glucocorticoids, leukotriene antagonists, multivitamins, aspirin and any other NSAIDs.</p>
Outcomes	<ul style="list-style-type: none"> • Symptom scores: measured by means of a symptom severity scale where 1 = mild intermittent, 2 = mild persistent, 3 = moderate persistent, and 4 = severe persistent. • Pulmonary function (% predicted FEV₁; FEV₁/FVC): measured by means of spirometry. • Cysteinyl-leukotrienes C₄, D₄, and E₄ levels; assayed in triplicate with the use of a Cayman Chemical Cysteinyl-Leukotriene Enzyme Immunoassay Kit (Ann Arbor, MI); expressed in pg/mL. • Adverse experiences: all symptoms that were not observed to be present at baseline were recorded as "adverse experiences"; it is not reported whether the participants or investigators or both recorded the symptoms. <p>Outcome data collected at baseline, at the end of the 4th week (after treatment with either the test drug or placebo) and at the end of the 8th week (after 4 weeks on the remaining treatment option).</p>
Notes	Funding source: the test drug and placebo was a "kind gift" of Cognis Corporation (Kankakee, IL). The study was also funded by Arizona Foundation and other unspecified grants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomly assigned to receive Pycnogenol® ...or placebo pills..." However, the randomisation method is not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not clear how many participants included in the analysis. In total, 7 out of 26 participants were lost to follow-up of which 4 were from the 1st period and 3 from the 2nd period. Furthermore, it is not reported whether the analysis of this cross-over trial was based on the 1st period data only, or both.
Selective reporting (reporting bias)	Unclear risk	Protocol not available. The study authors pre-specified study outcomes in the 'Methods' section and addressed these in the 'Results' section.
Other bias	Unclear risk	The intervention was provided at no cost by Cognis Corporation, a manufacturer of pharmaceutical as well as nutrition and health ingredients.
Was a paired analysis being used?	Low risk	"Paired two-tailed t-test", "Friedman measures analysis of variance on ranks", "student-Newman-Keuls".

Hosseini 2001a (Continued)

Is the cross-over design suitable?	Low risk	Yes, asthma is a stable condition not requiring long-term follow-up.
Are data of both periods available?	Unclear risk	Not reported.
Was there no carry-over effect?	Unclear risk	There was no wash-out period between the treatment and control periods; no tests were performed for assessing period effect, treatment-period interaction, or carry-over effect.
Are the results comparable to those from parallel group trials?	Unclear risk	There is one included parallel group design RCT on asthma. However, the participants in that trial were children between 6 and 18 years old. We cannot compare that results with the results of this cross-over trial on asthmatic adults (18 to 60 years old).

Hosseini 2001b
Study characteristics

Methods	<p>RCT.</p> <p>Design: cross-over design (no washout period).</p> <p>Country and setting: Tucson, Arizona, USA; setting not reported.</p> <p>Ethics approval by the Institutional Review Board of the University of Arizona, United States of America (USA).</p> <p>Treatment duration: 8 weeks per arm, after a 1 week run-in period. During the run-in period all participants took placebo pills.</p> <p>No follow-up after end of treatment.</p>
Participants	<p>Total participants: 11.</p> <p><u>Inclusion criteria:</u> non-smokers with mild hypertension (stage I) who complied fully to take the provided placebo pills during the run-in period; blood pressure measured 3x in sitting participants after a 15-minute rest should give a systolic blood pressure of between 140 and 159 mm Hg, and/or diastolic blood pressure between 90 and 99 mm Hg.</p> <p><u>Exclusion criteria:</u> taking antihypertensive medication; taking NSAIDs, including aspirin; use of tobacco; taking any vitamin supplements other than 1 multivitamin tablet daily.</p> <p><u>Baseline characteristics</u></p> <p>Gender: 63.6% males.</p> <p>Age, mean (SD): 50.3 (9.3) years.</p>
Interventions	<p><u>Treatment:</u> Pycnogenol® 4x 50 mg pills per day (encouraged to be taken in the morning) for 8 weeks.</p> <p><u>Control:</u> 4x placebo pills per day (encouraged to be taken in the morning) for 8 weeks.</p> <p>Route of administration: oral.</p> <p>Concomitant medication: permitted, but not specified.</p> <p>Diet: participants were asked to exclude wine from their diets for the duration of the study.</p>

Hosseini 2001b (Continued)

Outcomes

- Blood pressure (systolic and diastolic): collected at baseline (data from run-in period and week 0 combined), and then at the end of week 7 and 8 as well as at the end of week 15 and 16; the results of week 7 and 8 as well as of week 15 and 16 were combined to produce the final result after each period; measured in triplicate in a sitting position after a 15-minute rest; measured in mm Hg.
- Participants' treatment compliance: collected after the 1 week run-in period as well as after week 8 and week 16; measured by means of pill counting.
- Thromboxane B2 levels: collected at baseline and then at the end of week 7 and 8 as well as at the end of week 15 and 16; the results of week 7 and 8 as well as of week 15 and 16 were combined to produce the final result after each period; assayed in triplicate by Neogen Corporation (Lexington, KY) thromboxane B2 enzyme-linked immuno-absorbent assay (ELISA) kit; measured in ng/mL.
- Adverse events: not reported when collected, assumed to be after each 8-week arm; data collected by questioning participants.
- Safety by means of blood tests (liver function enzymes): collected at baseline and then at the end of week 7 as well as at the end of week 15 and 16; the results of week 7 and the combined results of week 15 and 16 were used for the final result after each period.

Notes

Funding source: "The Pycnogenol® pills and placebo were obtained from the Cognis Corporation (La-Grange, Illinois)." The study was "supported by a grant from Horphag, Inc".

Reason given for lack of washout period: "...we have previously shown that Pycnogenol®'s effects on platelet aggregation in smokers disappeared three days after the cessation of its use."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...randomised using a statistical formula prepared by the Biostatistics department..."
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were specified in the 'Methods' section.
Other bias	Unclear risk	The study was funded by 2 companies involved in selling pine bark extract ingredients.
Was a paired analysis being used?	Low risk	Yes. Paired t-test.
Is the cross-over design suitable?	Low risk	Yes, stable chronic condition requiring no long-term follow-up.

Hosseini 2001b (Continued)

Are data of both periods available?	Low risk	Not reported directly, but it is mentioned in the small print beneath the figures that "all 11 subjects data are analysed".
Was there no carry-over effect?	Unclear risk	There was no wash-out period between the treatment and control periods; no tests were performed for assessing period effect, treatment-period interaction, or carry-over effect.
Are the results comparable to those from parallel group trials?	Unclear risk	The same outcomes were not addressed.

Lau 2004
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: USA; recruited from the Pediatric Teaching Office of Loma Linda University Children's Hospital (California) and from local physicians' clinics.</p> <p>Ethics approval by the Loma Linda University Institutional Review Board for Human Studies, California, USA.</p> <p>Treatment duration: 3 months after a 1 week run-in period. It is not reported what the purpose of the run-in period was.</p> <p>No follow-up after end of treatment.</p> <p>Sample size calculation: not reported.</p>
Participants	<p>Total participants: 60 (30 in each group).</p> <p><u>Inclusion criteria:</u> children (6 - 18 years old) with mild to moderate asthma as defined by the American Thoracic Society criteria; 50% - 85% of predicted normal FEV₁ and increase of 12% or more after 2 puffs of rescue inhaler; a severe asthma attack or lower respiratory tract infection in 1 month before the start of the study.</p> <p><u>Exclusion criteria:</u> unable to co-operate with pulmonary function and/or laboratory tests; unable to follow instructions; unable to swallow pills; taking steroids or NSAIDs.</p> <p><u>Baseline characteristics</u></p> <p>Treatment group:</p> <p>Gender: 57% males.</p> <p>Age, mean (range): 14 (6 - 16) years.</p> <p>Condition indicators: mean (SE) % predicted PEF 69.7 (1.7); number of participants using rescue inhaler as needed 30; number of participants using oral medication (Accolate) 5.</p> <p>Control group:</p> <p>Gender: 60% males.</p> <p>Age, mean (range): 14 (7 - 18) years.</p>

Lau 2004 (Continued)

Condition indicators: mean (SE) % predicted PEF 69.9 (1.6); number of participants using rescue inhaler as needed 30; number of participants using oral medication (Accolate) 4.

Interventions	<p><u>Treatment</u>: Pycnogenol® 1 mg/lb body weight in 2 divided dosages daily for 3 months.</p> <p><u>Control</u>: placebo "indistinguishable" from the test drug; 2x per day for 3 months.</p> <p>Route of administration: oral.</p> <p>Concomitant medication: not reported whether specific medication was not permitted; however, change in use of rescue inhaler (albuterol) and oral medication Accolate (zafirlukast; leukotriene receptor antagonist) were reported as outcomes in the trial, therefore we know that these specifically were permitted.</p>
Outcomes	<ul style="list-style-type: none"> • PEF rate: measured with an Assess Peak Flow Meter (Respironics, Cedar Grove, New Jersey); participants were asked to take 3 PEF rate readings every evening and record the best on a diary card which was collected by an investigator at the end of each month of treatment; values are expressed in % predicted values. • Symptom scores: participants reported their scores every evening on diary cards which was collected by an investigator at the end of each month of treatment; measured on a scale from 0 to 4 where 0 = no symptoms, 1 = mild symptoms - not disturbing, 2 = moderate symptoms - somewhat disturbing, 3 = severe symptoms - interfered with daily activities, 4 = very severe symptoms - could not go anywhere. Results were also expressed in the number of participants with a decrease in symptom scores. • Use of oral medication (Accolate): recorded by participants every evening in their diary cards and collected by an investigator at the end of each month of treatment; measured as number of participants using oral medication. • Use of rescue inhaler (albuterol): recorded by participants every evening in their diary cards and collected by an investigator at the end of each month of treatment; recorded as the number of puffs per 24 hours as well as the number of participants off the rescue inhaler. • Participants' treatment compliance: bottles of capsules collected and the capsules counted to ascertain compliance; reported in terms of % compliance. • Urinary leukotriene C₄/D₄/E₄ levels: assayed in duplicate by an enzyme immunoassay system (Biotrak, Amersham Pharmacia Biotech, United Kingdom); unit of measurement is pg/mL. • Adverse side effects: not reported when it was collected, assumed to be during the 3 months treatment period via their diary cards; reported by participants. <p>Outcome data collected at baseline and then at the end of the 1st, 2nd and 3rd month of treatment (compliance and adverse effects not measured at baseline).</p>
Notes	<p>Funding source: "This study was supported by the Chan Shun International Foundation, San Francisco, CA, and Horphag Research, Geneva, Switzerland."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Sixty patients were randomised so that..." However, the randomisation method is not reported.
Allocation concealment (selection bias)	Unclear risk	The treatment was "identified by pre-assigned codes prepared by an independent laboratory that was not involved in conducting the experiment". It is not clear whether the coding was sufficient to protect sequence generation and whether this above quote refers to blinding rather than allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo were identical in appearance.

Lau 2004 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded. Assignment codes were only broken after completion of the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported whether all randomised participants completed the study, i.e. whether data from all participants for all outcomes were collected.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were specified in the 'Methods' section.
Other bias	Unclear risk	The study was, amongst others, funded by Horphag Research. This company is the holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Ledda 2010
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: not reported.</p> <p>Ethics approval: not reported.</p> <p>Treatment duration: 6 months.</p> <p>Follow-up after the treatment period? No.</p> <p>Method of diagnosis: The "erectile domain" of the IIEF questionnaire was used, and a score of 11 to 17 was considered as having mild to moderate ED.</p> <p>Sample size calculation: not reported.</p>
Participants	<p>Total number of participants randomised: 124 men, 111 completed the 6-month study period (13 were lost to follow-up); 54 in the Prelox group and 57 in the control group completed the study, respectively.</p> <p><u>Inclusion criteria:</u> aged 30 to 50 years; mild to moderate ED, IIEF scores $\geq 11 - 17$; stable sexual partnership in past 6 months.</p>

Ledda 2010 (Continued)

Exclusion criteria: testicular maldescent, varicocele, orchitis, globozoospermia, disturbances of semen deposition (hypospadias), endocrine, hypogonadism abnormality, psychiatric disorders, testicular tumours, infections, prostatitis or another prostate problem, UTIs during the past 3 months, handicaps or anatomical problems affecting erections, surgery within the past 3 years, diabetes mellitus, severe hypertension (diastolic ≥ 90 mm Hg; systolic ≥ 150 mm Hg), renal failure, hepatic insufficiency, having a clinical condition requiring medical treatment; using out-of-prescription drugs, alcohol or narcotics.

Baseline characteristics

Treatment group

Gender: 100% men.

Age, mean (SD): 44.5 (4.0) years.

Condition indicators, mean (SD): IIEF score 15.2 (6.6); total plasma testosterone: 15.9 (2.3) nmol/L.

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities, mean (SD): systolic blood pressure 138.9 (8.0) mm Hg; total cholesterol 212 (12) mg/dL.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Control group

Gender: 100% men.

Age, mean (SD): 44.0 (4.0) years.

Condition indicators, mean (SD): IIEF score 15.1 (7.0); total plasma testosterone: 16.9 (2.4) nmol/L

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities, mean (SD): systolic blood pressure 137.0 (6.8) mm Hg; total cholesterol 205 (18) mg/dL.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Overall

Gender: 100% men.

Age: not reported.

Condition indicators: "...testosterone levels...within the normal range...were comparable in both groups..."; erectile function score was "comparable at baseline", mild to moderate ED with IIEF scores of 11 - 17.

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: blood pressure not statistically significantly different; total cholesterol not reported on statistical significance; "Fasting blood glucose was at healthy levels in all patients."; blood chemistry did not differ across groups.

Ledda 2010 (Continued)

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Interventions

Treatment: Prelox[®], 4x tablets daily, 2 tablets in the morning after breakfast and another 2 after dinner, each tablet containing 20 mg Pycnogenol[®], 700 mg L-arginine aspartate.

Route of administration: oral.

Control: placebo, where dicalcium phosphate replaced active components; dose and frequency of intake not reported.

Route of administration: not reported.

Concomitant treatment: no participants were on antihypertensive medication before enrolment or during the trial; none had cholesterol medication either.

Diet: standard dietary suggestions for weight loss, decreased sodium intake and moderate exercise were provided.

Monitoring: not reported.

Outcomes

- IIEF erectile function domain: Question 1 to 5 and 15 of the IIEF questionnaire with a maximum score of 30 where a lower score indicates more severe ED.
- IIEF orgasmic function domain: Question 9 and 10 of the IIEF questionnaire with a maximum score of 10 where a lower score indicates poorer orgasmic function.
- IIEF sexual desire domain: Question 11 and 12 of the IIEF questionnaire with a maximum score of 10 where a lower score indicates poorer sexual desire.
- IIEF Intercourse satisfaction domain: Question 6 to 8 of the IIEF questionnaire with a maximum score of 15 where a lower score indicates poorer intercourse satisfaction.
- IIEF overall satisfaction domain: Question 13 and 14 of the IIEF questionnaire with a maximum score of 10 where a lower score indicates poorer overall satisfaction.
- Diastolic and systolic blood pressure.
- Haematology (haemoglobin, hematocrit, leukocytes, erythrocytes, thrombocytes).
- Blood chemistry (glucose, total cholesterol, uric acid, albumin, AST, ALT, GGT).
- Total plasma testosterone: quantified using the ACS 180 testosterone immunoassay (Bayer Health Care, Leverkusen, Germany).

Outcome data collected at baseline and at six months (no information on haematology or blood chemistry).

Notes

Funding source: supported by a grant from Horphag Research UK Ltd.

Study date: not reported.

Authors' conflict of interest declarations: "Frank Schönlau is an employee of Horphag Research; Gianni Belcaro is a study investigator for Horphag Research."

Protocol or trial registry entry? Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block allocation was randomly generated by a computer program.

Ledda 2010 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Corresponding placebo tablets were matched for colour, size, shape and weight; tablets were oblong, blue and film-coated, 330x745 and 1100 mg..."; Investigators were not informed about the identity of tablets until after evaluation of the study results."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were participant-reported, and participants were blinded as described above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	After randomisation, 13 participants were lost to follow-up. However, it is unclear how many per group and what the reasons for this were.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry entry reported. Outcomes were pre-specified in the article's 'Methods' section and addressed in the 'Results'.
Other bias	Unclear risk	Limited baseline characteristics per group were reported. However, erectile function scores at baseline were reported and that was similar across groups. The study was funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Liu 2004a
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: China (Beijing and ShanDong); recruited from 3 hospital outpatient departments.</p> <p>Ethics approval: not reported.</p> <p>Treatment duration: 12 weeks.</p> <p>No follow-up after end of treatment.</p>
Participants	Total participants: 77 participants.

Pine bark (*Pinus spp.*) extract for treating chronic disorders (Review)

Liu 2004a (Continued)

Inclusion criteria: diabetes mellitus type II according to the WHO 1999 diagnostic criteria.

Exclusion criteria: pregnant or breastfeeding; use of vitamin supplements during the study period.

Baseline characteristics

Treatment group (34 participants)

Gender: 52.9% males.

Age, median (IQR): 54 (45 - 62) years.

Condition indicators, median (range): weight 69 kg (64 - 77); height 168 cm (162 - 172).

Control group (43 participants)

Gender: 60.5% males.

Age, median (range): 58 (47 - 66) years.

Condition indicators, median (IQR): weight 68 kg (62 - 75); height 165 cm (162 - 171).

Interventions

Treatment: Pycnogenol® 100 mg for 12 weeks.

Control: placebo for 12 weeks.

Route of administration: oral.

Concomitant medication: conventional oral antidiabetic medication as needed was permitted.

Outcomes

- Blood glucose levels: collected at baseline and then in 2-week intervals until the end of the 12-week treatment; measured enzymatically; measured in mmol/L and reported as % decrease relative to pre-treatment levels.
- HbA1c levels: collected at baseline and then at the end of the 1st, 2nd and 3rd month of treatment; measured by HPLC and reported as % decrease relative to pretreatment levels.
- Endothelin-1 levels: collected at baseline and then at the end of the 1st, 2nd and 3rd month of treatment; measured by immuno-assay and reported as % decrease relative to pretreatment levels.
- 6-keto-prostaglandin F1_α levels: collected at baseline and then at the end of the 1st, 2nd and 3rd month of treatment; measured by immuno-assay and reported as % decrease relative to pretreatment levels.
- Change in nitrogen monoxide levels: assumed to be collected at baseline and then at the end of the 1st, 2nd and 3rd month of treatment; measured by colorimetric assay for nitrite/nitrate and reported in nmol/L.
- Unwanted effects: not reported when it was collected, assumed to be during the 12-week study period; it is not reported whether the participants or investigators recorded the symptoms.
- Safety (vital signs, ECG, blood urea nitrogen, electrolytes and creatinine concentration): collected at baseline and again at the end of the 12-week treatment period.

Notes

Funding source: Horphag Research.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The treatment groups were randomised in respect to gender, age and anti-diabetic medication." However, the randomisation method is not reported. We got in touch with the contact author but unfortunately he could not obtain this information from the principal investigator.
Allocation concealment (selection bias)	Unclear risk	Not reported.

Liu 2004a (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were specified in the 'Methods' section.
Other bias	Unclear risk	The study was funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Liu 2004c
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: China (Beijing and ShanDong); recruited from 3 hospital outpatient departments.</p> <p>Ethics approval: not reported.</p> <p>Treatment duration: 12-weeks after a 2-week run-in period. During the run-in period all participants received placebo instead of their usual medication to confirm diagnosis.</p> <p>No follow-up after end of treatment.</p>
Participants	<p>Total participants: 58 participants.</p> <p><u>Inclusion criteria</u>: hypertension according to the "hypertension inventory" of the WHO 1999; complied fully to take the provided placebo during the run-in period.</p>

Liu 2004c (Continued)

Exclusion criteria: pregnant or breastfeeding; malignant hypertension; use of vitamin supplements during the study period.

Baseline characteristics

Treatment group: (28 participants)

Gender: 53.6% males.

Age, median (IQR): 56 years (46 - 64).

Condition indicator, median (IQR): weight 69 kg (64 - 76); median "stature" 168 cm (162 - 172).

Control (30 participants)

Gender: 60% males.

Age, median (IQR): 58 years (46 - 66).

Condition indicator, median (IQR): weight 68 kg (62 - 75); median "stature" 164 cm (160 - 171).

Interventions

Treatment: Pycnogenol®; 100 mg; for 12 weeks.

Control: placebo; for 12 weeks.

Route of administration: oral.

Concomitant medication: after the 2-week run-in period on placebo, all participants were put on a calcium antagonist (nifedipine, sustained release tablets, 5 mg, Shanghai Pharmaceuticals Co, Ltd.) The dose nifedipine was 20 mg (frequency not reported, assumed to be daily) initially, and then adjusted at 2-week intervals (either reduced or increased with 5 mg) as needed to sustain "stable blood pressure".

Outcomes

- Nifedipine dose needed to control blood pressure: collected at the end of the 12-week treatment period; measured in terms of the number of participants using a specific dose nifedipine (10 mg, 15 mg, or "20 + 30 mg"). This outcome is dependent on the blood pressure measurements during the treatment period since the nifedipine dose was adjusted every 2 weeks as needed to sustain "stable blood pressure". Blood pressure was collected at baseline and then at 2 week intervals until the end of the 12-week treatment period; measured at 08:30 a.m., 90 minutes after intake of medication, after which they rested for 15 minutes followed by a measurement in the sitting upright position; the mean of the 2 measurements was recorded.
- Endothelin-1 levels: collected at baseline and then at the end of the 1st, 2nd and 3rd month of treatment; quantified in plasma by radio-immunoassay (Beijing Huaying Biological Technology Company); reported as percentage decrease relative to pretreatment levels.
- 6-keto-prostaglandin F_{1α} levels: collected at baseline and then at the end of the 1st, 2nd and 3rd month of treatment; quantified in plasma by radio-immunoassay (Beijing Huaying Biological Technology Company); reported as percentage decrease relative to pretreatment levels.
- Angiotensin II levels: collected at baseline and then at the end of the 1st, 2nd and 3rd month of treatment; quantified in plasma by radio-immunoassay (Beijing Huaying Biological Technology Company); reported as percentage decrease relative to pretreatment levels.
- Nitrogen monoxide levels: collected at baseline and then at the end of the 1st, 2nd and 3rd month of treatment; analysed using a calorimetric assay for nitrite/nitrate (Nanjing Jiancheng Biological Technology Company); measured in nmol/L.
- Unwanted effects. not reported when it was collected, assumed to be during the 12-week treatment period; reported by participants.
- Safety by means of determining electrolytes, creatinine, and blood urea nitrogen levels: collected at baseline and again at the end of the 12-week treatment period, no further detail reported.
- Safety by means of measuring heart rate: collected at baseline and then at 2-week intervals until the end of the 12-week treatment period; no further detail reported.

Notes

Funding source: Horphag Research.

Liu 2004c (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised to receive either...". However, the randomisation method is not reported. We got in touch with the contact author but unfortunately he could not obtain this information from the principal investigator.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were specified in the 'Methods' section.
Other bias	Unclear risk	The study was funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Panahande 2019
Study characteristics

Methods	RCT. Design: parallel group design. Country and setting: Shariati Hospital affiliated with Tehran University of Medical Sciences in Iran.
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Panahande 2019 (Continued)

Ethics approval: "Ethics committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.VCR.REC.1395.1408) has approved the protocol. The study was also registered in the Iranian Registry of Clinical Trials (IRCT2015071123153N1)."

Treatment duration: 12 weeks.

No follow-up after end of treatment.

Sample size calculation: "The sample size was determined based on Vanlint and Ried sample size formula and CTx1 was chosen as a key variable." This gave a sample size of 20 participants per group.

Participants

Total participants: 44 (22 in each group).

Inclusion criteria: postmenopausal women between 50 and 65 years old with osteopenia (BMD between -1 and -2.5 SD) and normal liver, thyroid and kidney function.

Exclusion criteria: morbid obesity (BMI ≥ 40); report of fractures during the study; unwillingness to continue the study; any visible side effects of supplements; severe hypovitaminosis D (serum 25-hydroxyvitamin D < 50 nmol/L); history of bone disease (Paget's disease, osteomalacia, etc); those suffering from serious medical conditions, including cancer, diabetes, kidney failure, liver disease, systemic inflammatory disease, degenerative joint diseases, and rheumatological disorders; gastrointestinal diseases, including celiac disease, chronic diarrhoea, ulcerative colitis, Crohn's disease, and gastric or duodenal ulcer or untreated gastrointestinal bleeding; history of surgery: ovariectomy, gastrectomy, intestinal bypass, and organ transplants; history of diseases or treatments that might influence bone remodeling: COPD, hyperparathyroidism, thalassaemia, and hemiplegia; taking medications that affect bone metabolism and having regularly consumed diuretics such as (Lasix and thiazides) anticonvulsants (phenytoin and phenobarbital), heparin, lithium, corticosteroids, cyclosporine, NSAIDs, hormone replacement therapy, bisphosphonates, and tobacco for at least 6 months in the past 2 years; motor disabilities; skeletal disorders; untreated psychiatric illnesses, such as psychosis, Alzheimer, and Parkinson; and unwillingness to accept randomisation.

Baseline characteristics

Treatment group

Age, mean (SD): 57.38 (0.97) years

Condition indicators, mean (SD): BMI 28.68 (5.6) kg/m²; BMD -1.87 (0.41) T-score; Ca intake 833.33 (315.17) mg/day; vitamin D intake 666.66 (1640.22) IU/day; 25-hydroxyvitamin D 26.34 (10.28) ng/mL; physical activity level 861.92 (262.65) metabolic equivalents/day.

Duration of the condition, mean (SD): menopause length 9.09 (4.89) years.

Control group

Age, mean (SD): 56.47 (3.64) years.

Condition indicators, mean (SD): BMI 28.23 (3.29) kg/m²; BMD -1.94 (0.4) T-score; Ca intake 868.42 (352.84) mg/day; vitamin D intake 678.94 (1720.65) IU/day; 25-hydroxyvitamin D 25.9 (10.34) ng/mL; physical activity level 854.5 (391.15) metabolic equivalents/day.

Duration of the condition, mean (SD): menopause length 7.21 (3.45) years.

Interventions

Treatment: Oligopin® 250 mg/day given as 5 capsules per day; 2 capsules after breakfast, 2 capsules after lunch and 1 capsule after dinner. "Each Oligopin® capsule contained 50 mg FMPBE that consisted of procyanidins (67–75%), catechin (4–10%), taxifolin (0.5–4%), taxifolin glucoside (3–8%), f glucoside (4–10%), gallic acid (0.1–1%), protocatechuic acid (0.5–3%), caffeic acid (0.5–3%), p-coumaric acid (0.3–2%), ferulic acid (1–5%), and other oligomers including monomeric and dimeric phenolic acids."

Control: placebo 250 mg/day medicinal starch given as 5 capsules per day; 2 capsules after breakfast, 2 capsules after lunch and 1 capsule after dinner; each capsule contains 50 mg medicinal starch.

Route of administration: oral.

Panahande 2019 (Continued)

Concomitant medication: not reported.

Diet: not reported.

Outcomes	<ul style="list-style-type: none"> Serum calcium, magnesium, phosphorus, parathyroid hormone, BAP, CTx1, ratio of CTx1/BAP, P1NP, receptor activator of nuclear factor k-B ligand and osteoprotegerin; collected at baseline and at 12 weeks; measured from fasting blood samples. 24-hour recall conducted at baseline, 8 and 12 weeks to assess usual dietary intake including calcium, calories and specific macro- and micronutrient content using Nutritionist Software Version IV. Physical activity levels collected at 8 weeks using International Physical Activity Questionnaire.
Notes	Funding source: "This study was supported by the Osteoporosis Research Center of Endocrinology and Metabolism Research Institute of Tehran University of Medical Sciences (grant 1395-03-103-2094)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation sequence generated is unclear.
Allocation concealment (selection bias)	Unclear risk	It is not clear how the randomisation sequence was protected from study personnel allocating participants to intervention or control.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and investigators. Intervention and control provided in identical capsules with green opaque coverage.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors. Outcomes were all objective.
Incomplete outcome data (attrition bias) All outcomes	Low risk	44 participants randomised, with 40 (90.9%) that completed the study. 1 woman in the control group dropped out as she was unwilling to continue with the study, while none in the intervention group dropped out for this reason. Also from the control group, 2 other participants discontinued due to personal reasons. 1 participant in the intervention group discontinued due to personal reasons.
Selective reporting (reporting bias)	High risk	Weight is listed as a secondary outcome in the trial registry IRC-T2015071123153N1, but is not reported in the paper. All other pre-specified outcomes in the registry are reported on in the 'Results' section.
Other bias	Unclear risk	The study is unlikely to have been influenced by the reported funder.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.

Panahande 2019 (Continued)

Are the results comparable to those from parallel group trials?	Low risk	Not applicable.
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Petrassi 2000

Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: not reported, assumed to be Italy; setting not reported.</p> <p>Ethics approval: not reported.</p> <p>Treatment duration: 2 months after a 2-week run-in period. During the run-in period participants were not allowed to take drugs acting on the cardiovascular system, diuretics, analgesics or anti-inflammatory compounds.</p> <p>No follow-up after end of treatment.</p>
Participants	<p>Total participants: 20 (10 in each group).</p> <p><u>Inclusion criteria</u>: participants with symptoms of CVI ("heaviness and subcutaneous swelling") and a venous blood pressure higher than 40 mm Hg.</p> <p><u>Exclusion criteria</u>: none reported.</p> <p><u>Baseline characteristics</u></p> <p>Treatment group</p> <p>Gender: 20% males.</p> <p>Age, mean (assumed SD): 47.7 (3.65) years.</p> <p>Control group</p> <p>Gender: 10% males.</p> <p>Age, mean (assumed SD): 36.7 (3.66) years.</p>
Interventions	<p><u>Treatment</u>: Pycnogenol® 100 mg 3x per day for 2 months.</p> <p><u>Control</u>: placebo (lactose) indistinguishable from the test drug 3x per day for 2 months.</p> <p>Route of administration: oral.</p> <p>Concomitant medication: during the 2-month treatment period participants were not allowed to take drugs affecting the cardiovascular system, diuretics, analgesics or anti-inflammatory compounds.</p> <p>Diet: a "standard diet" according to participants' energy needs was prescribed by a dietary service.</p>
Outcomes	<ul style="list-style-type: none"> Symptom scores (feeling of heaviness, swelling and evening oedema, localized or diffuse leg pain, night cramps, paraesthesiae): collected at baseline and then at the end of the 1st and 2nd month of treatment; assessed clinically using a "4-item scale" where 0 = absent, 1 = light, 2 = moderate, and 3 = severe; % participants showing disappearance of each symptom was also calculated and analysed. Ambulatory venous pressure*: collected at baseline and then at the end of the 1st and 2nd month of treatment; measured on each leg in a standing position after a 30-minute acclimatization period at room temperature (21 - 23 °C); measured in mm Hg.

Petrassi 2000 (Continued)

- Physician's judgement of efficacy and safety of the treatment*: collected at the end of the 2-month treatment period; assessed by a "semi-quantitative 4-point scale" where 1 = poor, 2 = moderate, 3 = good, and 4 = very good.
- Safety evaluated by means of biochemical tests (haematology, blood chemistry, hepatic functions, renal functions)*: collected at baseline and at the end of the 2-month treatment period; analysed by various laboratory tests; the unit of measurement for each blood test is specified in the article.
- Clinical tolerability*: collected during the study; not reported whether participants or investigator reported the "side effects".

Notes

Funding source: not reported.

Study design and results: after the 2-month treatment period 20 additional participants with CVI were added to the study without randomisation. They received the same Pycnogenol® or placebo (same dose) for the same time period (60 days). Results of many outcomes were pooled so that we could not extract the results from the randomised arm of the study separately. We reported all the outcomes, but indicated with an asterisk (*) those outcomes of which the results were pooled. We did not extract pooled results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...according to a computer-elaborated simple randomisation table."
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information reported. Only states intervention and placebo were identical in appearance.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For the outcomes of which the results were reported separately for the randomised and non-randomised phase of the study, all participants were included into the analyses.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were specified in the 'Methods' section. No results were reported for the outcomes 'change in night cramps' and 'change in paraesthesiae'.
Other bias	Unclear risk	Funding source not reported.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.

Petrassi 2000 (Continued)

Are the results comparable to those from parallel group trials?	Low risk	Not applicable.
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Reule 2017
Study characteristics

Methods	<p>RCT.</p> <p>Design: cross-over design.</p> <p>Country and setting: Germany; Clinical. BioTeSys GmbH, A Biotechnology company.</p> <p>Ethics approval: "This human study has been approved by the appropriate ethics committee (Landesaerztekammer Baden-Württemberg; internal reference number: F-2014-084) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments."</p> <p>Treatment duration: 4 weeks on experimental treatment or placebo, followed by a 8-week washout period before cross-over to treatment or placebo.</p> <p>Follow-up after the treatment period? No.</p> <p>Method of diagnosis: Mild to moderate hypertension (7-day mean of 130 to 149 mm Hg systolic blood pressure) and hyperhomocysteinaemia (≥ 10 $\mu\text{mol/L}$).</p> <p>Sample size calculation: "For sample size calculation an intervention effect of RHI = 0.3 with a standard deviation of 0.45 in comparison to placebo was assumed. A priori sample size calculation was performed, using the software g*power 3.1.2. with the following input details: Two tailed, effect size d = 0.7, Alpha error problem: $\alpha = 0.05$, actual power: 80%, correlation between groups: 0.5. Based on the calculations, the study should be performed with 20 subjects. Considering a drop-out rate of 20%, the study should be performed with 25 subjects."</p>
Participants	<p>Total number of participants randomised: N = 25; AbMIP-Placebo N = 12 and Placebo-AbMIP N = 13. No loss to follow-up.</p> <p><u>Inclusion criteria:</u> men and post-menopausal women; non-smoking, between 40 and 65 years old; BMI between 20 and 32 kg/m^2; homocysteine level ≥ 10 $\mu\text{mol/L}$; elevated systolic blood pressure (mean of 130 – 149 mm Hg measured during a period of 7 days before visit 1) but without requiring medical therapy.</p> <p><u>Exclusion criteria:</u> sleep apnoea; cardiovascular disease requiring medical intervention; additional chronic diseases such as diabetes mellitus, malignancy, kidney disease, liver disease, or psychosis; taking medication of nutritional supplements that could interfere with the study such as statins, blood pressure medication, vitamin B/folic acid, L-arginine, and Pycnogenol®; known HIV infection; hepatitis B or C infection; drug addiction; alcohol addiction.</p> <p><u>Baseline characteristics</u></p> <p>Not reported by treatment and control group.</p> <p>Overall</p> <p>Gender, n (%): 18/25 (72.0%) male.</p> <p>Age, mean (SD): total cohort 53.6 (7.3) years; men 51.6 (7.1) years; women 58.9 (4.9) years.</p> <p>Condition indicators, mean (SD): homocysteine levels - total cohort 13.61 (2.44) $\mu\text{mol/L}$, men 13.71 (2.49) $\mu\text{mol/L}$, women 13.37 (2.46) $\mu\text{mol/L}$; lnRHI - total cohort 0.57 (0.29), men 0.55 (0.27), women 0.63 (0.36); systolic blood pressure - total cohort 139.2 (5.7) mm Hg, men 140.1 (6.1) mm Hg, women 136.9</p>

Pine bark (*Pinus* spp.) extract for treating chronic disorders (Review)

Reule 2017 (Continued)

(3.8) mm Hg; diastolic blood pressure - total cohort 85.0 (3.9) mm Hg, men 84.6 (4.1) mm Hg, women 86.0 (3.2) mm Hg.

Condition duration: Not reported.

Nutritional status: no participants were taking nutritional supplements as per exclusion criteria.

Comorbidities, mean (SD): BMI: total cohort 25.3 (2.3) kg/m², men 25.5 (2.3) kg/m², women 25.1 (2.4) kg/m².

Lifestyle factors: non-smokers.

Family history: not reported.

Socio-economic status: not reported.

Interventions

Treatment: Verum 2x twice daily (4 tablets), together containing 2400 mg L-arginine, 80 mg Pyc-nogenol®, 45 µg vitamin K2, 10 mg alpha lipoic acid, 8 mg vitamin B6, 500 µg vita-min B12 and 600 µg folic acid.

Control: placebo tablets 2x twice daily (4 tablets) containing maize starch similar to the intervention in taste, smell, and appearance, but with maize starch replacing the active compounds.

Route of administration: oral.

Concomitant treatment: no participants were on blood pressure medication, treatment for cardiovascular disease, or statins.

Diet: No participants were on nutritional supplements which could interfere with the study, and participants were asked not to change their nutritional habits. Possible changes in nutritional habits were recorded at the end of each study phase. Consumption of alcohol was not permitted 48 hours prior to and during the study visit. The meal before each visit was standardised as bread with low-fat cream cheese and tomatoes or cucumber. Before the postprandial endothelial function test participants received a high-fat meal consisting of 200 mL cream with 30% fat content.

Monitoring: not reported; "Compliance rate for both study products was above 85%."

Outcomes

- InRHI-fasting: collected at four weeks (after the 1st treatment phase) and at 16 weeks (after the 2nd treatment phase); measured by post-to-pre-occlusion peripheral arterial tonometry signal ratio in occluded relative to control side, corrected for baseline vascular tone in occluded side; performed following overnight fasting, 20 minutes of acclimatisation at study site, and 10 minutes of supine rest with integrated EndoPAT 2000 Software at the fingertip with initial baseline assessment for 5.5 minutes followed by blood flow occlusion in non-dominant upper-arm for 5 minutes. After ischaemia dilatation of blood vessels was measured for 5 minutes.
- InRHI-post fat meal: (after the 1st treatment phase) and at 16 weeks (after the 2nd treatment phase); measured by post-to-pre-occlusion peripheral arterial tonometry signal ratio in occluded relative to control side, corrected for baseline vascular tone in occluded side; performed following overnight fasting, 20 minutes of acclimatization at study site, and 10 minutes of supine rest with the integrated EndoPAT 2000 Software at the fingertip with initial baseline assessment for 5.5 minutes followed by blood flow occlusion in non-dominant upper-arm for 5 minutes. After ischaemia dilatation of blood vessels was measured for 5 minutes. Test was performed before and 60 minutes after eating a high-fat meal consisting of 200 mL cream (30% fat content).
- Systolic blood pressure: measured daily by participants 7 days prior to visit 1 (start of 1st supplementation phase) to determine mean baseline value, again 7 days prior to visit 2 at 4 weeks (at the end of the 1st supplementation phase), again 7 days prior to visit 3 at 12 weeks (start of 2nd supplementation phase) and lastly 7 days prior to visit 4 at 16 weeks (end of 2nd supplementation phase); taken on the left arm, at home after at least 10 minutes of rest while in a sitting position with the 'boso medical, PC2' blood pressure device and recorded in the 7-day blood pressure diary; expressed in mm Hg.
- Diastolic blood pressure: measured daily by participants 7 days prior to visit 1 (start of 1st supplementation phase) to determine mean baseline value, again 7 days prior to visit 2 at 4 weeks (at the end of the 1st supplementation phase), again 7 days prior to visit 3 at 12 weeks (start of 2nd supplementation phase) and lastly 7 days prior to visit 4 at 16 weeks (end of 2nd supplementation phase); taken on the

Reule 2017 (Continued)

left arm, at home after at least 10 minutes of rest while in a sitting position with the 'boso medical, PC2' blood pressure device and recorded in the 7-day blood pressure diary; expressed in mm Hg.

- Triglycerides: collected at visit 1, visit 2 at 4 weeks (end of 1st supplementation phase), visit 3 at 12 weeks and visit 4 at 16 weeks (end of 2nd supplementation phase); measured as part of routine blood parameters and expressed in mg/dL.
- HbA1C: collected at visit 1, visit 2 at 4 weeks (end of 1st supplementation phase), visit 3 at 12 weeks and visit 4 at 16 weeks (end of 2nd supplementation phase); determined with HPLC using ethylenediaminetetraacetate (EDTA)-stabilised blood; expressed as %.
- Homocysteine: collected at visit 1, visit 2 at 4 weeks (end of 1st supplementation phase), visit 3 at 12 weeks and visit 4 at 16 weeks (end of 2nd supplementation phase); determined from serum using HPLC. Serum samples were centrifuged for exactly 30 minutes after sampling, transferred into aliquots, and stored below -70°C; expressed in µmol/L.
- ADMA: collected at visit 1, visit 2 at 4 weeks (end of 1st supplementation phase), visit 3 at 12 weeks and visit 4 at 16 weeks (end of 2nd supplementation phase); determined using an enzymatic test (Immunodiagnostik AG). Serum samples were centrifuged for exactly 30 minutes after sampling, transferred into aliquots, and stored below -70°C; expressed in µmol/L.
- No serious adverse events were reported. 1 participant reported mildly unpleasant tolerability due to bloating. "Routine blood parameters and adverse events did not indicate safety issues."

Notes

Funding source: "Dr. Loges & Co. GmbH sponsored the study and provided the study preparations."

Date of study: October 2014 to August 2015.

Authors' conflict of interest declarations: "The study execution, data analysis and reporting was done independently by BioTeSys GmbH (CR and CS). Data were completely blinded until final database lock. BG is employed by the sponsor of the study."

Protocol or trial registry entry: www.ClinicalTrials.gov identifier: NCT02392767.

The intervention was described under NCT02392767 as verum and in the paper as AbMIP (vasologes® protect, marketed by Dr Loges & Co. GmbH).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The study preparations were randomly assigned to the subjects (allocation ratio 1:1), according to the randomisation scheme generated by the sponsor (Dr. Loges & Co. GmbH, Germany), using the software "Multi- zufall" with block size 2 and stratified by gender."
Allocation concealment (selection bias)	Unclear risk	It is not clear how the randomisation sequence was protected during allocation. It is mentioned that study preparations were labelled, but insufficient information is provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind product assignment was ensured by labelled study preparations..." "Besides the subjects, all parties involved in the study performance were blinded until completion of the study..." The placebo tablets also corresponded to the intervention in terms of taste, smell, and appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Besides the subjects, all parties involved in the study performance were blinded until completion of the study..." Most outcomes were objective, laboratory-based tests. The only outcome with a measure of participant judgment/involvement was self-administered blood pressure measurement, but bias was mitigated here through participant blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"...all subjects finished the study according to the protocol."

Reule 2017 (Continued)

Selective reporting (re-reporting bias)	Unclear risk	No protocol could be found. However, all pre-specified outcomes stated in the 'Methods' section were reported on in the 'Results' section.
Other bias	Unclear risk	The funder is a company who sells natural preparations.
Was a paired analysis being used?	Low risk	"Changes within groups were analysed with paired test statistics (paired t-test or Wilcoxon matched-pairs signed-rank test)."
Is the cross-over design suitable?	Low risk	Stable condition with no requirement for long-term follow-up. The cross-over design is suitable, given the low persistence of Pycnogenol® in the human body as well as the rapid consumption thereof in the presence of oxidants coupled with a 8-week washout period. The authors also state that a treatment period of 4 weeks was chosen as it is long enough to detect potential effects, but short enough to minimise seasonal and other effects.
Are data of both periods available?	Unclear risk	Data for both periods are not available, but only the summarised data of within-patient changes between pre- and post-supplementation for the two study arms.
Was there no carry-over effect?	Low risk	"Before analysis, carry-over and period effects as well as baseline differences were checked for all parameters. No issues were found and consequently all parameters could be analysed using the statistical test procedure for cross-over trials."
Are the results comparable to those from parallel group trials?	Low risk	The authors state that published studies have demonstrated beneficial effects of various nutritional ingredients on early symptoms of cardiovascular disease, and cite several supporting studies.

Steigerwalt 2009
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: Italy; setting not reported.</p> <p>Ethics approval: not reported.</p> <p>Treatment duration: 2 months.</p> <p>Follow-up: 1 month after end of treatment, at the end of month 3.</p>
Participants	<p>Total participants: 46.</p> <p><u>Inclusion criteria</u>: moderate diabetic retinopathy as judged by existence of macular oedema and retinal swelling and presence of minor exudates and haemorrhages; diabetes mellitus type II for at least 4 years; well-controlled blood glucose levels by diet and oral antidiabetic medication (HbA1C < 7%).</p> <p><u>Exclusion criteria</u>: proliferative retinopathy, severe exudates, progressive haemorrhage and previous haemorrhage; any other ophthalmologic condition than diabetic retinopathy, including intraocular hypertension ≥ 21 mm Hg; those who had previous surgical or laser treatment or other invasive interventions; those with systemic hypertension requiring medical treatment.</p> <p><u>Baseline characteristics</u></p> <p>Treatment group (24 participants)</p>

Steigerwalt 2009 (Continued)

Gender: 58.3% males.

Age, mean (SD): 51.2 (5.4) years.

Condition indicators, mean (SD): HbA1C levels 6.9 (0.1) %.

Disorder duration, mean (SD): 6.4 (0.6) years.

Control group (22 participants)

Gender: 68.2% males.

Age, mean (SD) age: 52.3 (6.1) years

Condition indicators, mean (SD): HbA1C levels 6.8 (0.2) %.

Disorder duration, mean (SD): 6.5 (0.5) years.

Interventions	<p><u>Treatment</u>: Pycnogenol® 3x 50 mg tablets per day after breakfast for 2 months.</p> <p><u>Control</u>: placebo 3x tablets per day after breakfast for 2 months.</p> <p>Route of administration: oral.</p> <p>Concomitant medication: not reported, but control of blood glucose levels by oral antidiabetic medication was part of the inclusion criteria and thus permitted.</p>
Outcomes	<ul style="list-style-type: none"> Visual acuity as perceived by participants: "...subjectively perceived visual improvement..."; no detail reported. Visual acuity as measured by a professional: collected at baseline, after 2 months of treatment as well as 1 month after end of treatment; measured by means of the standard Snellen Chart. Retinal blood flow: collected at baseline, after 2 months of treatment as well as 1 month after end of treatment; measured quantitatively and noninvasively by colour duplex scanning; expressed in cm/s. Diastolic retinal blood flow relative to maximum systolic flow: collected at baseline, after 2 months of treatment as well as 1 month after end of treatment; "expressed as flow velocity at the central retinal artery". Retinal oedema score: collected at baseline, after 2 months of treatment as well as 1 month after end of treatment; measured on a scale ranged from 0 to 6 where 0 = no DMO, 2 = mild DMO, 4 = moderate DMO, and 6 = severe DMO. Retinal thickness: collected at baseline, after 2 months of treatment as well as 1 month after end of treatment; measured in μm by means of resolution ultrasound at 14 MHz from Esaote (Genoa, Italy); ultrasound was conducted 2x by 2 experienced physicians and the average of the 2 measurements is presented as % change from baseline set at 100%. Side effects: not reported how and by whom side effects were monitored.
Notes	<p>Funding source: Horphag Research.</p> <p>Contact author: the contact author is a director of Horphag Research, the company who manufacture Pycnogenol®.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were allocated to treatment groups using randomization by blocks. Block allocation sequences were created by using randomly generated numbers from a computer program."
Allocation concealment (selection bias)	Unclear risk	Not reported.

Steigerwalt 2009 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.
Selective reporting (reporting bias)	High risk	Protocol not available; not all outcomes reported in the 'Results' section were specified in the 'Methods' section.
Other bias	Unclear risk	The study was funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Theadom 2013

Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: Auckland, New Zealand; Participants' homes.</p> <p>Ethics approval: "This trial...received ethical approval from the Northern X Regional Ethics Committee."</p> <p>Treatment duration: 6 weeks (parallel-design section). Thereafter Group A received 6 weeks of placebo, 6 weeks of intervention followed by 4 weeks of placebo. Group B received 6 weeks of intervention, another 6 weeks of intervention followed by 4 weeks of placebo.</p> <p>Follow-up after the treatment period? Yes, group A and B received placebo for the last 4 weeks of the study which included an assessment at 12 weeks (end of intervention for group A and B) and at the end of the study at 16 weeks.</p> <p>Method of diagnosis: "Operational criteria for clinical identification included the presence of one or more of the following: (i) confusion or disorientation; (ii) loss of consciousness; (iii) post-traumatic amnesia; (iv) other neurological abnormalities (e.g. focal neurological signs, seizure, intracranial lesion)."</p>
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Pine bark (*Pinus* spp.) extract for treating chronic disorders (Review)

Theadom 2013 (Continued)

TBI was defined by the Glasgow Coma Scale score of 13 – 15 and post-traumatic amnesia < 24 h. Persons who had sustained mild traumatic brain injury 3 - 12 months prior to recruitment; and who were suffering persistent impairment of cognitive function (as defined by a Cognitive Failures Questionnaire score above 38).

Sample size calculation: "As this was a pilot study aimed at informing the design and sample size of the phase III trial, no sample size calculation was required and the convenience sample of 60 participants was driven by financial constraints."

Participants

Total number of participants randomised: 60 participants; 30 allocated to group A and 30 to group B. 3 participants withdrawn from group A, 1 participant lost to follow-up, 5 participants withdrawn and 1 participant contraindication in group B. 50 participants completed the study.

Inclusion criteria: persons who had experienced mild TBI aged 18 - 64 years; 3 to 12 months post-mild TBI as defined by the Glasgow Coma Scale score of 13 - 15 and post-traumatic amnesia for less than 24 hours; persistent cognitive difficulties as defined by a score above 38 on the Cognitive Failures Questionnaire (0.5 SD above the mean for healthy controls); and willingness to abstain from taking other antioxidant supplements, e.g. Gingko Biloba, Bacopa, or vitamins for the duration of the study.

Exclusion criteria: not fluent in English (this would have an impact on their ability to complete outcome assessments); inability to give informed consent; suffering from another medical condition which could influence the results of the study, e.g. advanced cancer, severe psychiatric conditions, significant substance abuse, diagnosed dementia, significant mental illness, diabetes requiring insulin therapy, severe agitation, or other severe conditions requiring nursing or hospitalisation; dependence on others for everyday activities before onset of TBI; pregnancy or nursing; known allergy to pine trees; and current use of anticoagulant medication.

Baseline characteristics

Treatment group

Gender, n (%): males 14 (46.67%); females 16 (53.33%).

Age, median (IQR width): 45 years (28).

Condition indicators, mean (SD): Cognitive Failures Questionnaire 61.27 (17.20); CVLT short-delay free recall -0.95 (1.14); CVLT long-delay free recall -0.86 (1.08); CVLT recognition -1.09 (1.31); CVLT mean total accuracy 84.51 (12.58)%; WAIS digit span 9.97 (2.51); WAIS letter number sequencing 8.28 (2.07); WAIS arithmetic: 8.00 (2.14); RPQ-3 total 4.36 (3.11); RPQ-13 total 27.48 (11.79); HADS anxiety 9.29 (4.40); HADS depression 6.00 (3.69).

Condition duration, mean (SD): time since injury 8.04 (2.46) months.

Nutritional status: supplement use 12 months prior 18 (60.0%); number of alcoholic drinks per week, median 1.00 (IQR width 3.0); overweight or obese: 14 (46.7%); fat-free mass, mean (SD) 36.63 (13.94) kg.

Comorbidities present, n (%): 9 (30.0%).

Lifestyle factors, n (%): current smokers 4 (13.3%).

Family history, n (%): ethnicity New Zealand European 21 (70%).

Socio-economic status, n (%): tertiary education and above 16 (53.33%); full-time paid work prior to injury 18 (60.0%); married or living with partner 15 (50.0%); living with others 18 (60.0%).

Control group

Gender, n (%): males 12 (40%), females 18 (60%).

Age, median (IQR width): 44 years (27).

Condition indicators, mean (SD): Cognitive Failures Questionnaire 59.34 (16.03); CVLT short-delay free recall -1.07 (1.01); CVLT long-delay free recall -0.98 (1.03); CVLT recognition -1.38 (1.44); CVLT mean total accuracy 81.18 (15.82)%; WAIS digit span 10.73 (2.35); WAIS letter number sequencing 8.70 (1.51); WAIS

Theadom 2013 (Continued)

arithmetic: 9.13 (3.24); RPQ-3 total 5.13 (2.80); RPQ-13 total 31.07 (8.08); HADS anxiety 10.45 (4.28); HADS depression 7.97 (3.56).

Condition duration, mean (SD): time since injury 7.1 (2.66) months.

Nutritional status: supplement use 12 months prior 18 (60.0%); number of alcoholic drinks per week: median (IQR width) 2.00 (3.0); overweight or obese: 14 (46.7%); fat-free mass: mean (SD) 38.67 (12.04) kg.

Comorbidities present, n (%): 11 (36.7%).

Lifestyle factors, n (%): current smokers 4 (13.3%).

Family history, n (%): ethnicity New Zealand European 25 (83.33%).

Socio-economic status, n (%): tertiary education and above 19 (63.3%); full-time paid work prior to injury 16 (53.3%); married or living with partner 19 (63.3%); living with others 20 (66.7%).

Details not reported for whole cohort.

Interventions

Treatment: Enzogenol[®], 2x capsules daily taken with a large glass of water in the morning (15 minutes before breakfast) each capsule contains 500 mg Enzogenol pine bark extract; consisting of proanthocyanidins (average 84%), taxifolin (1 to 2%), other flavonoids, phenolic acids and stillbenes (8% combined), including catechin, quercetin, myricetin, astrigenin, gallic acid, ferulic acid, caffeic acid, proto-catechuic acid, and carbohydrates (5 to 10%).

Control: placebo, 2x capsules daily taken with a large glass of water in the morning (15 minutes before breakfast) each capsule contains microcrystalline cellulose.

Route of administration: oral.

Concomitant treatment: Not reported, but "Possible contradiction with medication" cited as a reason for attrition in treatment group.

Diet: Not reported.

Monitoring: "Compliance was assessed on the percentage of capsules that had not been taken." "Overall adherence in taking the capsules as instructed was high, with 98% of prepared capsules taken over the course of the study." "Weekly phone calls between visits were made to monitor any side-effects and their duration/resolution."

Outcomes

- Cognitive Failure Questionnaire: participant-reported questionnaire which assesses everyday memory with a maximum score out of 100 where a higher score indicates more severe cognitive failure.
- CVLT short-delay free recall: investigator-reported questionnaire that assesses episodic memory where a lower score is beneficial; "raw scores on each subtest were transformed to standard scores to account for age and gender effects as specified in the manual". CVLT long-delay free recall: investigator-reported questionnaire that assesses episodic memory where a lower score is beneficial; "raw scores on each subtest were transformed to standard scores to account for age and gender effects as specified in the manual".
- CVLT recognition: investigator-reported questionnaire that assesses episodic memory where a lower score is beneficial; "raw scores on each subtest were transformed to standard scores to account for age and gender effects as specified in the manual".
- CVLT mean total accuracy: investigator-reported questionnaire that assesses episodic memory where a lower score is beneficial; "raw scores on each subtest were transformed to standard scores to account for age and gender effects as specified in the manual".
- WAIS digit span: investigator-reported questionnaire that assesses working memory where a higher score is beneficial; "raw scores for each subtest were then transformed to standard scores to account for age effect on cognitive ability, as specified in the respective WAIS-III or WAIS IV Administration and Scoring Manuals".
- WAIS letter number sequencing: investigator reported questionnaire that assesses working memory where a higher score is beneficial; "raw scores for each subtest were then transformed to standard scores to account for age effect on cognitive ability, as specified in the respective WAIS-III or WAIS IV Administration and Scoring Manuals".

Theadom 2013 (Continued)

scores to account for age effect on cognitive ability, as specified in the respective WAIS-III or WAIS IV Administration and Scoring Manuals".

- WAIS arithmetic: investigator-reported questionnaire that assesses working memory where a higher score is beneficial; "raw scores for each subtest were then transformed to standard scores to account for age effect on cognitive ability, as specified in the respective WAIS-III or WAIS IV Administration and Scoring Manuals".
- RPQ-3 total: participant-reported questionnaire which includes only the first 3 items of the questionnaire with a maximum score of 12 where a higher score indicates severe post concussion symptoms.
- RPQ-13 total: participant-reported questionnaire which includes items 4 - 16 of the questionnaire with a maximum score of 52 where a higher score indicates severe post concussion symptoms.
- HADS anxiety: participant-reported questionnaire that assesses mood disorders with a maximum of 21 where normal = score of 0 - 7, borderline normal = score 8 - 10 and abnormal = score 11 - 21.
- HADS depression: participant-reported questionnaire that assesses mood disorders with a maximum of 21 where normal = score of 0 - 7, borderline normal = score 8 - 10 and abnormal = score 11 - 21.

Relevant outcome data collected at baseline and 6 weeks.

Notes

Funding source: "The authors would like to acknowledge the financial support of ENZO Nutraceuticals and thank them for their assistance in providing the capsules for the study. The study was partially funded by ENZO Nutraceuticals who manufacture the Enzogenol supplement."

Study date: not reported.

Protocol or trial registry entry? "This trial was registered with the Australian New Zealand Clinical Trials Registry (ACT-RN12610000107022)..."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomised using computerized minimization randomisation software to receive either Enzogenol or matching placebo capsules."
Allocation concealment (selection bias)	Unclear risk	No explicit description of how the randomisation sequence was protected. The authors do state that the group allocation codes were held by the manufacturer until the end of data analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identically looking capsules containing the active ingredient or placebo were given in a white cardboard box which was marked 'Group A' or 'Group B'.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The authors state that the "...manufacturer of the supplement and placebo capsules held the group allocation codes until the data analysis had been completed so the research team remained blind to group allocation throughout the study." Most outcomes were objective, and subjective outcomes (such as depression and anxiety), which were assessed by the participants, also had low risk of bias as participants were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall attrition at 6 weeks was low in both trial arms, but the attrition in Group B was 10% compared to the 3% in Group A with one participant reporting potential contradiction with medication. Therefore, there might be systematic differences related to treatment causing differential attrition.
Selective reporting (reporting bias)	High risk	The registry entry for ACT-RN12610000107022 indicates that the Health Related Quality of Life Short Form SF36 was determined as a secondary outcome, but this outcome is not reported in the paper. Furthermore, the HADS was not listed as an outcome in the registry but is reported on in the paper. The study was also registered retrospectively.

Theadom 2013 (Continued)

Other bias	Unclear risk	This study was partially funded and the intervention capsules were provided by ENZO Nutraceuticals, the manufacturer of Enzogenol®.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

Trebatická 2006
Study characteristics

Methods	<p>RCT.</p> <p>Design: parallel group design.</p> <p>Country and setting: Slovakia, outpatients from the Department of Child Psychiatry at the Child University Hospital.</p> <p>Ethics approval by the Ethical Committee of the Children University Hospital, Slovakia.</p> <p>Treatment duration: 1 month.</p> <p>Follow-up: 1 month after end of treatment, at the end of month 2.</p>
Participants	<p>Total participants: 61.</p> <p><u>Inclusion criteria:</u> children with ADHD according to the International Statistical Classification of Diseases (ICD-10) which includes Hyperkinetic Disorder, Hyperkinetic Conduct Disorder, Attention Deficit without Hyperactivity; early onset of ADHD - chronicity by 6 to 7 years of age; ADHD symptoms for at least 6 months; general disposition as restless, inattentive, distractible and disorganized; disorders of cognitive function ("inattention, distractibility, difficulty to persist with any task, difficulty in selective process to information, disturbance of the executive functions, disturbance of motivation, effort and fortitude, visuospatial and memory disturbance"); disorders in control of activity ("inability to suppress activity, abnormality in control of activity, disorganisation and discontinuation of motoric activity"); impulsiveness ("acting without due reflection, engaging in rash and sometimes dangerous behaviour, disturbances or emotions and affectivity").</p> <p><u>Exclusion criteria:</u> situational hyperactivity; pervasive developmental disorders; schizophrenia; other psychotic disorders e.g. mood, anxiety, personality disorder as unsocial behaviour; personality change due to medical conditions; mental retardation; living in under stimulating environments; conduct disorders; tics; chorea and other dyskinesias; acute inflammatory diseases; renal disorders; cardiovascular disorders; diabetes mellitus.</p> <p><u>Baseline characteristics</u></p> <p>Treatment group (44 participants)</p>

Třebatická 2006 (Continued)

Gender: 84% males.

Age, "average" (range): 9.5 (6 - 14) years.

Condition indicators, average (SD): weight 35.28 (10.13) kg; BMI 17.41 (3.13) kg/m².

Control group: (17 participants).

Gender: 76.5% males.

Age, "average" (range): 8.8 (6 - 12) years.

Condition indicators, "average" (SD): weight 34.80 (10.05) kg; BMI 16.77 (2.61) kg/m².

Interventions

Treatment: Pycnogenol® 1 mg/kg body weight at breakfast daily for 1 month.

Control: placebo identical in shape and appearance as the test drug; the same number of tablets as the test drug per day for 1 month.

Route of administration: oral.

Concomitant medication: none were permitted - neither psychotropic drugs nor vitamins E and C supplements during the study period.

Diet: "Patients had a standard diet".

Outcomes

- Inattention symptom scores: measured by teachers and parents by means of 3 different scales (i) CAP Teacher Rating Scale, (ii) CTRS and (iii) CPRS; the score at baseline for the CTRS were put to 100%, the raw scores were reported for CAP and CPRS.
- Hyperactivity symptom scores: measured by teachers and parents by means of 3 different scales (i) CAP, (ii) CTRS, and (iii) CPRS; the score at baseline for the CTRS were put to 100%, the raw scores were reported for CAP and CPRS.
- Visual-motoric coordination and concentration: "weight score" % evaluated by psychologists and the score at baseline were put to 100%; "weight score" is the sum of values of 5 sub-tests of the Performance Scale for each participant, where a higher score represents a better psychological state.
- Urine catecholamine concentration (adrenaline, noradrenaline, dopamine): analysed by HPLC using electrochemical detection; expressed in %.
- Urine creatinine concentration: analysed using a commercial kit (DOT Diagnostics, Czech Republic) on Hitachi 911 automatic analyser (Roche); expressed in mmol/L.
- Total glutathione concentration, GSSG and GSH/GSSG: total glutathione and GSSG in whole blood was determined by gradient HPLC; GSH was calculated according to the following formula: [GSH] = [total glutathione] - (2 × [GSSG]).
- Level of oxidized purines represented by 8-oxo-7,8-dihydroguanine (8-oxoG) in lymphocytes: analysed by a Fpg-modified comet assay, levels of 8-oxoG were calculated from values of total damage to DNA using a calibration curve; expressed in 8-oxoG per 10⁶ guanine.
- TAS in plasma: analysed using a kit Randox (UK) on Hitachi 911 automatic analyser; the TAS concentration is expressed in mM of plasma using Trolox as a standard.
- Safety by means of basic biochemical parameters (bilirubin, glucose, gamma-glutamyl transferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, uric acid and lipid profile): analysed in plasma by standard biochemical procedures using the Hitachi 911 automatic analyser (Roche, Switzerland).
- Side effects.

Outcome data collected at baseline, after 1 month of treatment, as well as at the end of the 2nd month (1 month after end of treatment), except for side effects (not reported how these were monitored, we assumed that the parent, care-taker or teacher reported observed "side effects" to the investigator during the 2 months study period).

Notes

Funding source: "This study was supported by Horphag Res. Ltd. grant, partly by VEGA Grants No. 1/1157/04, 1/3037/06, Grant VV MVTs 03/LF of Ministry of Education of SR, by Drug Research Institute, Modra, SR and Mind&Health, civil association."

Trebatická 2006 (Continued)

Publication: 4 articles from 1 study are published, addressing different outcomes except for GSH/GSSG ratio and TAS which results were reported in 2 of the 4 publications.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers; ratio of Pycnogenol®:placebo was 5:2.
Allocation concealment (selection bias)	Low risk	After contacting the study authors we collected the following information: "Samples of PYC or Placebo (PL) were in identical boxes marked by numbers 1 - 61 and contents of box (PYC or PL) was not known to physician, psychologists or to analytical investigator. Boxes were allocated to patients according to ascending numbers of boxes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 out of 44 participants in the treatment group and 1 out of 17 in the control group were lost to follow-up.
Selective reporting (reporting bias)	High risk	No protocol available; not all outcomes reported in the 'Results' section were specified in the 'Methods' section.
Other bias	Unclear risk	The study was, amongst others, funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Unclear risk	Not applicable.
Was there no carry-over effect?	Unclear risk	Not applicable.
Are the results comparable to those from parallel group trials?	Unclear risk	Not applicable.

Valls 2016
Study characteristics

Methods	RCT.
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Pine bark (*Pinus* spp.) extract for treating chronic disorders (Review)

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Valls 2016 (Continued)

Design: cross-over design.

Country and setting: Spain; Community based.

Ethics approval: "The study was approved by the Clinical Research Ethical Committee of Hospital Universitari Sant Joan (HUSJ) de Reus (Spain) on May 13, 2013. Primary outcome data collection was conducted until 31 October 2014.

Treatment duration: 1 week run-in for dietary stabilisation followed by 5 weeks on experimental treatment or placebo, a 3-week washout period before cross-over to treatment or placebo for 5 weeks.

Follow-up after the treatment period? No.

Method of diagnosis: Stage 1 hypertension as defined by a systolic blood pressure ≥ 140 mm Hg and ≤ 159 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and ≤ 99 mm Hg.

Sample size calculation: "To detect differences between the two interventions (OP and placebo) of 10 mm Hg under an $\alpha = 0.05$ bilateral significance level, a power of 80% and assumption that the common standard deviation (SD) was 12.15 mm Hg, the sample size was 24 participants."

Participants

Total number of participants: 25 participants randomised (12 allocated to Oligopin and 13 to placebo first), 21 completed study. 1 participants withdrew consent and 3 excluded from analysis due to protocol deviation.

Inclusion criteria: men and women older than 18 years; suffering from stage 1 hypertension (systolic blood pressure ≥ 140 mm Hg and ≤ 159 mm Hg); with a diastolic blood pressure ≥ 90 mm Hg and ≤ 99 mm Hg; and not receiving blood pressure-lowering medication.

Exclusion criteria: BMI > 30 kg/m²; using anti-hypertensive medications; smoking; self-reported history of clinical cardiovascular disease, cancer, chronic kidney disease (or serum creatinine ≥ 1.7 mg/dL and 1.5 mg/dL for men and women, respectively), high cholesterol (LDL cholesterol ≥ 4.88 mmol/L), diabetes mellitus (or serum glucose ≥ 126 mg/dL); consumption of more than 14 drinks of alcoholic beverages per week; pregnant or nursing; or intending to become pregnant.

Baseline characteristics

Treatment group

Gender: not reported.

Age: not reported.

Condition indicators, mean (SD): systolic blood pressure 150.20 mm Hg (12.41); diastolic blood pressure 83.70 mm Hg (8.05).

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities: not reported.

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Control group:

Gender: not reported.

Age: not reported.

Condition indicators, mean (SD): systolic blood pressure 145.76 mm Hg (13.97); diastolic blood pressure 82.63 mm Hg (10.72).

Valls 2016 (Continued)

Condition duration: not reported.

Nutritional status: not reported.

Comorbidities, mean (SD): total cholesterol 5.44 mmol/L (0.65); LDL cholesterol 3.28 mmol/L (0.45); HDL cholesterol 1.58 mmol/L (0.25); triglycerides 1.27 mmol/L (0.72); apolipoprotein A-1 137.35 mg/dL (18.36); apolipoprotein B-100 101.26 mg/dL (15.02); ratio apolipoprotein B-100/A-1 0.75 (0.17).

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Overall

Gender: 7 (29.2%) females; 17 (70.8%) males "No significant differences were observed between intervention groups."

Age, mean (SD): 57.36 (11.25) years "No significant differences were observed between intervention groups."

Condition indicators, mean (SD): systolic blood pressure 149.65 (6.72) mm Hg; diastolic blood pressure 87.81 (7.67) mm Hg; glucose 96.13 (13.32) mg/dL; LDL cholesterol 132.13 (22.90) mg/dL; HDL cholesterol 56.46 (12.30) mg/dL; triglycerides 125.29 (64.54) mg/dL "No significant differences were observed between intervention groups."

Condition duration: not reported.

Nutritional status, mean (SD): weight 75.13 (12.82) kg; BMI 27.03 (2.81) kg/m²; waist circumference 94.81 (10.30) cm "No significant differences were observed between intervention groups."

Comorbidities, mean (SD): total cholesterol 5.56 mmol/L (0.77); LDL cholesterol 3.41 mmol/L (0.63); HDL cholesterol 1.55 mmol/L (0.29); triglycerides 1.36 mmol/L (0.74); apolipoprotein A-1 135.91 mg/dL (21.88); apolipoprotein B-100 105.82 mg/dL (21.22); ratio apolipoprotein B-100/A-1 0.81 (0.25).

Lifestyle factors: not reported.

Family history: not reported.

Socio-economic status: not reported.

Interventions

Treatment: Oligopin 2x daily, 1 capsule in the morning and 1 in the afternoon; each capsule contains 280 mg of total content consisting of 75 mg Oligopin, 175 mg maltodextrin, and 30 mg magnesium stearate.

Control: placebo 2x daily, 1 capsule in the morning and 1 in the afternoon; each capsule contains 280 mg of total content consisting of 250 mg maltodextrin and 30 mg magnesium stearate.

Route of administration: oral, as the product is water-soluble it could be taken before or after meals.

Concomitant treatment: None.

Diet: Stabilization diet containing 13% saturated fatty acids. During the intervention period participants followed the guidelines of the Adult treatment panel III and DASH diet.

Monitoring: "Compliance treatment monitoring was measured with a questionnaire filled-in by patients at a clinical interview in all visits, and the capsule bottles were returned afterwards. Consumption of >80% was considered an acceptable level of adherence." "...dietary compliance was monitored using 3 day dietary records and was confirmed in interviews with the dietician. In addition, the follow-up of the dietary recommendations was verified through a 24 hour record by trained dieticians in each follow-up visit."

Valls 2016 (Continued)

Outcomes

- Systolic blood pressure: measured 2x with a 1 minute interval following seated rest for 2 to 5 minutes; measurements were taken with an automatic sphygmomanometer (OMRON HEM-907); expressed in mm Hg.
- Diastolic blood pressure: measured 2x with a 1 minute interval following seated rest for 2 to 5 minutes; measurements were taken with an automatic sphygmomanometer (OMRON HEM-907); expressed in mm Hg.
- Triglycerides: measured in serum by standardised enzymatic automated methods in a PENTRA-400 autoanalyser; expressed in mmol/L.
- Total cholesterol: measured in serum by standardised enzymatic automated methods in a PENTRA-400 autoanalyser; expressed in mmol/L.
- LDL cholesterol: calculated using the Friedewald formula; expressed in mmol/L.
- Oxidized LDL: measured from EDTA plasma with an ELISA kit (Mercodia AB); expressed in U/L.
- HDL cholesterol: measured in serum by standardised enzymatic automated methods in a PENTRA-400 autoanalyser; expressed in mmol/L.
- Apolipoprotein A-1: measured in serum by standardised enzymatic automated methods in a PENTRA-400 autoanalyser; expressed in mg/dL.
- Apolipoprotein B-100: measured in serum by standardised enzymatic automated methods in a PENTRA-400 autoanalyser; expressed in mg/dL.
- Ratio apolipoprotein B-100/A-1.
- Weight: measured by body composition analyser with participants wearing lightweight clothing and no shoes; expressed in kg.
- BMI: weight measured by body composition analyser with participants wearing lightweight clothing and no shoes was divided by squared height measured by a wall-mounted stadiometer.
- Waist circumference: measured midway between the lowest rib and the iliac crest using an anthropometric tape; expressed in cm.
- High-sensitivity CRP: determined by standardised methods in a Cobas Mira Plus autoanalyser; expressed in mg/dL.
- Fasting glucose: measured in serum by standardised enzymatic automated methods in a PENTRA-400 autoanalyser; recorded in mg/dL.
- Insulin levels: measured using a specific ELISA kit (Mercodia AB).
- Nitrates: measured in serum using ELISA kits (R&D Systems); expressed in μ M.
- GSH: measured in heparin-lithium plasma by fluorometric method; expressed in nmol/mL.
- GSSG: measured in heparin-lithium plasma by fluorometric method; expressed in nmol/mL.
- Ratio GSH/GSSG: calculated as plasma GSH divided by plasma GSSG.
- Intracellular adhesion molecule-1: measured in serum using ELISA kits (R&D Systems); expressed in ng/mL.
- Vascular Cell Adhesion Molecule-1: measured in serum using ELISA kits (R&D Systems); expressed in ng/mL.
- E-selectin: measured in serum using ELISA kits (R&D Systems); expressed in ng/mL.
- Endothelin-1: measured in serum using ELISA kits (R&D Systems); expressed in pg/mL.
- Human angiotensin converting enzyme: measured in serum using ELISA kits (R&D Systems); expressed in ng/mL.
- Vascular endothelial growth factor: measured in serum using ELISA kits (R&D Systems); expressed in pg/mL.
- Adverse events: "There were no statistically significant differences between the 2 interventions with respect to the adverse events reported. The Oligopin product was well tolerated."

Outcome data collected after a run-in week, at the end of week 6 (end of 1st supplementation phase), at the end of week 9 (beginning of 2nd supplementation phase) and at the end of week 14 (end of 2nd supplementation phase)

Notes

Sponsorship source: "LES DÉRIVÉS RÉSIQUES TÉRPENIQUES (DTR, France) provided a grant to the Centre Tecnològic de Nutrició i Salut (Nutrition and Health Technology Centre; CTNS)-TECNIO CT09-1-0019, Reus (Spain). The funding bodies had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Logistic support, analysis and interpretation

Valls 2016 (Continued)

of the data were provided by CTNS; Hospital Universitari Sant Joan and Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, Reus (Spain)."

Date of study: February 2014 to October 2014.

Authors' conflict of interest declarations: none declared.

Protocol or trial registry entry: www.ClinicalTrials.gov identifier: NCT02063477

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomizations allocation sequence was generated by a statistician with SAS 9.2 (Cary, NC: SAS Institute Inc.) statistical software PROC PLAN. The statistician responsible for the randomisation did not participate in the study."
Allocation concealment (selection bias)	Low risk	The participant's sequence number and treatment assignment was allocated through an interactive electronic response system. Participants who met inclusion criteria were assigned a randomisation number from a randomisation list according to the chronological order in which they were enrolled.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The statistician responsible for generating the random sequence did not participate in the study. Blinding of participants and personnel was maintained through the use of placebo capsules which matched the active intervention in terms of appearance and other physical properties.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes were objective physical and chemical measurements, many of which were not performed at the patient interface. In addition, blinding of personnel who did come into contact with participants was adequately described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was more or less balanced across groups and there appears to be no differential attrition (based on the reasons for exclusion).
Selective reporting (reporting bias)	High risk	Endothelial function (listed as secondary outcome in the trial registry) was not reported on. Creatinine, transaminases, and albumin were also not reported; but these outcomes appear to be for ongoing study control.
Other bias	Unclear risk	The funder is a company which manufactures extracts from pine.
Was a paired analysis being used?	Low risk	Yes. "The efficacy analysis was evaluated by paired Student's t-test using employing the Base- line Observation Carried Forward (BOCF) approach on the Intention to Treat population (ITT)."
Is the cross-over design suitable?	Low risk	Stable condition with no requirement for long-term follow-up. The cross-over design is suitable, given the low persistence of Pycnogenol® in the human body as well as the rapid consumption thereof in the presence of oxidants coupled with a 3-week washout period.
Are data of both periods available?	Unclear risk	Data for both periods are not available, but only the summarised data of change from baseline and between treatments for each variable.
Was there no carry-over effect?	Low risk	3-week washout period. "Carryover effect determined by a period-by-treatment interaction was discarded." and "...possible interaction between the treatments and the treatment sequence (carryover effect) was discarded in all variables of the study."

Valls 2016 (Continued)

Are the results comparable to those from parallel group trials?

Low risk

Yes, a comparable parallel design trial is cited: [Belcaro 2013](#).

Zibadi 2008
Study characteristics
Methods

RCT.

Design: parallel group design.

Country and setting: Tucson, Arizona, USA; participants recruited through newspaper advertising.

Ethics approval by the institutional review board of the University of Arizona, USA.

Treatment duration: 12 weeks.

No follow-up after end of treatment.

Participants

Total participants: 48 (24 in each group).

Inclusion criteria: adults (40 - 75 years old) with type II diabetes and hypertension (baseline systolic blood pressure of 130 - 150 mm Hg); receiving ACE inhibitor for hypertension.

Exclusion criteria: type I diabetes; insulin treatment; use of supplements apart from 1 multivitamin daily; other major diseases e.g. cancer, asthma, heart failure; previous heart problems; pregnant or breast-feeding.

Baseline characteristics
Treatment group

Gender: 54% males.

Age, mean (SE): 61.3 (9.1) years.

Condition indicators, mean (SE): pretrial systolic blood pressure 139.0 (1.3) mm Hg.

Duration of condition, mean (SE): duration of diabetes mellitus 12.9 (11.6) years;

Control group

Gender: 58% males.

Age, mean (SE): 58.4 (11.5) years.

Condition indicators, mean (SE): pretrial systolic blood pressure 137.0 (1.0) mm Hg.

Duration of condition, mean (SE): duration of diabetes mellitus 14.2 (8.5) years.

Interventions

Treatment: Pycnogenol® 25 mg tablets 5x per day for 12 weeks.

Control: placebo that "matched" the test drug; for 12 weeks.

Route of administration: oral.

Concomitant medication: 1st generation sulphonylureas, 2nd generation sulphonylureas, metformin, and thiazolidinediones for glucose control were permitted.

Outcomes

- ACE inhibitor dosage: either left unchanged (equal to baseline dose), reduced by 50% or brought back to the baseline dosage until a "stable blood pressure" was obtained; adjustments were made every

Zibadi 2008 (Continued)

2 weeks after the systolic and diastolic blood pressure measurements were taken; expressed in % participants who could achieve blood pressure control with a 50% reduction in pretrial dose of ACE inhibitors at week 12. Blood pressure was measured at baseline and then at 2-week intervals up to week 12; measured in mm Hg on the left arm after a 10-minute rest; 3 repeated readings at an interval of 2 minutes were taken while sitting, and the average recorded; Korotkoff I and V were taken as the systolic and diastolic blood pressures respectively; dosage of ACE inhibitor was changed according to the systolic blood pressure measurements.

- Participants' treatment compliance: collected at the end of week 4, 8 and 12; unused pills were collected from participants and counted; reported in percentage.
- Endothelin-1 levels: collected at baseline and at the end of week 4, 8 and 12 after fasting for 8 hours; quantified in duplicate samples by ELISA (R&D Systems, Minneapolis, Minn); measured in pg/dL.
- LDL-cholesterol levels: collected at baseline and at the end of week 4, 8 and 12 after fasting for 8 hours; measured by the cholesterol esterase-cholesterol peroxidase coupling method; measured in mg/dL.
- HbA1C levels: collected at baseline and at the end of week 4, 8 and 12 after fasting for 8 hours; measured by inhibition of latex agglutination; reported in %.
- Blood glucose levels: collected at baseline and at the end of week 4, 8 and 12 after fasting for 8 hours; measured by double-enzyme assay with hexokinase and glucose-6-phosphate dehydrogenase using an Olympus AU640 analyser (Olympus America, Inc, Melville, New York); measured in mg/dL.
- Urinary albumin concentration: data at baseline and at the end of week 4, 8 and 12; the semi-qualitative screening dipstick test were used on spot urine samples; reported in mg/L.
- Adverse events: collected at "follow-up visits" (at the end of week 4, 8 and 12); collected from participants by means of questioning.
- Safety monitoring: heart rate and change in use of concomitant antidiabetic medication were monitored to make sure that it stayed the same and had no effect on the study outcomes as confounder.

Notes

Funding source: "This study was supported by a research grant of Horphag Research. This funding had no role in the collection, analysis, and interpretation of data or in the writing of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...subjects were randomly assigned...". However, the randomisation method is not reported. After contacting the study authors we learned that "subjects were randomly assigned, i.e. like a toss of a coin, using a computer program to receive either Pycnogenol® or placebo".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 out of 24 participants from the treatment and 2 out of 24 from the control group were lost to follow-up.
Selective reporting (reporting bias)	High risk	Protocol is available on the WHO's International Clinical Trials Registry Platform under the ID ISRCTN44961472. All outcomes specified in the protocol are addressed in the published article. However, there are outcomes in the article

Zibadi 2008 (Continued)

		that are not pre-specified in the protocol: ACE inhibitor dosage (as the indirect measurement of systolic blood pressure) and adverse events.
Other bias	Unclear risk	The study was funded by Horphag Research. This company is the manufacturer and holder of the Pycnogenol® registered trademark.
Was a paired analysis being used?	Low risk	Not applicable.
Is the cross-over design suitable?	Low risk	Not applicable.
Are data of both periods available?	Low risk	Not applicable.
Was there no carry-over effect?	Low risk	Not applicable.
Are the results comparable to those from parallel group trials?	Low risk	Not applicable.

ACE: angiotensin-converting enzyme; ADHD: attention deficit hyperactivity disorder; ALT: alanine transaminase; AST: aspartate transaminase; BAP: bone alkaline phosphatase; BCVA: best corrected visual acuity; BMD: bone mineral density; BMI: body mass index; BPH: benign prostatic hyperplasia; bpm: beats per minute; CAD: coronary artery disease; CAP: child attention problems; CMT: central macular thickness; COPD: chronic obstructive pulmonary disorder; COX-2 inhibitors: cyclo-oxygenase-2 inhibitors; CPRS: Conner's Parent Rating Scale; CRP: C-reactive protein; CTRS: Conner's Teacher Rating Scale; CTx1: C-terminal telopeptide of type I collagen; CVI: chronic venous insufficiency; CVLT: California Verbal Learning Test; DMO: diabetic macular oedema; DNA: deoxyribose nucleic acid; DRT: diffuse retinal thickening; D-ROM: direct reactive oxygen metabolites; ECG: electrocardiography; ED: erectile dysfunction; FEV₁: forced expiratory volume in 1 second; FORT: free oxygen radical test; FVC: forced vital capacity; FRAP: ferric reducing ability of plasma; FSFI: Female Sexual Function Index; GGT: gamma-glutamyl transferase; GSH: reduced glutathione; GSSG: oxidized glutathione concentration; HADS: Hospital Anxiety and Depression Scale; HbA1C: glycated haemoglobin; HDL cholesterol: high-density lipoprotein cholesterol; HPLC: high-performance liquid chromatography; IIEF-5: International Index of Erectile Function; InRHI: InReactive Hyperaemia Index; IPPS: International Prostate Symptom Score; IQR: interquartile range; LDF: laser Doppler flux; LDL cholesterol: low-density lipoprotein cholesterol; LUTS: lower urinary tract symptoms; NPDR: non-proliferative diabetic retinopathy; NSAIDS: non-steroidal anti-inflammatory drugs; OPC: oligomeric procyanidins; P1NP: procollagen type 1 N-terminal propeptide; PEF: peak expiratory flow; PSA: prostate specific antigen; PCO₂: amount of carbon dioxide in the blood; PO₂: amount of oxygen in the blood; QoL: quality of life; RCT: randomised controlled trial; RPQ: Rivermead Post-Concussion Symptoms Questionnaire; SD: standard deviation; SE: standard error; SF-36: Short Form-36; TAG: triacylglycerol; TAS: total antioxidant status; TBI: traumatic brain injury; UF: fort units; UTI: urinary tract infection; VAS: visual analogue scale; WAIS: Wechsler Adult Intelligence Scale; wDRT: without diffuse retinal thickening; WHO: World Health Organisation; WOMAC: Western Ontario and McMaster Universities.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aoki 2012	Not a RCT.
Belcaro 2005	Not a RCT.
Belcaro 2006b	Not a RCT.
Belcaro 2008b	Not a RCT.
Belcaro 2010	Not a RCT.

Study	Reason for exclusion
Belcaro 2011	Not a RCT.
Belcaro 2013	Not a RCT.
Belcaro 2014	Not a RCT.
Bottari 2013	Not a RCT.
Cesarone 2006a	Inappropriate control (supplement having antioxidant properties).
Cesarone 2006b	Not a RCT.
Cesarone 2006c	Not a RCT.
Cesarone 2010	Inappropriate control (not a supplement, placebo or no intervention).
Furumura 2012	Inappropriate control (two pine bark extracts dosages being compared).
Hosoi 2018	Not a RCT.
Hu 2015	Not a RCT.
Khurana 2013	Interventions given for less than 1 month.
Kobori 2015	Not a RCT.
Koch 2002	Inappropriate control (supplement having antioxidant properties).
Kohama 2004	Not a RCT.
Kohama 2007	Inappropriate control (gonadotropin-releasing hormone agonist medicine).
Kohama 2013	Not a chronic disorder (endometriosis).
Ledda 2018	Not a RCT.
Liu 2004b	Not a RCT.
Luzzi 2014	Not a RCT.
Luzzi 2016	Not a RCT.
Luzzi 2017	Not a chronic disorder (peri menopause).
Maia 2013	Not a RCT.
NCT03777683	Intervention given for less than 1 month.
Nemr 2010	Not a RCT.
Ni 2002	Not a RCT.
Nikolova 2007	Not a RCT.
Nishioka 2007	Not a chronic disorder (endothelium-dependent vasodilation).

Study	Reason for exclusion
Nuzum 2011	Not a RCT.
Riccioni 2004	Not a RCT.
Ryan 2008	Not a chronic disorder (cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population).
Sedighiyan 2018	Not a chronic disorder (participants obese women).
Smetanka 2019	Not a RCT.
Spadea 2001	Not a RCT (only half of the participants were randomised; results were not reported separately).
Stanislavov 2008	Not a RCT (quasi-randomised design).
Stanislavov 2014	Not a RCT (quasi-randomised design).
Stefanescu 2001	Not a RCT.
Suzuki 2008	Not a chronic disorder (dysmenorrhea).
Tenenbaum 2002	Intervention given for less than 1 month.
Thom 2005	Not a chronic disorder (looking at aging symptoms of the skin).
Vinciguerra 2006	Not a RCT.
Walter 2017	Not a RCT.
Wilson 2010	Prevention and not treatment.
Yang 2007	Not a RCT.

RCT: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

[Muchova 2014](#)

Methods	"Double blind randomised placebo controlled exploratory study". Target sample size: 20.
Participants	<u>Inclusion criteria</u> : men with diabetic retinopathy. <u>Exclusion criteria</u> : not reported.
Interventions	<u>Intervention</u> : Pycnogenol® 120 mg daily for 3 months. <u>Control</u> : placebo daily for 3 months.
Outcomes	<u>Primary outcomes</u> : not reported. <u>Secondary outcomes</u> : not reported.

Muchova 2014 (Continued)

Notes

Country: Slovakia

Status of study: Abstract published.

Sponsors and collaborators: "This study was supported by grant Ministry of Health 2012/8-ukba-8."

Characteristics of ongoing studies [ordered by study ID]

ACTRN12615000233527

Study name	Efficacy and Safety of Arborvitae Health and Wellbeing Supplement on the Blood Glucose Levels in Pre-Diabetic Participants.
Methods	"Phase IIa, randomised, double blind, placebo-controlled, parallel design clinical trial." Target sample size: 116.
Participants	<u>Inclusion criteria</u> : men and women above 18 years of age who demonstrate impaired fasting glucose from 6.1 - 6.9 mmol/L. <u>Exclusion criteria</u> : "Major illnesses that are deemed clinically significant; type II diabetes, anyone on anti-obesity medications, dietary supplements. Alcohol abuse. Commencing lifestyle interventions (dietary changes and increasing exercise duration/intensity)."
Interventions	<u>Treatment</u> : 50 mL of active components (containing aloe vera 1.75 mg/mL, papain 2.4 mg/mL, <i>Pinus pinaster</i> 2.6 mg/mL, sodium chloride 3 mg/mL) given by oral solution 2x daily for 12 weeks. <u>Control</u> : 50 mL of placebo (containing sodium chloride 3.0 mg/mL) given by oral solution 2x daily for 12 weeks.
Outcomes	<u>Primary outcomes</u> : impaired fasting glucose: collected at baseline, 4, 8 and 12 weeks. <u>Secondary outcomes</u> : quality of life survey questionnaire (SF-12v2): collected at baseline, 4, 8 and 12 weeks. The following blood samples were collected at baseline and at 12 weeks: impaired glucose tolerance, high-sensitivity CRP, HbA1c, LDL cholesterol, HDL cholesterol and triglycerides. The study assessed safety by measuring liver function tests, urea and a full blood count: collected at baseline and 12 weeks.
Starting date	March 2015.
Contact information	Dr Samantha Coulson; samantha_coulson@medlab.co; Medlab Pty Ltd 66 McCauley St, Alexandria NSW 2015.
Notes	Country: Australia. Status of study: Recruiting. Sponsors and collaborators: Arborvitae Health and Wellbeing Pty Ltd, 10 Gordon St, Bankstown NSW 2200, Australia.

IRCT20100408003664N21

Study name	The effect of pine bark extract supplementation on metabolic status, serum levels of ICAM-1 and VCAM-1 and anthropometric indices in type 2 diabetic patients with microalbuminuria.
Methods	Double-blind, placebo-controlled, parallel-design RCT. Target sample size: 46.
Participants	<u>Inclusion criteria</u> : people (males and females) with type 2 diabetes; diagnosed with diabetes for at least 1 year; women 30 - 50 years old and men 30 - 65 years old; microalbuminuria diagnosis based on ACR criteria in randomised urine specimen. <u>Exclusion criteria</u> : history of congestive heart failure, infectious diseases of the urine and prostate, acute febrile illness, uncontrolled blood pressure, glomerulonephritis, polycystic kidney disease, acute hyperglycaemia, hereditary nephropathy, on insulin therapy, smokers, extreme sports activity (24 hours before sample collection), pregnancy-lactation, use of any type of multivitamin supplement etc. during the study.
Interventions	<u>Treatment</u> : pine bark extract (Oligopin®) taken as 2x 50 mg capsules with a meal (breakfast and lunch) daily for 8 weeks, the product of Aramis Faramad Company. <u>Control</u> : 2x 50 mg capsules containing starch with meals (breakfast and lunch) daily for 8 weeks.
Outcomes	<u>Primary outcomes</u> : fasting blood sugar; HbA1C; HDL cholesterol; LDL cholesterol; total cholesterol; triglycerides; HOMA-IR; ICAM-1; serum insulin; VCAM-1. All primary outcomes were measured at baseline and at 2 months. No secondary outcomes specified.
Starting date	March 2018.
Contact information	Elham Navval Esfahlan; elham.navval@gmail.com; Tabriz University of Medical Science, Nutrition Faculty Attar Neyshabari, Golgasht Street, Tabriz, Iran.
Notes	Country: Iran. Status of study: recruiting. Sponsors and collaborators: not reported.

IRCT20140406017139N3

Study name	The effects of Oligopin supplementation on inflammatory and metabolic parameters in women with polycystic ovary syndrome.
Methods	Double-blind, placebo-controlled, parallel-design RCT. Target sample size: 80.
Participants	<u>Inclusion criteria</u> : women aged 18 to 40 years old with a polycystic ovary syndrome diagnosis according to Androgen Excess Society criteria, hyperandrogenism (hirsutism) or hyperandrogenemia (testosterone > 70ng/dL) and/or oligomenorrhoea (< 8 spontaneous menses per year) and/or polycystic ovarian morphology on ultrasound, normal prolactin levels, normal thyroid function, normal 17-OH progesterone levels, no evidence of androgenic hormone secretory tumours, no Cushing's syndrome or acromegaly.

IRCT20140406017139N3 (Continued)

	<p><u>Exclusion criteria:</u> oral contraception or steroid hormones for 1 month before study begin, medications that could modify the metabolism for 1 month before study begin.</p>
Interventions	<p><u>Treatment:</u> Oligopin® (50 mg capsule) after lunch, 1x daily for 12 weeks.</p> <p><u>Control:</u> placebo after lunch, 1x daily for 12 weeks.</p> <p>Route of administration: oral.</p>
Outcomes	<p><u>Primary outcomes:</u> fasting blood sugar; HbA1C; HDL cholesterol; LDL cholesterol; total cholesterol; triglycerides; DHEA-S; creatinine; prolactin; TSH; high-sensitivity CRP.</p> <p>All primary outcomes were measured at baseline and at 3 months.</p> <p>No secondary outcomes specified.</p>
Starting date	December 2018.
Contact information	Saeed Hosseini; saeedhmdphd@hotmail.com; Endocrinology & Metabolism Research Institute, 5th floor, Shariati Hospital, North Kargar Avenue, Tehran, 1411413137, Iran.
Notes	<p>Country: Iran.</p> <p>Status of study: recruiting.</p> <p>Sponsors and collaborators: Endocrinology and Metabolism Research Institute.</p>

IRCT2017060334308N1

Study name	Evaluating the effects of Oligopin® supplementation on the turnover of bone formation and antioxidant changes in postmenopausal osteopenic women: A randomised double-blind clinical trial with placebo-concurrent controls.
Methods	<p>Double-blind, placebo-controlled, parallel-design RCT.</p> <p>Target sample size: 44.</p>
Participants	<p><u>Inclusion criteria:</u> postmenopausal women aged 50 - 65 years with diagnosis of osteopenia based on T-score ($-2.5 \text{ SD} \leq \text{T-score} \leq -1 \text{ SD}$); to have equal physical, paediatric and complementary therapies for at least 3 months before entrance to study; absence of history of bone diseases; absence of the history of chronic diseases including cancer, diabetes, kidney failure, liver disease, systemic inflammatory diseases, degenerative joint diseases and rheumatologic disorders, primary thalassaemia, hyperparathyroidism, hyperthyroidism-Cushing's, hypercalcaemia syndrome, hyperglycemia; absence of gastrointestinal disease including Crohn's disease, ulcerative colitis, celiac disease, and chronic diarrhoea and gastric or duodenal ulcers treated or with a history of gastrointestinal bleeding (according to the patient's history); absence of history of the use of drugs that affect bone metabolism and have been regularly used for at least 6 months in the past 2 years: such as osteoporosis drugs (bisphosphonates, oestrogen receptor selective agonists or selective antagonists, alternative hormone replacement therapies, parathyroid hormone), diuretics, thiazides, anticonvulsants (phenytoin, phenobarbital, sodium valproate), glucocorticoids, NSAIDs such as analgesics (naproxen, aspirin and ibuprofen), cigarettes; absence of motor disabilities, skeletal disorders, untreated psychiatric illnesses such as psychosis, Alzheimer's disease, Parkinson's disease; to accept randomisation and absence of morbid obesity ($\text{BMI} > 40 \text{ kg/m}^2$).</p> <p><u>Exclusion criteria:</u> fractures reported during the study period; unwillingness of participants to continue the project and the occurrence of any visible side effects of supplemental effects.</p>
Interventions	<u>Treatment:</u> Oligopin® 150 mg 1x daily for 12 weeks.

IRCT2017060334308N1 (Continued)

Control: placebo 150 mg 1x daily for 12 weeks.

Outcomes	<p><u>Primary outcomes</u>: bone alkaline phosphatase; carboxy terminal collagen type.</p> <p><u>Secondary outcomes</u>: manganese superoxide dismutase activity in peripheral blood mononuclear cells; catalase activity in peripheral blood mononuclear cells; NrF2 protein levels in peripheral blood mononuclear cells; manganese superoxide dismutase expression in peripheral blood mononuclear cells; catalase expression in peripheral blood mononuclear cells; NrF2 expression in peripheral blood mononuclear cells; malondialdehyde plasma levels; plasma levels of total antioxidant capacity; plasma levels of protein carbonylation.</p> <p>All primary outcomes were measured at baseline and at 12 weeks.</p>
Starting date	August 2017.
Contact information	Solaleh Emamgholipour; s.emamgholipour@gmail.com; Department of Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Notes	<p>Country: Iran.</p> <p>Status of study: recruitment complete.</p> <p>Sponsors and collaborators: Vice Chancellor of Research, Tehran University of Medical Sciences.</p>

IRCT20180718040512N1

Study name	Evaluation of the effect of French Maritime pine bark extract on selected blood type indices in type 2 diabetic women.
Methods	<p>Double-blind, placebo-controlled, parallel-design RCT.</p> <p>Target sample size: 30.</p>
Participants	<p><u>Inclusion criteria</u>: females aged 45 - 65 years of age with at least 3 years of type 2 diabetes history and mild to moderate systolic blood pressure (120 - 159 mm Hg).</p> <p><u>Exclusion criteria</u>: males, type 1 diabetes mellitus, insulin usage, daily usage of any supplement multivitamin, any major diseases such as cancer, asthma, heart failure and other cardiovascular disorders, pregnancy and lactating females.</p>
Interventions	<p><u>Treatment</u>: 50 mg capsules of Oligopin® supplement per day for 6 weeks.</p> <p><u>Control</u>: "Proprietary" placebo per day for 6 weeks.</p>
Outcomes	<p><u>Primary outcomes</u>: fasting blood glucose; HDL cholesterol; LDL cholesterol; systolic blood pressure.</p> <p>All primary outcomes were measured at baseline and at 6 weeks of treatment.</p> <p>No secondary outcomes were specified.</p>
Starting date	July 2018.
Contact information	Rasool Orouji; orouji@health.gov.ir; No. 8, Bahar Alley, Tavan Boulevard, Ayatollah Kashani St. 1484774463, Tehran, Iran.
Notes	<p>Country: Iran.</p> <p>Status of study: recruitment complete.</p>

IRCT20180718040512N1 (Continued)

Sponsors and collaborators: not reported.

ISRCTN22412590

Study name	Pilot study for the treatment of heart failure with Pycnogenol®.
Methods	"...randomised, double-blind placebo-controlled matched pairs study". Target sample size: 30.
Participants	<u>Inclusion criteria:</u> adults > 40 years of age with chronic congestive heart failure (New York Heart Association class II), known for at least 6 months who were previously untreated or treated with a diuretic and/or a low dose of an ACE inhibitor; exercise capacity of at least 75 watts as assessed by seated bicycle ergometry. <u>Exclusion criteria:</u> New York Heart Association class I, III, or IV; treatment with digitalis within the previous 6 months; exercise capacity > 75 watts for 2 minutes at the test during run-in; unstable angina or myocardial infarction within the last 6 months; atrial fibrillation or ventricular arrhythmia ≥ "Lown III"; cardiac valvular disease or hypertrophic cardiomyopathy; significant hypertension or hypotension (diastolic blood pressure < 60 mm Hg or ≥ 105 mm Hg, or systolic blood pressure < 90 mm Hg or > 175 mm Hg); electrolyte disturbances, hyperuricaemia, hypovolaemia; impaired renal function (creatinine levels > 1.8 mg/dL) or impaired hepatic function; obstructive airways disease; insulin-dependent diabetes mellitus; malignant or other serious disease; hypersensitivity to the study drug Pycnogenol®; pregnant, unreliable contraception, breastfeeding; participation in another clinical trial within the last 6 weeks.
Interventions	<u>Treatment:</u> Pycnogenol® 200 mg (assumed) daily for 12 weeks. <u>Control:</u> placebo for 12 weeks.
Outcomes	<u>Primary outcomes:</u> maximal workload (determined by a symptom-limited bicycle exercise test in the seated position); pressure-heart product (measurement of systolic blood pressure and heart rate immediately after 2 minutes of work at 50 watts; it is calculated by units of systolic blood pressure (mm Hg) × heart rate per minute divided by 100). <u>Secondary outcomes:</u> participant-reported symptom scores for dyspnoea and fatigue for the previous 4 weeks where participants give severity scores for the following symptoms: early fatigability, dyspnoea, general capability, lassitude, feeling depressed, and anxiety (scores range as follows: 0 = not present, 1 = occasionally mild, 2 = frequently mild, 3 = moderate, 4 = severe); biochemical tests (CRP, troponin T, and B-type natriuretic peptide (BNP) (specifically NT-proBNP). Primary outcome data and symptom scores to be measured at baseline, as well as the end of week 4, 8 and 12 of treatment. Not reported how frequently biochemical tests were to be done.
Starting date	10 August 2007.
Contact information	A Matsumori; no email address reported; Kyoto University Graduate School of Medicine, Department of Cardiovascular Medicine, Sakyo-ku, Kyoto, Japan, 6068507.
Notes	Country: Japan. Status of study: "Completed". Sponsor: Kyoto University Graduate School of Medicine, Cardiomyopathy and Myocarditis Research Fund, Japan; website http://www.kyoto-u.ac.jp/index-e.html .

ISRCTN44961472

Study name	Pycnogenol® to reduce use of commercial anti-hypertensive medications: a randomised, double-blind, placebo-controlled, prospective, 15-week study.
Methods	"Single-centre, interventional, randomised double-blind placebo-controlled study " Target sample size: 80.
Participants	<u>Inclusion criteria</u> : males and females aged >40 and <75 years; non-insulin dependent type 2 diabetes; receiving pharmaceutical treatment (ACE-inhibitors) for hypertension; pre-study systolic blood pressure 130 - 150 mm Hg. <u>Exclusion criteria</u> : type 1 diabetes; use of insulin; supplements other than single daily multivitamin; major illness such as cancer, asthma, or heart failure; any previous cardiac events; pregnancy, or being nursing mother.
Interventions	<u>Treatment</u> : 25 mg Pycnogenol® pills 5x daily for 12 weeks. <u>Control</u> : inactive placebo for 12 weeks. Route of administration: oral.
Outcomes	<u>Primary outcomes</u> : systolic and diastolic blood pressure; serum endothelin-1; fasting LDL cholesterol; HbA1C; fasting plasma glucose; urinary albumin concentration. <u>Secondary outcomes</u> : systolic and diastolic blood pressure; serum endothelin-1; LDL cholesterol; HbA1C; fasting plasma glucose; urinary albumin concentration. All primary outcomes were measured at 12th week of treatment and all secondary outcomes were measured at 4th and 8th week of treatment.
Starting date	August 2003.
Contact information	Mel and Enid Zuckerman; no email address reported; College of Public Health University of Arizona Health Science Center 1295 N. Martin P. O. Box 245155 [FedEx building 202 room 252] Tucson; 85724-5155; USA.
Notes	Country: USA. Status of study: recruitment complete. Sponsors and collaborators: Horphag Research Ltd (Switzerland).

NCT00064857

Study name	Pycnogenol® for the treatment of lymphedema of the arm in breast cancer survivors.
Methods	"Randomized, placebo control, efficacy study, parallel assignment, double-blind". Estimated enrolment: 26.
Participants	<u>Inclusion criteria</u> : adult males and females aged 18 years and older with unilateral (ipsilateral to breast cancer resection side) lymphoedema of the upper extremity; extravascular water ratio of > 1.07/1 between affected versus normal arm using multiple frequency bioelectric impedance; last surgical or radiation treatment to the affected axilla was more than 2 months ago; renal and hepatic function (creatinine clearance > 50 mL/min, total bilirubin < 2 mg/dL, transaminases < 1.5 × ULN); not pregnant or breastfeeding, and use of barrier contraception if sexually active; Eastern Cooperative Oncology Group performance of 0 to 2; not allergic to Pycnogenol®.

NCT00064857 (Continued)

	<p><u>Exclusion criteria:</u> treated with 1st course of chemotherapy or radiation; chemotherapy or radiation to axillary lymph node will exclude participants for 8 weeks following treatment; more than 1 episode of arm cellulitis, venous clot, or woody fibrosis of the affected arm (antibiotics used to treat cellulitis must be completed at least 4 weeks prior to initial screening); participants with a defibrillator Midazolam study only; requiring or benefiting from supplemental oxygen; allergic to cherries.</p>
Interventions	<p><u>Treatment:</u> Pycnogenol® but no details on dose regimen reported.</p> <p><u>Control:</u> placebo but no details on dose regimen reported.</p>
Outcomes	<p>Outcomes are not explicitly reported nor grouped into primary and secondary outcomes.</p> <p><u>Planned measurements:</u> change in arm volume (comparison of correlation of both a single- and a multiple-frequency bioelectric impedance instrument to a standard assessment using water displacement); effects of Pycnogenol® on the activity of the common drug metabolizing enzyme CYP3A4 (using a small oral dose of midazolam and single blood sampling); effects of the test drug upon the activity of P-glycoprotein in participants already receiving digoxin (digoxin urine excretion); questionnaire of lymphedema symptoms (presently begin tested as a tool for assessing the severity and improvement of symptoms with treatment).</p>
Starting date	August 2003.
Contact information	JF Cleary; no email address provided; University of Wisconsin, Madison, Wisconsin, United States, 53706.
Notes	<p>Country: USA.</p> <p>Status of study: "This study has been completed."</p> <p>Sponsors and collaborators: National Center for Complementary and Alternative Medicine (NC-CAM).</p>

NCT00214032

Study name	Pycnogenol® for the treatment of lymphedema.
Methods	<p>"Randomized, active control, safety/efficacy study, single group assignment, double blind".</p> <p>Enrolment: 2 (we suppose this is a mistake).</p>
Participants	<p><u>Inclusion criteria:</u> females aged 18 years and older who have unilateral lymphedema of the upper extremity; received surgical and/or radiation treatment to the effected axilla more than 6 months ago.</p> <p><u>Exclusion criteria:</u> not receiving or be scheduled to receive cytotoxic or radiation chemotherapy treatment while part of the study.</p>
Interventions	<p><u>Treatment:</u> Pycnogenol® 300 mg daily, duration not reported.</p> <p><u>Control:</u> placebo 3 capsules daily, duration not reported.</p>
Outcomes	<p><u>Primary outcome:</u> reduction of arm lymphedema.</p> <p><u>Secondary outcomes:</u> "Comparison/validation of bioelectric impedance to measure lymphedema changes, validation of lymphedema questionnaire":</p> <p>All outcome data measured monthly.</p>

NCT00214032 (Continued)

Starting date	March 2002.
Contact information	PR Hutson; no email address provided; University of Wisconsin, Madison, Wisconsin, USA, 53792.
Notes	Country: USA. Status of study: "This study has been completed." Sponsors and collaborators: University of Wisconsin, Madison; National Center for Complementary and Alternative Medicine (NCCAM).

NCT00952627

Study name	Effects of Pycnogenol® on cardiac fibrosis and diastolic dysfunction in aged hypertensive subjects.
Methods	"Randomized, placebo control, efficacy study, parallel assignment, double blind". Estimated enrolment: 40.
Participants	<u>Inclusion criteria:</u> males and females aged 50 - 75 years of any race diagnosed with hypertension (diagnosis made over 6 months) and echocardiographic evidence of grade I or II diastolic dysfunction. "There is no need for standardization of hypertension treatment, as we select only patients who have diastolic dysfunction during treatment." <u>Exclusion criteria:</u> unstable angina or myocardial infarction in the past 3 months; biochemical evidence of renal or hepatic failure; severe anaemia (defined as haemoglobin levels < 7 g/dL); current cancer or other major illness not associated with the heart; bleeding disorders; taking anticoagulants including low-dose aspirin; diabetes; known allergy to Pycnogenol®; pregnant or breast-feeding; systolic blood pressure > 180 mm Hg or < 100 mm Hg, and diastolic blood pressure >110 mm Hg or < 50 mm Hg; current smoker; having breast implants; taking any of the following: birth control pills, diethylstilbestrol, ephedra, ephedrine or pseudoephedrine (except where used in prescription products), hormone replacement products, isotretinoin, any product containing mercury, phentermine in combination with fenfluramine (including but not limited to pondimin), or dexfenfluramine (redux).
Interventions	<u>Treatment:</u> Pycnogenol® 50 mg tablets, 4 tablets per day for 4 months. <u>Control:</u> placebo (no detail provided) for 4 months.
Outcomes	<u>Primary outcomes:</u> cardiac fibrosis (measured as the serum markers of myocardial fibrosis and collagen turnover); diastolic dysfunction (measured by transthoracic echocardiogram). <u>Secondary outcomes:</u> liver and kidney function tests; immunological measurements including the cytokine profile in serum (interleukin-4, interleukin-10, interferon-gamma, CRP). Outcome data collected at baseline and after 4 months of treatment.
Starting date	July 2009.
Contact information	RR Watson; rwatson@u.arizona.edu; University of Arizona, USA, 85724.
Notes	Country: USA. Status of study: "This study is currently [August 2009] recruiting participants". Sponsors and collaborators: University of Arizona; Horphag Research, Switzerland.

NCT01321281

Study name	Randomised, placebo-controlled study to determine if aquamin (as AquaCal and AquaPT) modulates inflammatory biomarkers in the blood of osteoarthritis and healthy subjects.
Methods	Phase II, double-blind, placebo-controlled, parallel-design RCT. Target sample size: 36.
Participants	<u>Inclusion criteria</u> : written informed consent; non-pregnant females aged 18 - 65 years; general good health as determined by the investigator; women with osteoarthritis must have a clinical diagnosis of moderate to severe osteoarthritis. <u>Exclusion criteria</u> : currently taking probiotics or vitamin supplements, or have taken them in the past 14 days; significant acute or chronic co-existing illness (cardiovascular, gastrointestinal, endocrinological, immunological, metabolic or any condition which contraindicates, in the investigators judgment, entry to the study); having a condition or taking a medication that the investigator believes would interfere with the objectives of the study, pose a safety risk or confound the interpretation of the study results by taking NSAIDs, steroids and vitamin; individuals who, in the opinion of the investigator, are considered to be poor attendees or unlikely for any reason to be able to comply; not receiving treatment involving experimental drugs; completion of any recent experimental study not less than 30 days prior to this study; malignant disease or any concomitant end-stage organ disease.
Interventions	<u>Treatment</u> : 4 capsules of AquaPT® daily (720 mg calcium, 200 mg green tea (polyphenols) and 50 mg pine bark extract), duration not stated. <u>Control</u> : 4 capsules of AquaCal® daily (800 mg calcium (the EU recommended daily allowance for calcium) and 74 mg magnesium (EU recommended daily allowance 375 mg), duration not stated.
Outcomes	<u>Primary outcomes</u> : plasma cytokine concentrations (including TNF α , IL- β , NFkB, COX2 & IL-6). <u>Secondary outcomes</u> : WOMAC questionnaire; full blood count (haemoglobin, white cell count, platelet count, hematocrit, differential white count); chemistry profile including sodium, potassium, chloride, urea, creatinine, protein, albumin. Outcome data reported at baseline and at six weeks.
Starting date	March 2011.
Contact information	Timothy Dinan; no email address available; University College Cork.
Notes	Country: Ireland. Status of study: recruitment completed. Sponsors and collaborators: Andrea Doolan; University College Cork.

NCT02909686

Study name	Effects of Botanical Microglia Modulators in Gulf War Illness.
Methods	Double blind, cross-over design RCT. Target sample size: 64.
Participants	<u>Inclusion criteria</u> : males aged 39 - 65 years; veterans who meet the Kansas inclusion criteria for Gulf War Illness and were present in Persian Gulf between 1990 and August 1991; participant-reported

NCT02909686 (Continued)

daily report during 2-week baseline period (at least 80% completion rate); able to receive a venous blood draw.

Exclusion criteria: positive rheumatoid factor at screening; positive anti-nuclear antibody at screening; CRP > 3 mg/L at screening; erythrocyte sedimentation rate > 40 mm/hr at screening; auto-immune disorder; diagnosed rheumatologic condition; major post traumatic stress disorder symptoms; hypotension (under 90/60 mm Hg) or history of cardiovascular disease; antihypertensive, anticoagulant medication, nitroglycerine, lithium medication use; diabetes with HbA1C > 9%; history of anaphylaxis to study botanical compounds; current daily use of opioid medication; HADS, depression subscale score of 16 or higher at baseline; current litigation of worker's compensation claim; blood or clotting disorder; acute infection (body temperature over 100 degrees F); current daily use of confounding-anti-inflammatory medication as part of regular medication regimen; not able to read and understand English.

Interventions

Treatment: 9 different supplements daily in capsule form (Boswellia Serrata 400 - 800 mg, curcumin 1000 - 2000 mg, epimedium 1000 - 2000 mg, fisetin 200 - 800 mg, luteolin 200 - 400 mg, nettle 435 - 1305 mg, Pycnogenol® 200 - 400 mg, Reishi mushroom 1600 - 3200 mg, resveratrol 200 - 600 mg).

Control: placebo in capsule form by mouth every day .

Route of administration: oral, but no information on duration was given.

Outcomes

Primary outcomes: change from baseline in overall Gulf War Illness disease severity (average disease severity during the last 2 weeks of each treatment compared to average severity during the last 2 weeks of placebo, as well as baseline); self-reported Gulf War Illness symptom severity reported 2x daily (morning and evening), for the duration of the study where each item scored 0 - 100 (0 = no symptoms; 100 = severe symptoms).

Secondary outcomes: pain severity (change from baseline) (average pain severity during the last 2 weeks of each treatment, compared to average severity during the last 2 weeks of placebo, as well as baseline); fatigue severity (change from baseline) (average fatigue severity during the last 2 weeks of each treatment, compared to average severity during the last 2 weeks of placebo, as well as baseline); cognitive symptom severity (change from baseline) (average cognitive symptom severity during the last 2 weeks of each treatment, compared to average severity during the last 2 weeks of placebo, as well as baseline); mood symptom severity (change from baseline) (average mood severity during the last 2 weeks of each treatment, compared to average severity during the last 2 weeks of placebo, as well as baseline); dermatological symptom severity (change from baseline) (average dermatological symptom severity during the last 2 weeks of each treatment, compared to average severity during the last 2 weeks of placebo, as well as baseline.); respiratory symptom severity (change from baseline) (average respiratory symptom severity during the last 2 weeks of each treatment, compared to average severity during the last 2 weeks of placebo, as well as baseline); gastrointestinal symptom severity (change from baseline) (average gastrointestinal symptom severity during the last 2 weeks of each treatment, compared to average severity during the last 2 weeks of placebo, as well as baseline).

Starting date

July 2016.

Contact information

Jarred W Younger, PhD; no email available; University of Alabama at Birmingham

Notes

Country: USA.

Status of study: not yet recruiting.

Sponsors and collaborators: University of Alabama at Birmingham; Congressionally Directed Medical Research Programs.

NCT03106584

Study name	Investigating the potential for Marigot's nutrition supplement to improve symptoms and physical function in those with mild to moderate knee osteoarthritis (KOA) versus the current market leader (glucosamine sulphate)
Methods	Double-blind, cross-over design RCT. No placebo used. Washout period of 4 weeks between intervention periods. Target sample size: 30.
Participants	<u>Inclusion criteria</u> : mild to moderate knee osteoarthritis (level 1 - 3 Kellgren and Lawrence and WOMAC in the lower 2 quartiles in the target knee); BMI 20 - 30 kg/m ² . <u>Exclusion criteria</u> : rheumatoid arthritis; gout; pseudo gout; Paget's disease; seizure disorder; insulin-dependent diabetes mellitus; uncontrolled hypertension; unstable cardiovascular disease; active hepatic or renal disease; active cancer and/or HIV infection; involved in other clinical trial or experimental treatments in the past 3 months; pregnant, lactating, or at risk of becoming pregnant; intramuscular or systemic corticosteroid injection within 4 weeks; intra-articular corticosteroid injection within 2 months or inter-articular hyaluronic acid injection within 4 months prior to enrolment.
Interventions	<u>Treatment</u> : 4x capsules Aquamin® daily (a calcium-rich marine multi-mineral containing 666.7 mg magnesium hydroxide, 66.66 mg pine bark, 30 mg vitamin d3 - 2.5µg - unclear if the dosage is per capsule or per 4 capsules) for 12 weeks. <u>Control</u> : 4x 500 mg capsules of glucosamine sulphate supplement daily for 12 weeks.
Outcomes	<u>Primary outcomes</u> : self-reported pain for knee osteoarthritis measured using the validated WOMAC pain and function sub-scale; data collected at baseline, mid-intervention (4 and 8 weeks) post-intervention (12 weeks), post-washout period (16 weeks), mid-intervention (20 and 24 weeks) post intervention (28 weeks). <u>Secondary outcomes</u> : quality of life questionnaire (EuroQoL-5D) assessing levels of function surrounding mobility, self-care, usual activities, pain or discomfort, anxiety or depression; knee flexor and extensor muscle strength (isometric strength of the quadriceps and hamstring muscles assessed using an isokinetic dynamometer (Cybex)); knee flexor and extensor muscle electrical activity (quadriceps and hamstring muscle activation (via electromyography) during the performance of the isometric testing), both the agonist and antagonist muscle activity will be assessed and a co-contraction value calculated; biomarkers* from a 10 mL venous blood sample; functional mobility (6-minute walk test and the Timed Up and Go Test); body composition assessed by DEXA scan. All secondary outcome data were collected at baseline, post intervention (12 weeks), post washout period (16 weeks), post intervention (28 weeks). * no indication of which biomarkers will be tested.
Starting date	May 2017.
Contact information	Shane M Heffernan, PhD; shane.heffernan@ucd.ie; 00353 1 716 3433. Mark McGroarty, MSc; mark.mcgroarty@ucd.ie; 00353 86 083 0034.
Notes	Country: Ireland. Status of study: not yet recruiting. Sponsors and collaborators: University College Dublin, Marigot Ltd.

NCT03260803

Study name	Oligopin supplementation and bone turnover markers and antioxidant changes in postmenopausal osteopenic women
Methods	Double-blind, placebo-controlled, parallel-design RCT. Target sample size: 43.
Participants	<p>Inclusion criteria: postmenopausal women aged 50 - 65 years with diagnosis of osteopenia based on T-score ($-2.5 \text{ SD} \leq \text{T-score} \leq -1 \text{ SD}$); equal physical, paediatric and complementary therapies for at least 3 months before entrance to study; no history of bone diseases; no history of chronic diseases including cancer, diabetes, kidney failure, liver disease, systemic inflammatory diseases, degenerative joint diseases and rheumatologic disorders, primary thalassaemia, hyperparathyroidism, hyperthyroidism-Cushing's, hypercalcaemia syndrome, hyperglycaemia; no gastrointestinal disease including Crohn's disease, ulcerative colitis, celiac disease, and chronic diarrhoea and gastric or duodenal ulcers treated or with a history of gastrointestinal bleeding (according to the patient's history); no history of use of drugs that affect bone metabolism and have been regularly used for at least 6 months in the past 2 years (e.g. osteoporosis drugs (bisphosphonates, oestrogen receptor selective agonists or selective antagonists, alternative hormone replacement therapy, parathyroid hormone), diuretics, thiazides, anticonvulsants (phenytoin, phenobarbital, sodium valproate), glucocorticoids, NSAIDs such as analgesics (e.g., naproxen, aspirin and ibuprofen), cigarettes; no motor disabilities, skeletal disorders, untreated psychiatric illnesses such as psychosis, Alzheimer's disease, Parkinson's disease; acceptance of randomisation; not morbidly obese ($\text{BMI} > 40 \text{ kg/m}^2$).</p> <p>Exclusion criteria: fractures reported during the study period; unwillingness of participants to continue the project and the occurrence of any visible side effects of supplemental effects.</p>
Interventions	<p>Treatment: Oligopin® 150 mg 1x daily for 12 weeks.</p> <p>Control: placebo 150 mg 1x daily for 12 weeks.</p>
Outcomes	<p>Primary outcomes: bone alkaline phosphatase; cCarboxy terminal collagen type.</p> <p>Secondary outcomes: manganese superoxide dismutase activity in peripheral blood mononuclear cells; catalase activity in peripheral blood mononuclear cells; NrF2 protein levels in peripheral blood mononuclear cells; manganese superoxide dismutase expression in peripheral blood mononuclear cells; catalase expression in peripheral blood mononuclear cells; NrF2 expression in peripheral blood mononuclear cells; malondialdehyde plasma levels; plasma levels of total antioxidant capacity.</p> <p>Outcome data at baseline and at 12 weeks of treatment.</p>
Starting date	February 2018.
Contact information	Solaleh Emamgholipour; s.emamgholipour@gmail.com; Department of Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Notes	<p>Country: Iran.</p> <p>Status of study: recruitment complete.</p> <p>Sponsors and collaborators: Tehran University of Medical Sciences.</p>

NCT03368690

Study name	Therapeutic effects of pine bark extracts in attention deficit hyperactivity disorder.
Methods	Double-blind, cross-over RCT.

Pine bark (*Pinus* spp.) extract for treating chronic disorders (Review)

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NCT03368690 (Continued)

Target sample: 32.

Participants	<p><u>Inclusion criteria:</u> children or adolescents ADHD aged 7 - 20 years not being treated with ADHD drugs, antihypertensive drugs and dietary supplements more than 4 weeks. Adults with ADHD aged from 20 - 65 years no being treated with antihypertensive drugs and dietary supplements more than 4 weeks.</p> <p><u>Exclusion criteria:</u> children or adolescents treated with ADHD drugs, antihypertensive drugs and dietary supplements, adults treated with antihypertensive drugs and dietary supplements, nervous system diseases (including brain or other central nervous system diseases, e.g. epilepsy), autism spectrum disorder, intellectual disability, other mental disorders (e.g. schizophrenia, bipolar disorder, major depressive disorder, anxiety disorder, personality disorders, conduct disorder, Tourette syndrome.), hepatic, renal, gastrointestinal and cardiovascular disorders, biochemical abnormalities.</p>
Interventions	<p><u>Treatment:</u> Oligopin® dietary supplement, polyphenolic extract from pine bark for 10 weeks. Children and adolescents 20 - 50 kg body weight, 25 mg Oligopin®/day; > 50 kg body weight, 50 mg Oligopin®/day. Adults 40 - 60 kg body weight, 100 mg Oligopin®/day; > 60 kg body weight, 150 mg Oligopin®/day.</p> <p><u>Control:</u> placebo (identical capsules containing maltodextrin and magnesium stearate) for 10 weeks.</p>
Outcomes	<p><u>Primary outcomes:</u> Swanson, Nolan and Pelham Teacher and Parent Rating Scale (SNAP-IV); adult ADHD Self-Report Scale-V1.1 (ASRS-V1.1); Individual Subjective Perception Job Stress Scale (ISPJSS); Conners' Continuous Performance Test (CPT-III); Wechsler Memory Scale (WMS-III); Wisconsin Card Sorting Test (WCST).</p> <p><u>Secondary outcomes:</u> serum AST, ALT and bilirubin-total units/L; serum BUN, creatine and urine acid mg/dL; serum HDL cholesterol, LDL cholesterol, triglyceride and total cholesterol mg/dL; serum whole blood count in 1000/uL; red blood cells 1000000/uL; haemoglobin g/dL; haematocrit %; mean corpuscular volume fL; mean cell haemoglobin pg; , mean corpuscular haemoglobin concentration g/dL, platelet 1000/uL; neutrophils %; lymphocytes %; monocytes %; eosinophils%; basophils %; serum iron, ferritin and TIBC mcg/dL; thiobarbituric acid-reactive substance, glutathione to oxidized glutathione ratio, and plasma 8-isoprostane; food frequency questionnaire; 3-day dietary record.</p> <p>Outcomes measured at baseline, at 4 weeks and at 10 weeks.</p>
Starting date	October 2017.
Contact information	Taipei Medical University. Contact details not reported.
Notes	<p>Country: Taiwan.</p> <p>Status of study: Recruiting completed.</p> <p>Sponsors and collaborators: Taipei Medical University.</p>

NCT03704454

Study name	The use of Pycnogenol® to alleviate menopausal symptoms induced or increased by breast and gynaecological cancer treatments.
Methods	<p>Double-blind, cross-over RCT. Washout period not reported.</p> <p>Target sample: 40.</p>

NCT03704454 (Continued)

Participants	<p>Inclusion criteria: women > 18 years of age currently undergoing treatment for cancer, with menopausal symptoms induced either by surgical or medical (participant on tamoxifen or aromatase inhibitor) interventions for cancer, willing to travel to a Legacy Health facility if necessary, agree to attend study visits outside of standard of care visits, if needed, willing to stop other supplements or medications that are aimed at treating menopausal symptoms at least 7 days before beginning study treatment, willing to engage in pre/post testing and survey/phone calls.</p> <p>Exclusion criteria: women < 18 years of age, currently undergoing chemotherapy treatment, unable to comply with protocol, unable to provide written informed consent, investigator does not believe study participation is in the best interest of the patient, concurrent menopausal symptoms prior to the start of cancer treatment, menopausal symptoms are unrelated to surgical or medical treatment of breast or gynaecological cancers.</p>
Interventions	<p>Treatment: 50 mg or 100 mg of Pycnogenol® for 4 weeks.</p> <p>Control: placebo for 4 weeks.</p>
Outcomes	<p>Primary outcomes: menopause rating scale (data collected at baseline, after 4 weeks, after 8 weeks, 10 weeks and 12 weeks with the intention of calculating dysfunctional bleeding score at each time point).</p> <p>No secondary outcomes specified.</p>
Starting date	October 2018.
Contact information	Meg Christ; mchrist@lhs.org; 503-413-8199.
Notes	<p>Country: USA.</p> <p>Status of study: recruitment complete.</p> <p>Sponsors and collaborators: Legacy Health System.</p>

Verlaet 2017

Study name	Effect of a polyphenol-rich plant extract on attention-deficit hyperactivity disorder (ADHD)
Methods	<p>"A Randomized, Double Blind, Placebo and Active Product Controlled Multicenter Trial."</p> <p>Target sample size: 144.</p>
Participants	<p>Inclusion criteria: boys and girls aged 6 - 12 years; satisfies the DSM-IV criteria for ADHD or ADD; has a responsible caregiver who is able to provide information about the patient's functional status; written informed consent from the patient and the legally accepted representative.</p> <p>Exclusion criteria: does not satisfy the DSM-IV for autism spectrum disorder; has situational hyperactivity, pervasive developmental disorders, schizophrenia, other psychotic disorders such as mood or anxiety disorder, personality disorder as unsocial behaviour, personality change due to a general medical condition, mental retardation (IQ < 70), under stimulating environments, conduct disorder, chorea and other dyskinesias; no tics or Tourette's syndrome, or personal or family history of psychotic disorder, bipolar illness, depression, or suicide attempt; any chronic medical disorder (diabetes, epilepsy or other seizure disorder, autoimmune disorder, gastrointestinal disorder, renal or cardiovascular disorders, etc.) or acute inflammatory disease; glaucoma, heart disease, heart rhythm disorder, high blood pressure, or peripheral vascular disease such as Raynaud's syndrome; patient used any of these medications during the 3 months before entering the study: clonidine, guanethidine, blood thinners (e.g. warfarin or Coumadin), antidepressants (e.g. amitriptyline, citalopram, doxepin, fluoxetine, nortriptyline, paroxetine, sertraline), cold or allergy medicine that contains a decongestant, medications to treat high or low blood pressure, seizure medi-</p>

Verlaet 2017 (Continued)

	cine (e.g. phenobarbital, phenytoin, primidone), or diet pills; taken monoamine oxidase inhibitors (isocarboxazid, linezolid, phenelzine, rasagiline, selegiline or tranylcypromine) in the past 14 days; any other contraindication for the use of methylphenidate; use of vitamin or mineral or herbal or omega-3 supplements or other any medication (psychoactive medication, antibiotics, anti-inflammatory drugs, melatonin, etc.) > 1 week during the 3 months before inclusion.
Interventions	<p><u>Treatment</u>: Pycnogenol® dietary supplement (standardised extract of French maritime pine bark) for 10 weeks; dose stratified by body weight: < 30 kg body weight, 20 mg Pycnogenol®/day; ≥ 30 kg body weight, 40 mg Pycnogenol®/day.</p> <p><u>Control</u>: placebo treatment identical capsules containing excipients only for a period of 10 weeks.</p> <p><u>Active comparator</u>: slow release methylphenidate (standard pharmaceutical treatment for ADHD) for a period of 10 weeks; dose stratified by body weight: < 30 kg body weight, 20 mg methylphenidate 1x daily; ≥ 30 kg body weight, 30 mg methylphenidate 1x daily.</p>
Outcomes	<p><u>Primary outcome</u>: summed ADHD score of the ADHD-Rating Scale as rated by teachers collected at 10 weeks.</p> <p><u>Secondary outcome</u>: summed ADHD score of the ADHD-Rating Scale as rated by teachers collected at 5 weeks.</p>
Starting date	September 2017.
Contact information	Annelies Verlaet, MSc; annalies.verlaet@uantwerpen.be; 003232652706.
Notes	<p>Country: Belgium.</p> <p>Status of study: Abstract published.</p> <p>Sponsors and collaborators: Nina Hermans, PhD; Universiteit Antwerpen.</p> <p>Trial registry number: NCT02700685</p>

17-OH: 17-hydroxyprogesterone
 ACE: angiotensin-converting enzyme
 ACR: albumin to creatinine ratio
 ADHD: attention deficit hyperactivity disorder
 ALT: alanine transaminase
 AST: aspartate transaminase
 BMI: body mass index
 CRP: C-reactive protein
 DEXA: dual-energy X ray absorptimetry
 DHEA-S: dehydroepiandrosterone sulfate
 HADS: Hospital Anxiety and Depression Scale
 HbA1C: glycated haemoglobin
 HDL cholesterol: high-density lipoprotein
 HOMA-IR: homeostatic model assessment of insulin resistance
 ICAM-1: intracellular adhesion molecule 1
 LDL cholesterol: low-density lipoprotein
 NSAIDs: non-steroidal anti-inflammatory drugs
 RCT: randomised controlled trial
 SD: standard deviation
 TSH: thyroid-stimulating hormone
 ULN: upper limit of normal
 VCAM-1: vascular cell adhesion molecule 1
 WOMAC: Western Ontario and McMaster Universities Arthritis

DATA AND ANALYSES

Comparison 1. Pine bark extract versus placebo: Asthma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Decrease in asthma symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1.1 At three months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2 Participants off albuterol inhaler	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2.1 At three months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3 Number of albuterol inhaler puffs per 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.1 At three months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Change in FEV ₁ % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5 Change in FEV ₁ % predicted/FVC	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Pine bark extract versus placebo: Asthma, Outcome 1: Decrease in asthma symptoms

Analysis 1.2. Comparison 1: Pine bark extract versus placebo: Asthma, Outcome 2: Participants off albuterol inhaler

Analysis 1.3. Comparison 1: Pine bark extract versus placebo: Asthma, Outcome 3: Number of albuterol inhaler puffs per 24 hours

Analysis 1.4. Comparison 1: Pine bark extract versus placebo: Asthma, Outcome 4: Change in FEV₁ % predicted

Analysis 1.5. Comparison 1: Pine bark extract versus placebo: Asthma, Outcome 5: Change in FEV₁ % predicted/FVC

Comparison 2. Pine bark extract versus placebo: ADHD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Change in inattention as measured by CAP scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2 Change in inattention as measured by CTRS scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.3 Change in inattention as measured by CPRS scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.3.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.4 Change in hyperactivity as measured by CAP scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.4.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.5 Change in hyperactivity as measured by CTRS scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.5.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.6 Change in hyperactivity as measured by CPRS scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.6.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.7 Change in visual-motoric coordination and concentration	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.7.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.8 8-oxo-7,8-dihydroguanine levels	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.8.1 At one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

**Analysis 2.1. Comparison 2: Pine bark extract versus placebo:
ADHD, Outcome 1: Change in inattention as measured by CAP scores**

**Analysis 2.2. Comparison 2: Pine bark extract versus placebo: ADHD,
Outcome 2: Change in inattention as measured by CTRS scores**

**Analysis 2.3. Comparison 2: Pine bark extract versus placebo: ADHD,
Outcome 3: Change in inattention as measured by CPRS scores**

**Analysis 2.4. Comparison 2: Pine bark extract versus placebo: ADHD,
Outcome 4: Change in hyperactivity as measured by CAP scores**

**Analysis 2.5. Comparison 2: Pine bark extract versus placebo: ADHD,
Outcome 5: Change in hyperactivity as measured by CTRS scores**

**Analysis 2.6. Comparison 2: Pine bark extract versus placebo: ADHD,
Outcome 6: Change in hyperactivity as measured by CPRS scores**

**Analysis 2.7. Comparison 2: Pine bark extract versus placebo: ADHD,
Outcome 7: Change in visual-motoric coordination and concentration**

Analysis 2.8. Comparison 2: Pine bark extract versus placebo: ADHD, Outcome 8: 8-oxo-7,8-dihydroguanine levels

Comparison 3. Pine bark extract versus placebo: CVD and risk factors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Reduction of nifedipine dose	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.1 At three months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2 Dose reduced to 10 mg nifedipine	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.1 At three months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.3 Systolic blood pressure (mmHg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.3.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4 Systolic blood pressure (mmHg): cross-over trials	2	74	Mean Difference (IV, Fixed, 95% CI)	-1.53 [-4.96, 1.91]
3.4.1 At one month	1	50	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-5.00, 2.80]
3.4.2 At five weeks	1	24	Mean Difference (IV, Fixed, 95% CI)	-2.98 [-10.19, 4.23]
3.5 Diastolic blood pressure (mmHg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6 Diastolic blood pressure (mmHg): cross-over trials	2	74	Mean Difference (IV, Fixed, 95% CI)	0.16 [-2.07, 2.39]
3.6.1 At one month	1	50	Mean Difference (IV, Fixed, 95% CI)	0.40 [-2.17, 2.97]
3.6.2 At five weeks	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-5.04, 3.90]
3.7 Fasting blood glucose (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.7.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.8 Fasting blood glucose (mmol/L): cross-over trials	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.8.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.9 Insulin levels (pmol/L): cross-over trial	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.9.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.10 Total cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.10.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.11 Total cholesterol (mmol/L): cross-over trials	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.11.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.12 HDL (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.12.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.13 HDL (mmol/L): cross-over trials	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.13.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.14 LDL (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.14.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.15 LDL (mmol/L): cross-over trials	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.15.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.16 Triglycerides (mmol/L): cross-over trials	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.16.1 At one month	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.16.2 At five weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.17 CRP (µg/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.17.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.18 High sensitivity CRP (mg/L): cross-over trials	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.18.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.19 Weight (kg): cross-over trial	1	24	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.19.1 At five weeks	1	24	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.20 BMI (kg/m ²): cross-over trial	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.20.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.21 Waist circumference (cm): cross-over trial	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.21.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.22 Oxidised glutathione (nmol/mL): cross-over trial	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.22.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.23 Reduced glutathione (nmol/mL): cross-over trial	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.23.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.24 Ratio reduced/oxidised glutathione (nmol/mL): cross-over trial	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.24.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.25 Nitrates (microM): cross-over trial	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.25.1 At five weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.26 Oxidative stress D-ROM test (carr units)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.26.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 1: Reduction of nifedipine dose

Analysis 3.2. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 2: Dose reduced to 10 mg nifedipine

Analysis 3.3. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 3: Systolic blood pressure (mmHg)

Analysis 3.4. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 4: Systolic blood pressure (mmHg): cross-over trials

Analysis 3.5. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 5: Diastolic blood pressure (mmHg)

Analysis 3.6. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 6: Diastolic blood pressure (mmHg): cross-over trials

Analysis 3.7. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 7: Fasting blood glucose (mmol/L)

Analysis 3.8. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 8: Fasting blood glucose (mmol/L): cross-over trials

Analysis 3.9. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 9: Insulin levels (pmol/L): cross-over trial

Analysis 3.10. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 10: Total cholesterol (mmol/L)

Analysis 3.11. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 11: Total cholesterol (mmol/L): cross-over trials

Analysis 3.12. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 12: HDL (mmol/L)

**Analysis 3.13. Comparison 3: Pine bark extract versus placebo:
CVD and risk factors, Outcome 13: HDL (mmol/L): cross-over trials**

Analysis 3.14. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 14: LDL (mmol/L)

**Analysis 3.15. Comparison 3: Pine bark extract versus placebo:
CVD and risk factors, Outcome 15: LDL (mmol/L): cross-over trials**

**Analysis 3.16. Comparison 3: Pine bark extract versus placebo: CVD
and risk factors, Outcome 16: Triglycerides (mmol/L): cross-over trials**

Footnotes

(1) This study used Verum®

(2) This study used Pyconogenol®

Analysis 3.17. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 17: CRP (µg/L)

Analysis 3.18. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 18: High sensitivity CRP (mg/L): cross-over trials

Analysis 3.19. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 19: Weight (kg): cross-over trial

**Analysis 3.20. Comparison 3: Pine bark extract versus placebo:
CVD and risk factors, Outcome 20: BMI (kg/m²): cross-over trial**

**Analysis 3.21. Comparison 3: Pine bark extract versus placebo: CVD
and risk factors, Outcome 21: Waist circumference (cm): cross-over trial**

**Analysis 3.22. Comparison 3: Pine bark extract versus placebo: CVD and
risk factors, Outcome 22: Oxidised glutathione (nmol/mL): cross-over trial**

**Analysis 3.23. Comparison 3: Pine bark extract versus placebo: CVD and
risk factors, Outcome 23: Reduced glutathione (nmol/mL): cross-over trial**

Analysis 3.24. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 24: Ratio reduced/oxidised glutathione (nmol/mL): cross-over trial

Analysis 3.25. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 25: Nitrates (microM): cross-over trial

Analysis 3.26. Comparison 3: Pine bark extract versus placebo: CVD and risk factors, Outcome 26: Oxidative stress D-ROM test (carr units)

Comparison 4. Pine bark extract versus placebo: CVI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Heaviness scores	2	60	Mean Difference (IV, Fixed, 95% CI)	-0.72 [-0.91, -0.54]
4.1.1 At two months	2	60	Mean Difference (IV, Fixed, 95% CI)	-0.72 [-0.91, -0.54]
4.2 Swelling scores	2	60	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.67, -0.25]
4.2.1 At two months	2	60	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.67, -0.25]
4.3 Pain scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.3.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Disappearance of heaviness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.4.1 At two months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5 Disappearance of swelling	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5.1 At two months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.6 Disappearance of pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.6.1 At two months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.7 Treatment efficacy as judged by physician	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.7.1 At two months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Pine bark extract versus placebo: CVI, Outcome 1: Heaviness scores

Analysis 4.2. Comparison 4: Pine bark extract versus placebo: CVI, Outcome 2: Swelling scores

Analysis 4.3. Comparison 4: Pine bark extract versus placebo: CVI, Outcome 3: Pain scores

Analysis 4.4. Comparison 4: Pine bark extract versus placebo: CVI, Outcome 4: Disappearance of heaviness

Analysis 4.5. Comparison 4: Pine bark extract versus placebo: CVI, Outcome 5: Disappearance of swelling

Analysis 4.6. Comparison 4: Pine bark extract versus placebo: CVI, Outcome 6: Disappearance of pain

**Analysis 4.7. Comparison 4: Pine bark extract versus placebo:
CVI, Outcome 7: Treatment efficacy as judged by physician**

Comparison 5. Pine bark extract versus control: DM type I

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Microcirculation-related symptom scores: oral Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.2 Microcirculation-related symptom scores: local Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.2.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.3 Microcirculation-related symptom scores: oral and local Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.3.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.4 Area of ulceration: oral Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.4.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.5 Area of ulceration: local Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.5.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.6 Area of ulceration: oral and local Pycnogenol® (mm²)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.6.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.7 Transcutaneous PO ₂ : oral Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.7.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.8 Transcutaneous PCO ₂ : oral Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.8.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.9 Transcutaneous PO ₂ : oral and local Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.9.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.10 Transcutaneous PCO ₂ : oral and local Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.10.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.11 Skin flux at rest: oral Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.11.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.12 Skin flux at rest: oral and local Pycnogenol®	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.12.1 At six weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Pine bark extract versus control: DM type I, Outcome 1: Microcirculation-related symptom scores: oral Pycnogenol®

Study or Subgroup	Pine bark (oral)			Control			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
5.1.1 At six weeks								
Belcaro 2006a	3.8	2.2	6	5.1	3	8	-1.30 [-4.02, 1.42]

**Analysis 5.2. Comparison 5: Pine bark extract versus control: DM type I,
Outcome 2: Microcirculation-related symptom scores: local Pycnogenol®**

**Analysis 5.3. Comparison 5: Pine bark extract versus control: DM type I,
Outcome 3: Microcirculation-related symptom scores: oral and local Pycnogenol®**

**Analysis 5.4. Comparison 5: Pine bark extract versus control:
DM type I, Outcome 4: Area of ulceration: oral Pycnogenol®**

**Analysis 5.5. Comparison 5: Pine bark extract versus control:
DM type I, Outcome 5: Area of ulceration: local Pycnogenol®**

Analysis 5.6. Comparison 5: Pine bark extract versus control: DM type I, Outcome 6: Area of ulceration: oral and local Pycnogenol® (mm²)

Analysis 5.7. Comparison 5: Pine bark extract versus control: DM type I, Outcome 7: Transcutaneous PO₂: oral Pycnogenol®

Analysis 5.8. Comparison 5: Pine bark extract versus control: DM type I, Outcome 8: Transcutaneous PCO₂: oral Pycnogenol®

Analysis 5.9. Comparison 5: Pine bark extract versus control: DM type I, Outcome 9: Transcutaneous PO₂: oral and local Pycnogenol®

Analysis 5.10. Comparison 5: Pine bark extract versus control: DM type I, Outcome 10: Transcutaneous PCO₂: oral and local Pycnogenol®

Analysis 5.11. Comparison 5: Pine bark extract versus control: DM type I, Outcome 11: Skin flux at rest: oral Pycnogenol®

Analysis 5.12. Comparison 5: Pine bark extract versus control: DM type I, Outcome 12: Skin flux at rest: oral and local Pycnogenol®

Comparison 6. Pine bark extract versus placebo: DM type II

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Visual acuity	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1.1 At two months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2 Reduction in fasting blood glucose levels (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.2.1 At three months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.3 HbA1c levels (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.3.1 At three months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.4 Reduction in urinary albumin levels (mg/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.4.1 At three months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.5 Central macular thickness (μm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.5.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.6 Best corrected visual acuity (logMAR)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.6.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.7 Nitrogen monoxide (nmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.7.1 At three months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.8 Free oxygen radical test (mg/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.8.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6: Pine bark extract versus placebo: DM type II, Outcome 1: Visual acuity

Analysis 6.2. Comparison 6: Pine bark extract versus placebo: DM type II, Outcome 2: Reduction in fasting blood glucose levels (mmol/L)

Analysis 6.3. Comparison 6: Pine bark extract versus placebo: DM type II, Outcome 3: HbA1c levels (%)

Analysis 6.4. Comparison 6: Pine bark extract versus placebo: DM type II, Outcome 4: Reduction in urinary albumin levels (mg/L)

Analysis 6.5. Comparison 6: Pine bark extract versus placebo: DM type II, Outcome 5: Central macular thickness (µm)

Analysis 6.6. Comparison 6: Pine bark extract versus placebo: DM type II, Outcome 6: Best corrected visual acuity (logMAR)

Analysis 6.7. Comparison 6: Pine bark extract versus placebo: DM type II, Outcome 7: Nitrogen monoxide (nmol/L)

Analysis 6.8. Comparison 6: Pine bark extract versus placebo: DM type II, Outcome 8: Free oxygen radical test (mg/L)

Comparison 7. Pine bark extract versus placebo: DM types I and II combined

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Diabetic Peripheral Neuropathy Symptom Score: number of participants who showed no change	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1.1 At six months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.2 Diabetic Peripheral Neuropathy Symptom score: number of participants who showed improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.2.1 At six months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.3 Diabetic Peripheral Neuropathy Symptom Score: number of participants who had worsened symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.3.1 At six months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.4 Change in HbA1C (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.4.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.5 Total cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.5.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.6 LDL (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.6.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.7 HDL (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.7.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.8 Triglycerides (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.8.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.9 hsCRP (mg/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7: Pine bark extract versus placebo: DM types I and II combined, Outcome 1: Diabetic Peripheral Neuropathy Symptom Score: number of participants who showed no change

Study or Subgroup	Pine bark		Control		Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
7.1.1 At six months						
Chous 2016	25	39	23	28	0.78 [0.58 , 1.04]

Analysis 7.2. Comparison 7: Pine bark extract versus placebo: DM types I and II combined, Outcome 2: Diabetic Peripheral Neuropathy Symptom score: number of participants who showed improvement

Analysis 7.3. Comparison 7: Pine bark extract versus placebo: DM types I and II combined, Outcome 3: Diabetic Peripheral Neuropathy Symptom Score: number of participants who had worsened symptoms

Analysis 7.4. Comparison 7: Pine bark extract versus placebo: DM types I and II combined, Outcome 4: Change in HbA1C (%)

Analysis 7.5. Comparison 7: Pine bark extract versus placebo: DM types I and II combined, Outcome 5: Total cholesterol (mmol/L)

Analysis 7.6. Comparison 7: Pine bark extract versus placebo: DM types I and II combined, Outcome 6: LDL (mmol/L)

Analysis 7.7. Comparison 7: Pine bark extract versus placebo: DM types I and II combined, Outcome 7: HDL (mmol/L)

Analysis 7.8. Comparison 7: Pine bark extract versus placebo: DM types I and II combined, Outcome 8: Triglycerides (mmol/L)

Analysis 7.9. Comparison 7: Pine bark extract versus placebo: DM types I and II combined, Outcome 9: hsCRP (mg/L)

Comparison 8. Pine bark extract versus placebo: ED

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 IIEF-5	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1.1 At three months	2		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 IIEF Erectile function domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.2.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.3 International Prostate Symptom Score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.3.1 At three months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.4 Total plasma testosterone (nmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.4.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.5 Systolic blood pressure (mmHg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.5.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.6 Diastolic blood pressure (mmHg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.6.1 At six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.7 Antioxidant activity (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.7.1 At three months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Pine bark extract versus placebo: ED, Outcome 1: IIEF-5

Study or Subgroup	Pine bark			Control			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
8.1.1 At three months								
Cai 2013	19.3	1	83	16.1	1.2	46	3.20 [2.79 , 3.61]
Duracková 2003	3.6	4.79	13	-2.4	0.84	8	6.00 [3.33 , 8.67]	
							-10 -5 0 5 10	Favours control Favours pine bark

Analysis 8.2. Comparison 8: Pine bark extract versus placebo: ED, Outcome 2: IIEF Erectile function domain

Analysis 8.3. Comparison 8: Pine bark extract versus placebo: ED, Outcome 3: International Prostate Symptom Score

Analysis 8.4. Comparison 8: Pine bark extract versus placebo: ED, Outcome 4: Total plasma testosterone (nmol/L)

Analysis 8.5. Comparison 8: Pine bark extract versus placebo: ED, Outcome 5: Systolic blood pressure (mmHg)

Analysis 8.6. Comparison 8: Pine bark extract versus placebo: ED, Outcome 6: Diastolic blood pressure (mmHg)

Analysis 8.7. Comparison 8: Pine bark extract versus placebo: ED, Outcome 7: Antioxidant activity (%)

Comparison 9. Pine bark extract versus control: female sexual dysfunction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 FSFI desire domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.2 FSFI arousal domain	1	75	Mean Difference (IV, Fixed, 95% CI)	3.20 [1.12, 5.28]
9.2.1 At two months	1	75	Mean Difference (IV, Fixed, 95% CI)	3.20 [1.12, 5.28]
9.3 FSFI lubrication domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.3.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.4 FSFI orgasm domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.4.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.5 FSFI satisfaction domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.5.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.6 FSFI pain domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.6.1 At two months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Pine bark extract versus control: female sexual dysfunction, Outcome 1: FSFI desire domain

Analysis 9.2. Comparison 9: Pine bark extract versus control: female sexual dysfunction, Outcome 2: FSFI arousal domain

Analysis 9.3. Comparison 9: Pine bark extract versus control: female sexual dysfunction, Outcome 3: FSFI lubrication domain

Analysis 9.4. Comparison 9: Pine bark extract versus control: female sexual dysfunction, Outcome 4: FSFI orgasm domain

Footnotes

(1) Question 11 to 13 of FSFI. Max score is 15. Lower the score the worse the dysfunction.

Analysis 9.5. Comparison 9: Pine bark extract versus control: female sexual dysfunction, Outcome 5: FSFI satisfaction domain

Footnotes

(1) Question 14 to 16 of FSFI. Max score 15. Lower the score the worse the dysfunction.

Analysis 9.6. Comparison 9: Pine bark extract versus control: female sexual dysfunction, Outcome 6: FSFI pain domain

Footnotes

(1) Question 17 to 19 of FSFI. Max score 15. Lower score indicates dysfunction.

Comparison 10. Pine bark extract versus placebo: osteoarthritis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Pain scores	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1.1 At three months	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.2 Pain score (VAS)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.2.1 At three months	1	84	Mean Difference (IV, Fixed, 95% CI)	-3.16 [-14.02, 7.70]
10.3 Physical function score	2		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3.1 At three months	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.4 Stiffness scores	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
10.4.1 At three months	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
10.5 Composite WOMAC score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.5.1 At three months	1	37	Mean Difference (IV, Fixed, 95% CI)	-730.00 [-1011.95, -448.05]
10.6 Reduction of NSAIDs	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.6.1 At three months	1	100	Risk Ratio (M-H, Fixed, 95% CI)	4.75 [1.74, 12.97]
10.7 Change in NSAIDs and COX-2 inhibitor usage (number of pills taken)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.7.1 At three months	1	35	Mean Difference (IV, Fixed, 95% CI)	-18.30 [-25.14, -11.46]
10.8 Change in number of days in taking NSAIDs and COX-2 inhibitor	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.8.1 At three months	1	35	Mean Difference (IV, Fixed, 95% CI)	-11.80 [-16.00, -7.60]

Analysis 10.1. Comparison 10: Pine bark extract versus placebo: osteoarthritis, Outcome 1: Pain scores

Analysis 10.2. Comparison 10: Pine bark extract versus placebo: osteoarthritis, Outcome 2: Pain score (VAS)

Analysis 10.3. Comparison 10: Pine bark extract versus placebo: osteoarthritis, Outcome 3: Physical function score

Analysis 10.4. Comparison 10: Pine bark extract versus placebo: osteoarthritis, Outcome 4: Stiffness scores

Analysis 10.5. Comparison 10: Pine bark extract versus placebo: osteoarthritis, Outcome 5: Composite WOMAC score

Analysis 10.6. Comparison 10: Pine bark extract versus placebo: osteoarthritis, Outcome 6: Reduction of NSAIDs

Analysis 10.7. Comparison 10: Pine bark extract versus placebo: osteoarthritis, Outcome 7: Change in NSAIDs and COX-2 inhibitor usage (number of pills taken)

Analysis 10.8. Comparison 10: Pine bark extract versus placebo: osteoarthritis, Outcome 8: Change in number of days in taking NSAIDs and COX-2 inhibitor

Comparison 11. Pine bark extract versus placebo: osteopenia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Bone alkaline phosphatase (ug/L)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	2.21 [0.58, 3.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 Procollagen type 1 N-terminal propeptide (ng/mL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.2.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	73.00 [17.03, 128.97]
11.3 C-terminal telopeptide of type I collagen (ng/mL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.3.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.19, 0.03]
11.4 Bone alkaline phosphatase/C-terminal telopeptide of type I collagen	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.4.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	38.19 [3.09, 73.29]
11.5 Receptor activator of nuclear factor k-B ligand (ng/mL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.5.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	-54.43 [-133.33, 24.47]
11.6 Osteoprotegerin (ng/mL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.6.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	0.14 [-1.82, 2.10]
11.7 Parathyroid hormone (pg/mL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.7.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.86 [-10.67, 6.95]
11.8 Serum calcium (mg/dL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.8.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	0.02 [-1.98, 2.02]
11.9 Serum magnesium (mg/dL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.9.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	0.04 [-1.90, 1.98]
11.10 Serum phosphorus (mg/dL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.10.1 At three months	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-2.17, 1.97]

Analysis 11.1. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 1: Bone alkaline phosphatase (ug/L)

Analysis 11.2. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 2: Procollagen type 1 N-terminal propeptide (ng/mL)

Analysis 11.3. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 3: C-terminal telopeptide of type I collagen (ng/mL)

Analysis 11.4. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 4: Bone alkaline phosphatase/C-terminal telopeptide of type I collagen

Analysis 11.5. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 5: Receptor activator of nuclear factor k-B ligand (ng/mL)

Analysis 11.6. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 6: Osteoprotegerin (ng/mL)

Analysis 11.7. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 7: Parathyroid hormone (pg/mL)

Analysis 11.8. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 8: Serum calcium (mg/dL)

Analysis 11.9. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 9: Serum magnesium (mg/dL)

Analysis 11.10. Comparison 11: Pine bark extract versus placebo: osteopenia, Outcome 10: Serum phosphorus (mg/dL)

Comparison 12. Pine bark extract versus placebo: TBI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Cognitive failure questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	-2.24 [-11.17, 6.69]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 Rivermead Post Concussion symptom questionnaire: questions 1 to 3	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.2.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-1.66, 1.16]
12.3 Rivermead Post Concussion symptom questionnaire: questions 1 to 13	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.3.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	-0.76 [-5.39, 3.87]
12.4 Hospital Anxiety and Depression scale: anxiety	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.4.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	-1.77 [-4.07, 0.53]
12.5 Hospital Anxiety and Depression scale: depression	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.5.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	-1.17 [-2.90, 0.56]
12.6 California Verbal Learning Test: short-delay free recall	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.6.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	0.26 [-0.30, 0.82]
12.7 California Verbal Learning Test: long-delay free recall	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.7.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.26, 0.82]
12.8 California Verbal Learning Test: recognition	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.8.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.46, 0.94]
12.9 California Verbal Learning Test: mean total accuracy (%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.9.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	2.04 [-4.37, 8.45]
12.10 Wechsler Adult Intelligence scale: digit span	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.10.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	-1.02 [-2.47, 0.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.11 Wechsler Adult Intelligence Scale: letter number sequencing	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.11.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-1.49, 0.71]
12.12 Wechsler Adult Intelligence Scale: arithmetic	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.12.1 At six weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-1.41, 1.39]

Analysis 12.1. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 1: Cognitive failure questionnaire

Analysis 12.2. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 2: Rivermead Post Concussion symptom questionnaire: questions 1 to 3

Analysis 12.3. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 3: Rivermead Post Concussion symptom questionnaire: questions 1 to 13

Analysis 12.4. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 4: Hospital Anxiety and Depression scale: anxiety

Analysis 12.5. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 5: Hospital Anxiety and Depression scale: depression

Analysis 12.6. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 6: California Verbal Learning Test: short-delay free recall

Analysis 12.7. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 7: California Verbal Learning Test: long-delay free recall

Analysis 12.8. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 8: California Verbal Learning Test: recognition

Analysis 12.9. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 9: California Verbal Learning Test: mean total accuracy (%)

Analysis 12.10. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 10: Wechsler Adult Intelligence scale: digit span

Analysis 12.11. Comparison 12: Pine bark extract versus placebo: TBI, Outcome 11: Wechsler Adult Intelligence Scale: letter number sequencing

**Analysis 12.12. Comparison 12: Pine bark extract versus placebo:
TBI, Outcome 12: Wechsler Adult Intelligence Scale: arithmetic**

Comparison 13. Pine bark extract versus control: serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Withdrawal from study because of pine bark extract supplements	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1.1 At three months	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 1.97]
13.2 Hospitalisation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.2.1 At two months	1	46	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.02]
13.2.2 At three months	1	130	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 74.54]
13.3 Emergency department visits	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.3.1 At three months	1	130	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.96]

Analysis 13.1. Comparison 13: Pine bark extract versus control: serious adverse events, Outcome 1: Withdrawal from study because of pine bark extract supplements

Analysis 13.2. Comparison 13: Pine bark extract versus control: serious adverse events, Outcome 2: Hospitalisation

Footnotes

- (1) Cross-over trial
(2) Parallel group design trial

Analysis 13.3. Comparison 13: Pine bark extract versus control: serious adverse events, Outcome 3: Emergency department visits

ADDITIONAL TABLES

Table 1. Description of interventions per condition

Condition	Study	Brand	Manufacturer	Composition	Dosage, frequency and duration	Mode	Concomitant treatment
Asthma	Hosseini 2001a	Pycnogenol®	Horphag Research, Geneva, Switzerland.	Bioflavonoid mixture extracted from <i>Pinus maritima</i> .	1 mg/lb body weight/day (maximum 200 mg/day) for 4 weeks.	Not reported.	Usual medications could be used except for glucocorticoids, leukotriene antagonists, multivitamins, aspirin and any other NSAIDs.
	Lau 2004	Pycnogenol®	Horphag Research, Geneva, Switzerland.	Proprietary mix of water-soluble bioflavonoids from French maritime pine (<i>Pinus maritima/pinaster</i> Aiton); broadly divided into catechin, epicatechin and taxifolin as monomers, and condensed flavonoids (procyanidins and proanthocyanidins).	1 mg/lb body weight in 2 divided dosages daily for 3 months.	Not reported.	Not reported whether specific medication was not permitted; however, change in use of rescue inhaler (albuterol) and oral medication Accolate (zafirlukast; leukotriene receptor antagonist) were reported as outcomes in the trial, therefore we know that these specifically were permitted.
Attention deficit hyperactivity disorder	Trebatická 2006	Pycnogenol®	Drug Research Institute, Modra, Slovakia.	French maritime pine (<i>Pinus pinaster</i>) consisting of phenolic acids, catechins, taxifolin and procyanidins.	1 mg/kg body weight at breakfast daily for 1 month.	Not reported.	None were permitted - neither psychotropic drugs nor vitamins E and C supplements during the study period.
Cardiovascular disease and risk factors	Cesarone 2008	OPC-3®	nutraMetrix, Division of Market America, Greensboro, NC, USA.	400 mg flavonoids (consisting of equal amounts of Pycnogenol®, grape seed, bilberry, citrus, and red wine); as well as inactive ingredients i.e. fructose, glucose, citric acid, potassium bicarbonate, silica, calcium sulfate, and pectin.	1x 10 g pouch daily for 2 months	Orally, following solubilization of sachet contents with 180 mL water resulting in an isotonic solution.	"...none of the subjects was on a medical intervention..."
	Drieling 2010	Flavangenol®	Toyo-FVG, Toyo Bio-Pharma, Torrance, Cal-	OPC extracted from the milled bark of <i>Pinus pinaster</i> (also known as <i>Pinus maritima</i> and <i>Pinus maritimus</i>); comprising approximately 40%	50 mg 4x daily every morning for 3 months.	Oral.	Participants were queried about their use of dietary supplements and medications at screening and

Table 1. Description of interventions per condition (Continued)

		ifornia and Shinyaku Co, Ltd, Saga, Japan.	proanthocyanidin oligomers, 42% other polyphenols and 18% other substances. This is compounded with excipients of palatinit sugar, caramel, sucrose, fatty acid ester, and calcium stearate.			were asked to report any changes.
Enseleit 2012	Pycnogenol®	Horphag Research (UK) Ltd, London, UK.	Proprietary bark extract of <i>Pinus pinaster</i> ssp. <i>atlantica</i> .	200 mg daily for 8 weeks with a 2-week washout period.	Not reported.	Concomitant treatment: optimal standard cardiovascular therapy "The patients were advised not to take their usual drugs in the morning of the examination day...medical therapy was unchanged throughout the study."; participants on concomitant medication were as follows: aspirin 100%; statin 87%; ACE-inhibitor/ARB 78%; beta blocker 74%; diuretics 35%; calcium-antagonist 17%; clopidogrel 17%; ezetimibe 17%; oral anti-diabetics 17%; marcoumar 4%; alpha-antagonist 4%.
Hosseini 2001b	Pycnogenol®	Cognis Corporation (La-Grange, Illinois, USA).	Proprietary bark extract of the French maritime pine tree (<i>Pinus pinaster</i>) containing flavonoids as monomers (catechin and taxifolin) and 85% as condensed polymers (including procyanidins) as well as phenolic acids, as minor constituents, and glycosylation products.	1 mg/lb body weight/day (maximum 200 mg/day) for 4 weeks.	Oral.	Usual medications could be used except for glucocorticoids, leukotriene antagonists, multivitamins, aspirin and any other NSAIDs.
Liu 2004c	Pycnogenol®	Horphag Research Ltd.	Extract from the bark of the French maritime pine (<i>Pinus pinaster</i> Aiton), consists of a concentrate of polyphenols. Main constituents are procyanidins, pharmacologically active biopolymers composed	100 mg for 12 weeks.	Oral.	After the 2-week run-in period on placebo, all participants were put on a calcium antagonist (nifedipine, sustained release tablets, 5 mg, Shanghai Pharma-

Table 1. Description of interventions per condition (Continued)

				from units of catechin and epicatechin. Additionally, containing the bioflavonoids catechin and taxifolin and a number of phenolic acids		ceuticals Co, Ltd.) The dose nifedipine was 20 mg (frequency not reported, assumed to be daily) initially, and then adjusted at 2-week intervals (either reduced or increased with 5 mg) as needed to sustain "stable blood pressure".	
	Reule 2017	AbMIP (L-arginine-based multi ingredient product)	vasoLoges® protect, Dr. Loges & Co. GmbH, Germany.	4 tablets together containing 2400 mg L-arginine, 80 mg Pycnogenol®, 45 µg vitamin K2, 10 mg alpha lipoic acid, 8 mg vitamin B6, 500 µg vitamin B12 and 600 µg folic acid.	2 tablets 2x daily (4 tablets) 4 weeks on experimental treatment or placebo, followed by a 8-week washout period before cross-over to treatment or placebo.	Oral.	No participants were on blood pressure medication, treatment for cardiovascular disease, or statins.
	Valls 2016	Oligopin®	Les Derivés Résiniques & Térpeniques (DRT, France).	Specific selective extraction and purification of French maritime pine bark (<i>Pinus pinaster</i> Aiton) resulting in a product with < 1% tannins and a high content of low molecular weight oligomeric procyanidins (> 70%) and ~ 20% dimers. Each capsule contains 280 mg of total content consisting of 75 mg Oligopin, 175 mg maltodextrin, and 30 mg magnesium stearate.	2x daily, 1 capsule in the morning and 1 in the afternoon; 1 week run-in for dietary stabilisation followed by 5 weeks on experimental treatment or placebo, a 3-week washout period before cross-over to treatment or placebo for 5 weeks.	Oral, as the product is water-soluble it could be taken before or after meals.	None.
Chronic venous insufficiency	Arcangeli 2000	Pycnogenol®	Not reported.	French maritime pine bark (<i>Pinus maritima</i> Lam.) containing bioflavonoids, catechin, phenolic acids	100 mg 3x per day for 2 months.	Not reported; assumed to be oral.	Participants were not allowed to take drugs which act upon the cardiovascular system.

Table 1. Description of interventions per condition (Continued)

				and a large number of procyanidins.			lar system, diuretics, or analgesic and anti-inflammatory combinations during the treatment period.
	Petrassi 2000	Pycnogenol®	Not reported.	French maritime pine bark extract (<i>Pinus maritima</i>) with main constituents being phenolic compounds (catechin, epicatechin and taxifolin), condensed flavonoids (procyanidins/proanthocyanidins), and phenolic acids.	100 mg 3x per day for 2 months.	Oral.	During the 2-month treatment period participants were not allowed to take drugs affecting the cardiovascular system, diuretics, analgesics or anti-inflammatory compounds.
Diabetes mellitus	Belcaro 2006a	Pycnogenol® for all 3 treatment groups.	Horphag Research Management SA, Geneva, Switzerland.	Extract of bark from the French maritime pine.	<u>Group 1</u>	<u>Group 1</u>	All participants received general ulcer care daily that included washing and cleaning in water and a mild disinfectant (Citrosil, Italy), drying with soft paper tissue and dressed with nonallergic paper and a elastic-adhesive bandage (Tensoplast, South Africa).
					3x daily for 6 weeks	oral and local on ulcerated area.	
					50 mg capsule orally together with 100 mg powder from 2x 50 mg capsules placed on ulcerated area.		
					<u>Group 2</u>	<u>Group 2</u>	
					Once daily for 6 weeks	local on ulcerated area only.	
					100 mg powder from 2x 50 mg capsules placed on ulcerated area.		
					<u>Group 3</u>	<u>Group 3</u>	
					3x daily for 6 weeks	oral only.	
					50 mg capsule.		
	Chous 2016	DiVFuSS	ZeaVision, LLC, Chester-	Each capsule containing vitamins C, D3, and E (d-alpha-tocopherol),	2x capsules daily for 6 months.	Oral.	With the exception of a single, daily multivitamin

Table 1. Description of interventions per condition (Continued)

			field, Missouri, USA.	zinc oxide, eicosapentaenoic acid, docosahexaenoic acid, alpha-lipoic acid (racemic mixture), coenzyme Q10, mixed tocotrienols/tocopherols, zeaxanthin, lutein, benfotiamine, N-acetyl cysteine, grape seed extract, resveratrol, turmeric root extract, green tea leaf, and French maritime pine bark extract (Pycnogenol®, Horphag Research, Geneva, Switzerland).			and mineral supplement (23 of 67 participants), no participants were currently using dietary supplements containing ingredients found in the test formula.
	Domanico 2015	Diaberet	Visufarma, Rome, Italy.	Each tablet containing 50 mg Pycnogenol®; 30 mg vitamin E; and 20 mg Coenzyme Q.	1x tablet daily for 6 months.	Oral.	Single type of oral metformin monotherapy at a dose of 1000 mg 2x daily for the duration of the study and at least 6 months before enrolment.
	Liu 2004a	Pycnogenol®	Horphag Research Ltd.	French maritime pine (<i>Pinus pinaster</i> Aiton) bark extract with main constituents oligomeric procyanidins. Monomeric catechin, taxifolin, and various phenolic acids are also present.	100 mg for 12 weeks.	Oral.	Conventional oral antidiabetic medication as needed was permitted.
	Steigerwalt 2009	Pycnogenol®	Manhattan Drug Company, Inc., New York, USA.	French maritime pine bark extract.	3x 50 mg tablets per day after breakfast for 2 months.	Oral.	Not reported, but control of blood glucose levels by oral antidiabetic medication was part of the inclusion criteria and thus permitted.
	Zibadi 2008	Pycnogenol®	Not reported.	Extract from the bark of French maritime pine (<i>Pinus maritima</i>), mainly comprising phenolic compounds (catechin, epicatechin and taxifolin) and flavonoids (procyanidins).	25 mg tablets 5x per day for 12 weeks.	Oral.	1st generation sulphonylureas, 2nd generation sulphonylureas, metformin, and thiazolidinediones for glucose control were permitted.
Erectile dysfunction	Cai 2013	IDIProst® Gold	Not reported.	Each capsule contained <i>Serenoa repens</i> (320 mg), <i>Crocus sativus</i> (100 mg) and <i>Pinus massoniana</i> (120 mg).	1x 950 mg capsule per day for 3 months.	Oral.	None.

Table 1. Description of interventions per condition (Continued)

	Duracková 2003	Pycnogenol®	Not reported.	French maritime pine (<i>Pinus pinaster</i>) bark extract. Mixture of flavonoids as catechin, taxifolin, and procyanidins. Minor constituents: phenolic acids.	2x 20 mg pills 3x per day (total of 120 mg/day) for 3 months.	Oral.	None permitted (also no vitamin C and E supplements).
	Ledda 2010	Prelox®	Horphag Research UK Ltd, London, UK.	Each tablet contained 20 mg Pycnogenol®, 700 mg L-arginine aspartate.	4x tablets daily, 2 tablets in the morning after breakfast and another 2 after dinner for 6 months.	Not reported.	No participants were taking antihypertensive medication before enrolment or during the trial; none had cholesterol medication either.
Female sexual dysfunction	Bottari 2012	Lady Prelox®	Horphag Research.	Each capsule contained 20 mg Pycnogenol®, 200 mg L-arginine, 200 mg L-citrulline, 50 mg Rosvita rose-hip extract.	2x capsules in morning and 2x in evening for 8 weeks.	Oral.	"No medications or other supplements were permitted during the trial period, with the exception of daily vitamins and minerals."
Osteoarthritis	Belcaro 2008a	Pycnogenol®	Manhattan Drug Company Inc., New York, USA.	Extract of French maritime pine bark. Concentrate of plant polyphenols, predominantly procyanidins.	50 mg capsule 2x per day (after breakfast and dinner) for 3 months.	Oral.	Associated treatments prescribed by the participant's general practitioner were to be reported in a diary. After contacting the study authors we learned that NSAIDs, paracetamol and ibuprofen were allowed during the study.
	Cisár 2008	Pycnogenol®	Manhattan Drug Company, New York, USA.	French maritime pine (<i>Pinus pinaster</i>) bark extract consisting of a concentrate of polyphenols, several phenolic acids, catechin, taxifolin, and procyanidins.	50 mg tablets 3x per day with meals for 12 weeks.	Oral.	Participants could use NSAIDs or other analgesics prescribed prior to the start of the study and could change the dose and frequency of drug intake, but they had to report changes at each visit.
	Farid 2007	Pycnogenol®	Horphag Research Ltd, Geneva, Switzerland.	Extract from the bark of French maritime pine (<i>Pinus maritima</i>) containing monomeric phenolic compounds (catechin, epicatechin and taxifolin), condensed	50 mg tablets 3x per day for 3 months.	Oral.	COX-2 and other NSAIDs as medical treatment for pain in the target knee.

Table 1. Description of interventions per condition (Continued)

				flavonoids (procyanidins), and phenolic acids.			
Osteopenia	Panahande 2019	Oligopin®	France Purextract (DRT) Co.	Oligopin® containing 50 mg French maritime pine (<i>Pinus pinaster</i>) bark extract consisting of procyanidins (67 - 75%), catechin (4 - 10%), taxifolin (0.5 - 4%), taxifolin glucoside (3 - 8%), f glucoside (4 - 10%), gallic acid (0.1 - 1%), protocatechuic acid (0.5 - 3%), caffeic acid (0.5 - 3%), p-coumaric acid (0.3 - 2%), ferulic acid (1 - 5%), and other oligomers including monomeric and dimeric phenolic acids.	250 mg/day given as 5 capsules per day; 2 capsules after breakfast, 2 capsules after lunch and 1 capsule after dinner for 12 weeks.	Oral.	Not reported.
Traumatic brain injury	Theadom 2013	Enzogenol®	ENZO Nutraceuticals.	Pine bark extract from New Zealand-grown <i>Pinus radiata</i> . Each capsule contained 500 mg Enzogenol pine bark extract; consisting of proanthocyanidins (average 84%), taxifolin (1 - 2%), other flavonoids, phenolic acids and stillbenes (8% combined), including catechin, quercetin, myricetin, astringenin, gallic acid, ferulic acid, caffeic acid, protocatechuic acid, and carbohydrates (5 - 10%).	2x capsules daily taken with a large glass of water in the morning (15 minutes before breakfast) for 6 weeks.	Oral.	Not reported, but "Possible contradiction with medication" cited as a reason for attrition in treatment group.

ACE: angiotensin-converting enzyme

COX-2: cyclooxygenase-2

NSAID: non-steroidal anti-inflammatory drug

Table 2. Incomplete results: asthma

Study ID	Outcome	Pine bark ^a		Placebo		Pine bark ^a versus placebo
		Baseline Mean (SE)	Month 3 Mean (SE)	Baseline Mean (SE)	Month 3 Mean (SE)	Mean difference (SE)
Hosseini 2001a	Asthma symptom scores	#	1.75* (#)	#	2.15* (#)	#
Lau 2004	Asthma symptom scores	2.25 (0.13)	0.27 (0.06)	#	#	#
Lau 2004	Peak expiratory flow	69.7 (1.7)	♣	69.9 (1.6)	♣	#
Lau 2004	Use of albuterol inhaler (puffs/24 hours)	2.57 (0.16)	0.22 (0.07)	2.59 (0.14)	2.32 (0.21)	#

^a both studies used Pycnogenol® as the active intervention

Not reported

* Extracted from figure

♣ Only reported in figure from which results cannot be extracted accurately

SE: standard error

Table 3. Incomplete results: ADHD

Study ID	Outcome	Pine bark ^a		Placebo		Pine bark ^a versus placebo
		Baseline Mean (SE)	Month 1 Mean (SE)	Baseline Mean (SE)	Month 1 Mean (SE)	Mean difference (SE)
Trebatická 2006	GSSG (μmol/l)	4.60 (0.09)	3.58 (0.51)	#	♣	#
Trebatická 2006	GSH (μmol/l)	102.89 (19.08)	130.44 (7.94)	#	♣	#
Trebatická 2006	GSH/GSSG	35.93 (4.27) [^]	52.26 (3.81)	35.93 (4.27) [^]	♣	#
Trebatická 2006	8-oxoG levels/10 ⁶ guanine	0.558 (♣)	0.412 (♣)	♣	0.638 (♣)	#
Trebatická 2006	Total antioxidant status (mM)	1.026 (0.021) ^{^^}	1.05 (0.016)	1.026 (0.021) ^{^^}	#	#

^a both studies used Pycnogenol® as the active intervention

Not reported

[^] "In patients with ADHD, the calculated GSH/GSSG ratio was 35.93±4.27 at the beginning of the trial." Therefore the baseline values for the two groups were not reported separately.

^{^^} "...TAS in plasma of children with ADHD (1.026±0.021 mM)..." ; therefore the baseline values for the two groups were not reported separately.

♣ Only reported in figure from which results cannot be extracted accurately

ADHD: attention deficit hyperactivity disorder

GSH: reduced form of glutathione
GSSG: oxidized form of glutathione
SE: standard error

Table 4. Incomplete results: CVD and risk factors

Study ID	Outcome	Pine bark ^a			Placebo			Pine bark ^a versus placebo MD (SE)
		Baseline	Week 4	Week 8	Baseline	Week 4	Week 8	
		Mean (SD) ^b	Mean (SD)	Mean (SD) ^b	Mean (SD) ^b	Mean (SD)	Mean (SD) ^b	
Hosseini 2001b	Systolic blood pressure (mm Hg)	139.9 (3.3)		132.7 (4.18)	#		#	#
Hosseini 2001b	Diastolic blood pressure (mm Hg)	93.8 (1.23)		92.0 (1.7)	#		#	#
Enseleit 2012	Systolic blood pressure (mm Hg)	125.8 (8.7)		125.5 (8.1)	124.8 (9.7)		125.7 (8.1)	1.2 (#)
Enseleit 2012	Diastolic blood pressure (mm Hg)	75.0 (7.0)		74.3 (7.3)	73.9 (7.5)		74.4 (6.6)	1.2 (#)
Enseleit 2012	Fasting blood glucose (mmol/L)	5.7 (1.4)		5.6 (1.3)	5.7 (1.1)		5.7 (1.3)	0.1 (#)
Enseleit 2012	Total cholesterol (mmol/L)	4.6 (0.6)		4.6 (0.7)	4.7 (0.7)		4.8 (0.8)	0.1 (#)
Enseleit 2012	HDL cholesterol (mmol/L)	1.4 (0.4)		1.4 (0.4)	1.4 (0.4)		1.4 (0.4)	0 (#)
Enseleit 2012	LDL cholesterol (mmol/L)	2.5 (0.5)		2.5 (0.6)	2.6 (0.6)		2.7 (0.7)	0.1 (#)
Enseleit 2012	Triglycerides (mmol/L)	1.4 (0.7)		1.5 (0.7)	1.5 (0.9)		1.5 (0.9)	0.1 (#)
Enseleit 2012	High sensitivity CRP	1.52 (1.37)		1.52 (1.33)	1.63 (1.71)		1.91 (3.4)	0.28 (#)

Table 4. Incomplete results: CVD and risk factors (Continued)
(mg/L)

Enseleit 2012	15-F2t-Isoprostane	0.71 (0.09)	0.66 (1.3)	0.72 (0.09)	0.75 (0.1)	0.08 (#)
	(pg/mL)					
Enseleit 2012	Total antioxidant capacity	10.12 (1.65)	10.1 (1.28)	9.65 (2.72)	9.78 (2.7)	0.15 (#)
	(mM)					
Reule 2017	HbA1c	#	5.37 (0.41)	#	5.34 (0.38)	#
	(%)					

^a Hosseini and Enseleit studies used Pycnogenol® and Reule used Verum® as the active intervention

^b Hosseini reports mean (SE) not mean (SD)

Not reported

CRP: C-reactive protein

HbA1c: glycated haemoglobin

MD: mean difference

SD: standard deviation

SE: standard error

Table 5. Incomplete results: CVI

Study ID	Outcome	Pine bark ^a		Placebo		Pine bark ^a versus placebo
		Baseline Mean (SE)	Month 2 Mean (SE)	Baseline Mean (SE)	Month 2 Mean (SE)	Mean difference (SE)
Arcangeli 2000	Heaviness score	2.06 (0.13)	0.94 (0.19)	1.72 (0.11)	1.67 (0.11)	1.07 (#)
Arcangeli 2000	Swelling score	1.68 (0.13)	0.60 (0.21)	1.50 (0.12)	1.39 (0.12)	0.97 (#)
Arcangeli 2000	Pain score	1.61 (0.12)	0.58 (0.19)	1.42 (0.15)	1.17 (0.11)	0.78 (#)
Petrassi 2000	Heaviness score	2.22 (0.222)	0.88 (0.227)	1.83 (0.167)	1.60 (0.245)	1.11 (#)
Petrassi 2000	Swelling score	1.25 (0.164)	0.33 (0.333)	1.00 (0.00)	0.71 (0.184)	0.63 (#)
Petrassi 2000	Pain score	#	#	#	#	#
Petrassi 2000	Disappearance of heaviness	#	#	#	#	#
Petrassi 2000	Disappearance of swelling	#	#	#	#	#
Petrassi 2000	Disappearance of pain	#	#	#	#	#

^a both studies used Pycnogenol® as the active intervention

Not reported

SE: standard error

Table 6. Incomplete results: DM (type I)

Study ID	Outcome	Pine bark ^a (oral & local)#		Pine bark ^a (local)#		Pine bark ^a (oral)#		Control#	
		Baseline	Week 6	Baseline	Week 6	Baseline	Week 6	Baseline	Week 6
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Belcaro 2006a	Microcirculation-related symptom scores	7.0 (3.0)	2.2 (2.0)	7.1 (3.0)	4.0 (2.0)	7.2 (2.2)	3.8 (2.2)	7.1 (2.0)	5.1 (3.0)
Belcaro 2006a	Change in area of ulceration (mm ²)	43.0 (4.0)	11.0 (4.0)	46.0 (6)	27.0 (7.0)	45.0 (4.0)	30.0 (6.0)	44.0 (5.2)	35.0 (5.0)
Belcaro 2006a	Transcutaneous PO ₂	47.0 (4.0)	58.0 (3.0)	-	-	46.0 (3.0)	55.0 (4.0)	48.0 (4.2)	48.0 (3.0)
Belcaro 2006a	Transcutaneous PCO ₂	33.0 (2.0)	27.0 (3.0)	-	-	32.0 (3.0)	28.8 (2.0)	32.0 (2.2)	29.8 (3.3)
Belcaro 2006a	Skin flux at rest	3.6 (1.0)	2.0 (0.7)	-	-	3.5 (0.7)	2.1 (1.0)	3.8 (0.2)	3.8 (0.8)

the SD of the mean change was not given for any outcome or treatment group (we contacted the study authors who responded that "the requested data is not available")

- Not assessed

^a study used Pycnogenol[®] as the active intervention

PO₂: pressure of oxygen

PCO₂: carbon dioxide partial pressure

SD: standard deviation

Table 7. Blood glucose (mmol/L) and plasma HbA1c (%): DM type II

Study ID	Outcome	Pine bark ^a	Placebo	Pine bark ^a versus placebo
		Change from baseline at 3 months Median (IQR)	Change from baseline at 3 months Median (IQR)	Change from baseline at 3 months
Liu 2004a	Blood glucose (mmol/L)	-1.96 (-3.25 to -1.24)	-1.11 (-2.00 to -0.44)	P < 0.01
Liu 2004a	HbA1c (%)	-0.69 (-1.07 to -0.43)	-0.53 (-0.75 to -0.16)	P > 0.05

^a study used Pycnogenol® as the active intervention
HbA1c: glycated haemoglobin
IQR = Interquartile range

Table 8. Incomplete results: DM (type II)

Study ID	Outcome	Pine bark ^a		Placebo		Pine bark ^a versus placebo
		Baseline	Week 12	Baseline	Week 12	Mean difference (SE)
		Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Zibadi 2008	HbA1c levels (%)	7.9 (0.3)	7.1 (0.2)	8.1 (0.4)	8.0 (0.4)	0.7 (#)

Not reported

^a study used Pycnogenol® as the active intervention
HbA1c: glycated haemoglobin
SE: standard error

Table 9. Additional results from study authors: DM type II

Study ID	Outcome	Pine bark ^a		Placebo	
		Baseline	Month 3	Baseline	Month 3
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Liu 2004a	nitrogen monoxide (nmol/L)	61.48 (17.93)	76.15 (19.73)	60.03 (19.87)	71.06 (15.66)

^a study used Pycnogenol® as the active intervention
SD: standard deviation

Table 10. Incomplete results: osteoarthritis

Study ID	Outcome	Pine bark ^a	Placebo	Pine bark ^a versus placebo

Table 10. Incomplete results: osteoarthritis (Continued)

		Baseline	Month 3	Baseline	Month 3	Mean difference
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	(SD)
Belcaro 2008a	Sum of pain scores	17.3 (#)	7.7 (#)	17.1 (#)	15.2 (#)	#
Farid 2007	Pain score	292 (101)	164 (72)	301 (119)	306 (103)	133 (#)
Belcaro 2008a	Sum of stiffness scores	6.6 (#)	3.1 (#)	6.7 (#)	6.7 (#)	#
Farid 2007	Stiffness score	110 (66)	75 (54)	120 (63)	108 (56)	23 (#)
Belcaro 2008a	Sum of physical function scores	55.3 (#)	23.8 (#)	53.1 (#)	47.6 (#)	#
Farid 2007	Physical function score	997 (352)	485 (259)	1042 (420)	1014 (385)	484 (#)
Belcaro 2008a	Global WOMAC score	79.2 (#)	34.6 (#)	76.9 (#)	69.5 (#)	#
Farid 2007	Composite WOMAC score	1400 (482)	725 (346)	1463 (552)	1455 (509)	667 (#)
Belcaro 2008a	Negative alterations in social functions	23.1 (#)	9.9 (#)	21.3 (#)	20.4 (#)	#
Belcaro 2008a	Emotional parameters	31.4 (#)	11.5 (#)	28.2 (#)	24.4 (#)	#

Not reported

^a study used Pycnogenol® as the active intervention

SD: standard deviation

WOMAC: Western Ontario and McMaster Universities

Table 11. Additional results of osteoarthritis symptoms from study authors

Study ID	Outcome	Pycnogenol®		Placebo		Pyc-nogenol® versus placebo
		Baseline	Week 12	Baseline	Week 12	Mean difference
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	(SD)
Cisár 2008	Pain (WOMAC A score)	13.52 (3.25)	15.96 (3.20)	13.42 (4.21)	15.0 (4.47)	0.86 (#)
Cisár 2008	Pain (VAS)	41.2 (20.27)	29.74 (25.34)	42.74 (26.26)	32.90 (25.23)	1.62 (#)
Cisár 2008	Stiffness in % (WOMAC B score)	5.24 (1.52)	6.24 (1.46)	5.52 (1.91)	5.95 (2.07)	0.57 (#)
Cisár 2008	Ability to perform daily activities (WOMAC C score)	45.64 (11.57)	52.70 (10.85)	44.74 (14.89)	49.34 (15.32)	2.46 (#)
Cisár 2008	Overall reduction in osteoarthritis symptoms (WOMAC overall score)	65 (#)	74.5 (#)	64 (#)	72 (#)	1.5 (#)

not reported

SD: standard deviation

VAS: visual analogue score

WOMAC: Western Ontario and McMaster Universities

Table 12. Safety

Disorder	Study ID	Country	Number of participants	Age group	Treatment duration	Serious adverse events	Non-serious adverse events
Asthma	Hosseini 2001a	Iran	26	Adults	1 month	None found.	One participant complained of gastrointestinal disturbances which occurred within the first 3 to 4 days of treatment (assumed to be Pycnogenol®).
	Lau 2004	USA	60	Children	3 months	None found.	None found.
ADHD	Trebatická 2006	Slovakia	61	Children	1 month	None found.	<p>1 out of 44 participants in the Pycnogenol® group reported a "rise in slowness"; another reported moderate gastric discomfort. No adverse events in the placebo group (N = 17) were reported.</p> <p>2 out of 43 participants withdrew from the study "even though they received medication" (Pycnogenol®). 1 out of 17 participants from the placebo group discontinued participation in the study. It is not reported what the reason(s) for withdrawal were.</p>
CVD and risk factors	Cesarone 2008	Not reported	61	Adults	2 months	None found.	None found.
	Drieling 2010	Not reported	130	Adults	3 months	In the pine bark extract group, there was 1 hospitalisation and no emergency department visits. In the placebo group, there were no hospitalizations and 2 emergency department visits.	"At 12 weeks, the most commonly reported symptoms were headache (45.5% in the pine bark extract group vs 45.2% in the placebo group), sleepiness (40.9% vs 45.2%), frequent urination (38.6% vs 31.0%), gastrointestinal tract discomfort (38.6% vs 35.7%), and insomnia (34.1% vs 31.0%)."
	Enseleit 2012	Not reported	23	Adults	2 months	"One patient in the Pycnogenol group was hospitalised for acute decompensated heart failure; one patient in the placebo group was excluded after devel-	None found.

Table 12. Safety (Continued)

						opment of an itching rash."	
	Hosseini 2001b	USA	11	Adults	2 months	None found.	None found.
	Liu 2004c	China	58	Adults	3 months	None found.	"Gastrointestinal problems, nausea, dizziness, headache and sleepiness had been reported. The difference in the rate of side effects in Pycnogenol® group (39%) and in placebo group (27%) was not statistically significant."
	Reule 2017	Germany	25	Adults	1 month	None found.	None found.
	Valls 2016	Spain	21	Adults	5 weeks	None found.	None found.
CVI	Arcangeli 2000	Italy	40	Adults	2 months	None found.	None found.
	Petrassi 2000	Italy	20	Adults	2 months	None found.	None found.
DM	Belcaro 2006a	Italy	30	Adults	6 weeks	None found.	None found.
	Chous 2016	Not reported	67	Adults	6 months	Not assessed.	Not assessed.
	Domanico 2015	Not reported	64	Adults	6 months	Not assessed.	Not assessed.
	Liu 2004a	China	77	Adults	3 months	None found.	7 out of 34 participants in the Pycnogenol® group complained about dizziness compared to 4 out of 43 in the placebo group. 5 out of 34 participants in the Pycnogenol® group reported gastro-intestinal problems compared to 2 out of 43 in the placebo group. "Other complaints of headache, nausea and sleepiness occurred only in one or two patients in both groups."
	Steigerwalt 2009	Italy	46	Adults	2 months	None found.	None found.

Table 12. Safety (Continued)

	Zibadi 2008	USA	48	Adults	3 months	None found.	None found.
ED	Cai 2013	Italy	129	Adults	3 months	None found.	"In Group A, 1 out of 83 patients (1.2%) had mild adverse effects that did not require treatment suspension. Also in Group B, 1 out of 46 patients (2.1%) reported mild adverse effects."
	Duracková 2003	Slovak Republic	21	Adults	3 months	Not assessed.	Not assessed.
	Ledda 2010	Not reported	111	Adults	6 months	Not assessed.	Not assessed.
Female sexual dysfunction	Bottari 2012	Not reported	36	Adults	2 months	Not assessed.	Not assessed.
Osteoarthritis	Belcaro 2008a	Italy	156	Adults	3 months	The study authors reported results for the perceived protective effect that the treatment had on "unwanted effects" (gastro-intestinal problems) which "were exclusively attributed to the NSAIDs". No results for adverse events per se during the intervention period were reported.	
	Cisár 2008	Slovakia	100	Adults	3 months	2 out of 50 participants from the Pycnogenol® group and 5 out of 50 from the placebo group left the study because they did not want to use the treatment received any longer. 1 participant (with previous myocardial infarction) from the Pycnogenol® group left the study because of chest pain; another left because of bad breath. 3 participants from the placebo group left because of worsening pain, 1 because of gas-	None found.

Table 12. Safety (Continued)

						tric pain and another 1 felt ill.	
	Farid 2007	Iran	37	Adults	3 months	None found.	None found.
Osteopenia	Panahande 2019	Iran	44	Adults	3 months	None found.	None found.
TBI	Theadom 2013	New Zealand	50	Adults	6 weeks	None found.	"Two participants experienced a headache whilst taking Enzogenol® and two whilst taking the placebo capsules; two participants reported sleep distur- bance (Enzogenol® one; placebo one); one participant reported experiencing blurred vision whilst on the placebo cap- sules. All reported side-effects lasted for <3 weeks (range 8–20 days)."

ADHD: attention deficit and hyperactivity disorder
 CVD: cardiovascular disease
 CVI: chronic venous insufficiency
 DM: diabetes mellitus
 ED: erectile dysfunction
 NSAIDs: non-steroidal anti-inflammatory drugs
 TBI: traumatic brain injury
 vs: versus

Table 13. Evaluating the methodological quality of systematic reviews with the AMSTAR tool (Shea 2007)

Criteria	Yes/No/Can't answer/Not applicable					
	Bartlett 2008	Clark 2010	Henrotin 2011	Zhang 2018	Hadi 2019	Cochrane Review
1. Was an ' <i>a priori</i> ' design provided? - The research question and inclusion criteria should be established before the conduct of the review.	Yes	Yes	Yes	Can not say.	Can not say.	Yes
2. Was there duplicate study selection and data extraction? - There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	No	Yes	No	Can not say.	Yes	Yes
3. Was a comprehensive literature search performed? - At least two electronic sources should be searched. The report must include years and databases used (e.g. CENTRAL, EMBASE and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers or experts in the particular field of study, and by reviewing the references in the studies found.	Yes	Yes	No	Yes.	Yes	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? - The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	No	Can not answer	Yes	No.	Can not say.	No
5. Was a list of studies (included and excluded) provided? - A list of included and excluded studies should be provided.	No	Yes. A list of excluded studies was not provided, but the authors presented the number of excluded studies per reason	No	No	No	Yes

Table 13. Evaluating the methodological quality of systematic reviews with the AMSTAR tool (Shea 2007) (Continued)
in a PRISMA
flow chart.

6. Were the characteristics of the included studies provided?	No, it is incomplete.	Yes	No, it is incomplete.	Yes	No, it is incomplete.	Yes
- In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity or other diseases should be reported.						
7. Was the scientific quality of the included studies assessed and documented?	No. It is reported that only "double-masked randomised controlled trials" were selected, but one of the three included studies (Spadea 2001) on Pycnogenol® was not fully randomised.	Yes. The Cochrane risk of bias assessment tool was used to evaluate adequate sequence generation, allocation concealment and blinding.	Yes. "The methodological quality of each clinical...was determined according to an assessment model adapted from EFSA and FDA recommendations; AFSSA guidelines and other relevant references." This entails that the "quality is scored according to a set of 14 criteria...one point is marked for each criterion presented in the description of the clinical trial." The total scores allow classification as follows: < 6 poor; 7 to 9 medium; 10 to 11 good; and 12 to 14 very good methodological quality.	Yes. The Jadad score of these trials was relatively low, and only four trials had a score of not lower than 3.	Yes. The Cochrane risk of bias assessment tool was used to evaluate adequate sequence generation, allocation concealment and blinding.	Yes
- 'A priori' methods of assessment should be provided (e.g. for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.						

Table 13. Evaluating the methodological quality of systematic reviews with the AMSTAR tool (Shea 2007) (Continued)

8. Was the scientific quality of the included studies used appropriately in formulating conclusion?	No	Yes	Yes, however we do not agree with their judgement of "good to very good" methodological quality.	No	No	Yes
- The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.						
9. Were the methods used to combine the findings of studies appropriate?	Not applicable	Yes	Not applicable	Yes	Yes	Yes
- For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi ² test for homogeneity, I ²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).						
10. Was the likelihood of publication bias assessed?	Not applicable	Not applicable	Not applicable	Yes	Yes	Not applicable
- An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) and/or statistical tests (e.g. Egger regression test).						
11. Was the conflict of interest stated?	No	Yes	Yes	Yes	Yes	Yes
- Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.						

AFSSA: Agence Française de Sécurité Sanitaire des Aliments

EFSA: European Food Safety Agency

FDA: Food and Drug Administration

APPENDICES

Appendix 1. Electronic search strategies

Database	Search strategy	Date searched
CENTRAL (The Cochrane Library)	#1 Pycnogenol #2 pine bark #3 Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine #4 #1 or #2 or #3 with Publication Year from 2017 to 2019, in Trials	30 September 2019
PubMed	1 Search pycnogenol	30 September 2019

Pine bark (*Pinus* spp.) extract for treating chronic disorders (Review)

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(Continued)

- 2 Search "pine bark"
- 3 Search Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine
- 4 Search (((Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine)) OR "pine bark") OR pycnogenol
- 5 Search (((prelog OR flvangenol OR enzogenol OR oligolinx OR proven OR pinexol OR tru-pine)) OR "pine bark") OR pycnogenol
- 6 Search (((Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine)) OR "pine bark") OR pycnogenol[all]
- 7 Search (pycnogenol) OR "pine bark"
- 8 Search (((pycnogenol) OR "pine bark")) OR (Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine)
- 9 Search (((pycnogenol) OR "pine bark")) OR (prelog OR flvangenol OR enzogenol OR oligolinx OR proven OR pinexol OR tru-pine)
- 10 Search (((pycnogenol) OR "pine bark")) OR (Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine)[all]
- 11 Search (((pycnogenol) OR "pine bark")) OR (Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine)[all] Filters: Publication date from 2017/01/01
- 12 Search (((pycnogenol) OR "pine bark")) OR (Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine)[all] Filters: Clinical Trial; Publication date from 2017/01/01
- 13 Search ((((((pycnogenol) OR "pine bark")) OR (Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine)[all]) AND ("2017/01/01"[PDat]: "3000/12/31"[PDat]))) AND (trial[Title/Abstract] OR random*[Title/Abstract] OR placebo[Title/Abstract] OR groups[Title/Abstract] OR participants[Title/Abstract] OR controlled[Title/Abstract]) Filters: Publication date from 2017/01/01

Embase (Ovid)	1 exp pycnogenol/ 2 Pycnogenol.mp. 3 "pine bark".mp. 4 bark/ and pine/ 5 (Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine).mp. 6 1 or 2 or 3 or 4 or 5 7 (random* or factorial* or cross?over or crossover* or placebo* or allocat* or (doubl* and blind*) or (singl* and blind*)).ab. 8 (random* or factorial* or cross?over or crossover* or placebo* or allocat* or (doubl* and blind*) or (singl* and blind*)).ti. 9 (assign* or volunteer*).ti. or (assign* or volunteer*).ab. 10 crossover procedure/ 11 single blind procedure/ 12 double blind procedure/ 13 randomized controlled trial/ or controlled clinical trial/ 14 7 or 8 or 9 or 10 or 11 or 12 or 13 15 6 and 14 16 limit 15 to yr="2017 -Current"	30 September 2019
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ClinicalTrials.gov	[Advanced Search Form]	30 September 2019
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(Continued)

Other terms: Pycnogenol or Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine

Study type: Interventional Studies (Clinical Trials)

ISRCTN Registry (www.isrctn.com/) (formerly known as Current Controlled Trials)	[Basic Search] Pycnogenol or Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine	30 September 2019
WHO International Clinical Trials Registry Platform (ICTRP)	[Basic Search] Pycnogenol or Prelox or Flavangenol or Enzogenol or Oligopin or ProVens or PineXol or Tru-Pine	30 September 2019

Appendix 2. Search strategies for previous versions of this review

Database/Resource	Strategy
CENTRAL (The Cochrane Library) Last searched: 18 September 2010	1 (Pycnogenol):ti,ab,kw in Clinical Trials 2 (pine bark):ti,ab,kw in Clinical Trials 3 (#1 OR #2) 4 (randomized controlled trial):pt in Clinical Trials 5 (controlled clinical trial):pt in Clinical Trials 6 (randomized):ti,ab,kw in Clinical Trials 7 (placebo):ti,ab,kw in Clinical Trials 8 (drug therapy):ti,ab,kw in Clinical Trials 9 (randomly):ti,ab,kw in Clinical Trials 10 (trial):ti,ab,kw in Clinical Trials 11 (groups):ti,ab,kw in Clinical Trials 12 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) 13 (#3 AND #12)
PubMed Last searched: 18 September 2010	1Pycnogenol [tiab] 2 pine bark [tiab] 3 #1 OR #2 4 randomized controlled trial [pt] 5 controlled clinical trial [pt] 6 randomized [tiab] 7 placebo [tiab]

(Continued)

	8 drug therapy [sh]
	9 randomly [tiab]
	10 trial [tiab]
	11 groups [tiab]
	12 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
	13 animals [mh] NOT (humans [mh] AND animals [mh])
	14 #12NOT#13
	15 #3 AND #14
Embase Ovid Last searched: 13 October 2010	1 random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over:ti OR cross?over:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'single-blind procedure'/exp OR 'randomized controlled trial'/exp OR allocat*:ti OR allocat*:ab AND [embase]/lim 2 'Pycnogenol'/exp OR 'pine bark' AND [embase]/lim 3 'pine'/exp AND 'bark'/exp AND [embase]/lim 4 #2 OR #3 5 #1 AND #4
Clinicaltrials.gov Last searched: 18 September 2010	SEARCH 1: Pycnogenol SEARCH 2: pine bark
Current Controlled Trials Last searched: 18 September 2010	SEARCH 1: Pycnogenol SEARCH 2: pine bark
WHO ICTRP Last searched: 18 September 2010	SEARCH 1: Pycnogenol SEARCH 2: pine bark

WHAT'S NEW

Date	Event	Description
30 September 2019	New search has been performed	<p>A search of the Cystic Fibrosis and Genetic Disorders Review Group's Trials Registers did not identify any new studies potentially eligible for inclusion in this review.</p> <p>The authors searched MEDLINE, CENTRAL and Embase and realised that there are now, more than previously, trials that assessed the efficacy of a wide range of pine bark extracts, most</p>

Date	Event	Description
		of which are intended for treating chronic disorders. We have included 12 new trials in this update
30 September 2019	New citation required but conclusions have not changed	<p>The title of this review has been changed from "Pycnogenol® (extract of French maritime pine bark) for the treatment of chronic disorders" to allow the inclusion of other brands of supplements containing pine bark extract.</p> <p>Nina Robertson and Amanda Brand joined the author team for the review update and Jimmy Volmink, who was the senior author on the first review, stepped down.</p>

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 2, 2012

Date	Event	Description
22 May 2012	Amended	Contact details updated.
27 February 2012	Amended	Title changed to indicate the generic contents of the specific brand stated in the review title.
27 February 2012	New citation required but conclusions have not changed	Title has been changed, but the contents of the review remain the same.

CONTRIBUTIONS OF AUTHORS

Original review

Anel Schoonees (AS) developed the idea. AS wrote the protocol and review under the guidance of Prof Jimmy Volmink (JV). AS and JV extracted all the data; Alfred Musekiwa extracted the results for all relevant outcomes. AM and AS summarised and analysed the results, with input from JV. Janicke Visser (JVi) provided input at all stages and revised the protocol and review.

Update 2020

NR lead the review update. NR and AS screened search results in duplicate. NR and AB extracted data and results and assessed RoB; any discrepancies were resolved with the author team. AS, AB and JVi provided input at all stages and revised the completed review.

DECLARATIONS OF INTEREST

All authors: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

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- Foreign, Commonwealth and Development Office, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Initial review

The title of the review protocol was changed from 'Proanthocyanidin supplements for the treatment of chronic disorders' to 'Pycnogenol® for the treatment of chronic disorders'. The reasons for this were threefold. Firstly, Pycnogenol® is a standardised formulation for an extract (a concentrate of plant polyphenols, predominantly procyanidins) from the bark of the French maritime pine. Secondly, there is a lack of specificity of proanthocyanidin-containing products. During the screening process we realised that many proanthocyanidin-containing supplements also contain a variety of other compounds, and that the various supplements vary widely in content. The source of proanthocyanidin also varies (pine bark, grape seed extract, etc.) as do the additional ingredients across the various supplements. Lastly, Pycnogenol® is the most researched proanthocyanidin-containing product and the manufacturer believes that their product is a "well-researched, evidence-based product".

Review update 2020

Title

In the review update the title was changed again to 'Pine bark extract for the treatment of chronic disorder' to broaden the scope of the review so as to include different brands containing pine bark extract and to aid consumers.

As a consequence of this change in title, we revised the following sections of the protocol: 'Description of the intervention', 'Objectives' and 'Criteria for considering studies for this review'.

Methods

We have clarified and clearly stated that quasi-randomised studies are not eligible for inclusion in the review.

The searches strategies have been updated to match the new research question and title. For the review update we updated search terms to not only mention "Pycnogenol OR pine bark" for the intervention, but also to mention all other brand names that we know of ([Appendices](#)).

We have expanded our definition of chronic disorders under types of participants, so it reads more clearly. We based the expansion on the definition that has been used in another Cochrane Review ([Drum 2014](#)).

We initially listed adverse events (both serious and not serious) as a secondary outcome. However, we have now removed this outcome and present safety data separately from the efficacy data. We think it is important to provide the total picture of the evidence for safety across all chronic disorders.

For the subgroup analysis section in this version of the review update we kept age, and removed dose since multiple brands of pine bark are now included. We also added a subgroup analysis for different brands where pine bark was the main ingredient compared to where it is not the main ingredient compared to where it is unclear.

We have added a subgroup under the diabetes comparison, to allow for one study that included participants with both type 1 and type 2 diabetes ([Chous 2016](#)). As this is not relevant for all comparisons, we have not added this as a formal post hoc subgroup to the subgroup analysis section.

We defined substantial heterogeneity as $I^2 = 50\%$ or more and P value of χ^2 test < 0.1 . We did not pool data when heterogeneity between studies was substantial.

We changed our plans with regards to the analysis of parallel and cross-over studies, initially we planned to parallel and cross-over trials ([Unit of analysis issues](#)). However, in chapter 23.2.8 the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* recommends reporting them separately.

In our protocol and initial review version we did not pre-specify which domains we considered when assessing the overall risk of bias per included study ([Schoonees 2011](#); [Schoonees 2012b](#)). For this review update, we made this decision by looking overall at the domains addressing allocation concealment, performance and detection bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Antioxidants [*therapeutic use]; Asthma [drug therapy]; Attention Deficit Disorder with Hyperactivity [drug therapy]; Bias; Bone Diseases, Metabolic [drug therapy]; Brain Injuries, Traumatic [drug therapy]; Cardiovascular Diseases [drug therapy]; Chronic Disease [*drug therapy]; Diabetes Mellitus, Type 1 [drug therapy]; Diabetes Mellitus, Type 2 [drug therapy]; Erectile Dysfunction [drug therapy]; Flavonoids [*therapeutic use]; Hypertension [drug therapy]; Osteoarthritis [drug therapy]; Pinus; Plant Bark [*chemistry]; Plant Extracts [*therapeutic use]; Randomized Controlled Trials as Topic; Sexual Dysfunctions, Psychological [drug therapy]; Venous Insufficiency [drug therapy]

MeSH check words

Adolescent; Adult; Child; Female; Humans; Male; Middle Aged