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Chinese herbal medicines for hypercholesterolemia

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Abstract

Background—Hypercholesterolemia is an important key contributory factor for ischemic heart disease and is associated with age, high blood pressure, a family history of hypercholesterolemia, and diabetes. Chinese herbal medicines have been used for a long time as lipid-lowering agents.

Objectives—To assess the effects of Chinese herbal medicines on hypercholesterolemia.

Search strategy—We searched the following databases: *The Cochrane Library* (issue 8, 2010), MEDLINE (until July 2010), EMBASE (until July 2010), Chinese BioMedical Database (until July 2010), Traditional Chinese Medical Literature Analysis and Retrieval System (until July 2010), China National Knowledge Infrastructure (until July 2010), Chinese VIP Information (until July 2010), Chinese Academic Conference Papers Database and Chinese Dissertation Database (until July 2010), and Allied and Complementary Medicine Database (until July 2010).

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CONTRIBUTIONS OF AUTHORS

Zhaolan Liu: protocol development, literature searches, study selection, data abstraction, risk of bias assessment and data analyses, review development.

Jianping Liu: title conception, protocol revised, study selection, data extraction, risk of bias assessment, the full review revised.

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DECLARATIONS OF INTEREST

None known.

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Selection criteria—We considered randomized controlled clinical trials in hypercholesterolemic participants comparing Chinese herbal medicines with placebo, no treatment, and pharmacological or non-pharmacological interventions.

Data collection and analysis—Two review authors independently extracted data and assessed the risk of bias. We resolved any disagreements with this assessment through discussion and a decision was achieved based by consensus. We assessed trials for the risk of bias against key criteria: random sequence generation, allocation concealment, blinding of participants, incomplete outcome data, selective outcome reporting and other sources of bias.

Main results—We included 22 randomized trials (2130 participants). The mean treatment duration was 2.3 ± 1.3 months (ranging from one to six months). Twenty trials were conducted in China and 18 trials were published in Chinese. Overall, the risk of bias of included trials was high or unclear. Five different herbal medicines were evaluated in the included trials, which compared herbs with conventional medicine in six comparisons (20 trials), or placebo (two trials). There were no outcome data in any of the trials on cardiovascular events and death from any cause. One trial each reported well-being (no significant differences) and economic costs. No serious adverse events were observed. Xuezhikang was the most commonly used herbal formula investigated. A significant effect on total cholesterol (two trial, 254 participants) was shown in favor of Xuezhikang when compared with inositol nicotinate (mean difference (MD) -0.90 mmol/L, 95% confidence interval (CI) -1.13 to -0.68).

Authors' conclusions—Some herbal medicines may have cholesterol-lowering effects. Our findings have to be interpreted with caution due to high or unclear risk of bias of the included trials.

BACKGROUND

Description of the condition

Hypercholesterolemia is a condition characterized by high levels of cholesterol in the blood. It is not a disease but a metabolic derangement. The guidelines of the American Heart Association (AHA) and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) define hypercholesterolemia as a blood cholesterol concentration of equal to or greater than ($\geq$) 6.22 mmol/L (240 mg/dL) (NCEP 2001). Elevated cholesterol in the blood (high blood cholesterol) is due to an increase in the amount of lipoproteins, i.e. particles that carry cholesterol in the bloodstream. There are two major types of cholesterol complexes: HDL (high-density lipoprotein) and LDL (low-density lipoprotein) cholesterol. Hypercholesterolemia usually means high levels of total blood cholesterol or LDL-cholesterol (LDL-C) with normal or low levels of HDL-cholesterol (HDL-C).

High levels of cholesterol is a common risk factor for heart diseases and is often accompanied by other risk factors including increased age, raised blood pressure, family history of hypercholesterolemia, and diabetes. Therefore, the diagnosis and treatment of hypercholesterolemia are often considered together with other heart disease risk factors. The results of the 'Multinational MONItoring of trends and determinants in CARDiovascular disease' (MONICA) project showed that the prevalence of hypercholesterolemia (defined as a total cholesterol (TC) ≥ 6.5 mmol/L, or as people taking lipid-lowering drugs) varied substantially across populations from 3% to 53% in men, and from 4% to 40% in women (Tolonen 2005). Recent data show that about 15.9% of adult Americans aged 20 years and older had high TC, with cholesterol being 6.22 mmol/L or above (U.S. CDC 2009). The prevalence of high TC (above 5.68 mmol/L) among adults aged 20 years and older was reported to be 3.4% in China (Meng 2007). Hypercholesterolemia is associated with many forms of vascular diseases, most notably ischemic heart disease (Barzi 2005; Critchley 2004;

Kuulasmaa 2000). The World Health Report 2002 estimates that 7.6% of all disease burden in developed countries and around 2% in developing countries were caused by raised blood cholesterol, and that 56% of ischemic heart disease and 32% of ischemic stroke in the WHO regions are due to high blood cholesterol levels (WHO 2002). Population studies conducted as part of the Asia-Pacific Cohort Studies Collaboration (APCSC) suggest that for each 1 mmol/L higher than usual cholesterol level, the risk of coronary death was approximately 35% (95% confidence interval (CI) 26% to 44%) greater (Zhang 2003).

Description of the intervention

Elevated cholesterol levels are associated with a diet high in fat, especially saturated fat, coupled with an inactive 'lifestyle'. Therefore, therapeutic lifestyle changes which consist primarily of dietary modification and physical exercise should be implemented for hypercholesterolemia before, or simultaneously with, initiating drug therapy (NECP 2001). Statins are considered the first line medications as they are relatively safe and in standard doses it is possible to achieve a reduction of LDL-C of about 30% to 40%, which is greater than for any other single cholesterol-lowering therapy (Mackenny 2005). Other kinds of 'conventional medicines' that can be used to manage hypercholesterolemia include fibrates, nicotinic acids, bile acid sequestrants and hormones especially for postmenopausal women. Although statins and other cholesterol-lowering drugs are generally well-tolerated, adverse effects may occur in some patients (Beltowski 2009; Jacobson 2009).

In contrast to conventional medicines, herbal medicines are plants and are often perceived as 'natural'. Therefore, herbs are thought to be generally safe, both with regards to adverse effects and interactions with other compounds (Ernst 1998). A growing number of people are using herbal products for preventive and therapeutic purposes (Eisenberg 1998).

Herbal medicines form one of the main therapies within Traditional Chinese Medicine (TCM), which is a 3000 year-old holistic system of medicine combining medicinal herbs, acupuncture, diet, massage, and therapeutic exercise for both treatment and prevention of various diseases. TCM is based on the idea that opposing principles or forces exist in nature and human bodies, suggesting that a healthy person balances those two opposing forces, such as heat and cold, joy and sadness. When the balance is disturbed, diseases are said to occur. TCM therapies focus on recovering this balance. Chinese herbal medicines, in this review, refer to any form of medicinal plants other than raw herbs. It includes herbal extracts, formulated as capsules, tablets, decoctions, or injections. Chinese herbal medicines may offer an inexpensive and safe alternative to pharmaceuticals.

Different herbs have been tested in clinical trials and some herbs are claimed to be effective in lowering cholesterol (Becker 2009; Jing 2009; Liu 2006; Nohr 2009; Zhang 2007). For example, composite *Salviae* dropping pill (a formula of different herbs, such as *Radix Salviae miltiorrhizae*, *Radix Notoginseng*, borneol) could decrease serum lipid levels without damaging liver function (Zhang 2007). One clinical study found that Daming capsule may be a good candidate for the treatment of hyperlipidemia (Jing 2009). Another review indicated that artichoke leaf extracts also have the potential of lowering cholesterol levels (Wider 2009).

Adverse effects of the intervention

Herbal medicines used for treating hypercholesterolemia are associated with low appetite, nausea, stomach-ache, abdominal distension, diarrhea, increased blood urea nitrogen (BUN) and increased alanine-aminotransferase levels (ALT). No serious adverse effects have been reported in relation to these herbs (Chen 2007; Liu 2006). However, the safety profile of herbal medicines in longterm use has not been sufficiently assessed.

How the intervention might work

The mechanisms of herbal medicines in treating hypercholesterolemia are complex. Some potentially active ingredients from medicinal herbs have been identified. Berberine lowers cholesterol levels by increasing mRNA (messenger ribonucleic acid) and protein as well as the function of hepatic LDL-receptors (Kong 2004). Panax ginseng extracts elevate antioxidant potentials by decreasing malondialdehyde levels, and by increasing erythrocyte superoxide dismutase which acts as a scavenger to reduce hypercholesterolemia (Kim 2003). However, the mechanisms of most herbal medicines for lowering cholesterol are still not clear.

Why it is important to do this review

Chinese herbal medicines are widely used to treat all kinds of diseases and conditions including hypercholesterolemia. Although there is evidence from randomized controlled clinical trials (RCTs) that herbal medicines reduce serum cholesterol, the evidence is not conclusive. One review of the lipid-lowering effects of 11 herbal products concluded that many herbal medicinal products have potential hypocholesteremic activities (Thompson 2003). Another review on Chinese red yeast rice for primary hyperlipidemia inferred short-term beneficial effects of red yeast rice preparations on lipid modification (Liu 2006). A systematic review critically appraising the available evidence on the potential benefits and harms of Chinese herbal medicines used in hypercholesterolemia is needed to update the body of evidence and to help people make informed decisions.

OBJECTIVES

To assess the effects of Chinese herbal medicines for hypercholesterolemia.

METHODS

Criteria for considering studies for this review

Types of studies—We included RCTs irrespective of blinding, publication status, and language. We excluded quasi-randomized trials (QRCTs) and nonrandomized studies. We planned to include randomized cross-over trials, if available. We considered trials with significant skewed distributions of participants in groups that could not be explained by the randomization principle to be non-randomized controlled trials and we excluded them.

Intervention / control	No treatment	Placebo	Non-pharmaceutical intervention	Conventional intervention
Herbal medicines	Yes	Yes	Yes	Yes
Herbal medicines plus conventional intervention	No	No	No	Yes

Types of participants—Adults (18 years or older) of any ethnic origin, who had hypercholesterolemia.

Diagnostic criteria—We included studies if participants were individuals with hypercholesterolemia defined as a mean TC level greater than 6.22 mmol/L (240 mg/dL). We accepted other definitions because the diagnostic criteria have changed during the last decade. We excluded familial hypercholesterolemia and secondary hypercholesterolemia.

Types of interventions—Chinese herbal medicines include extracts from mixtures of herbs, single herbs, Chinese proprietary medicines, or a compound of herbs that are prescribed by a Chinese medicine practitioner. We included all available interventions under this category regardless of the potential mechanisms of action. We grouped herbal interventions as single herbs, Chinese proprietary medicine, and mixtures of different herbs when conducting analyses. We allowed any co-intervention to the experimental or control interventions as long as all arms of the randomized allocation received the same co-intervention. We included trials with a minimum treatment duration of at least 30 days.

The following comparisons were investigated:

Types of outcome measures—The main outcome measures we sought at the end of treatment and at maximal follow-up after completion of the treatment were:

Primary outcomes—

- cardiovascular events (both fatal and non-fatal events, including myocardial infarction, angina pectoris, stroke (any stroke, hemorrhagic and non-hemorrhagic), peripheral arterial disease, sudden death);
- serum cholesterol levels (including TC, LDL-C and HDL-C).

Secondary outcomes—

- death from any cause;
- health-related quality of life (evaluated by a validated instrument);
- serum triglyceride concentrations;
- weight, body mass index (BMI), waist-to-hip ratio (WHR);
- adverse events (we analyzed two types of adverse events, serious adverse events and adverse events not considered serious: a serious adverse event is defined as any untoward medical occurrence that resulted in death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in persistent or significant disability/incapacity, is an event that may jeopardize the patient or requires intervention to prevent one of the former serious adverse events (ICH-GCP 1997); all other adverse events were considered non-serious);
- health costs.

Covariates, effect modifiers and confounders—

- age;
- gender;
- compliance.

Timing of outcome measurement—The minimum treatment duration of treatment was one month (30 days). We planned to group outcome data into those measured at one month, at six months, at one year and annually thereafter. We also considered data reported at other time periods.

Search methods for identification of studies

Electronic searches—We used the following sources for the identification of trials:

- *The Cochrane Library* (issue 8, 2010);
- MEDLINE (until July 2010);
- EMBASE (until July 2010);
- Chinese BioMedical Database (until July 2010);
- Traditional Chinese Medical Literature Analysis and Retrieval System (until July 2010);
- China National Knowledge Infrastructure (until July 2010);
- Chinese VIP Information (until July 2010);
- Chinese Academic Conference Papers Database and Chinese Dissertation Database (until July 2010);
- Allied and Complementary Medicine Database (until July 2010).

For detailed search strategies please see under Appendix 1.

Additional key words of relevance could have been detected during the search process. If this was the case, we would have modified electronic search strategies to incorporate these terms. We included studies published in any language.

Searching other resources—We contacted pharmaceutical companies that produce Chinese herbal medicines for additional studies. In addition, we tried to identify additional studies by searching the reference lists of included trials, (systematic) reviews, meta-analyses and health technology assessment reports .

Data collection and analysis

Selection of studies—To determine the studies to be assessed further, two review authors (ZLL, QW) independently scanned the abstract, title or both of every record retrieved. When there was any unclear information in the title or abstract, we retrieved the full article for clarification. We investigated all potentially relevant articles using the full text. An adapted PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow-chart (Figure 1) of study selection is included (Liberati 2009).

Data extraction and management—For studies that fulfilled inclusion criteria, two review authors (ZLL, YR) independently extracted relevant population and intervention characteristics using standard data extraction templates (for details see Characteristics of included studies; Table 1; Appendix 2; Appendix 5; Appendix 8; Appendix 11; Appendix 14) with any disagreements resolved by discussion, or if required by a third party (JPL). We sought any relevant missing information on the trial from the original author(s) of the article, if required. We planned to translate non-English or non-Chinese eligible paper(s) into English.

Dealing with duplicate publications—In the case of duplicate publications and companion papers of a primary study, we tried to maximize yield of information by simultaneous evaluation of all available data. In cases of doubt, we gave the original publication (usually the oldest version) priority.

Assessment of risk of bias in included studies—Two authors (ZLL, YR) assessed each trial independently. In particular, we checked the following components: the generation of the allocation sequence; allocation concealment; blinding, and incomplete outcome data.

We assessed risk of bias using the Cochrane Collaboration's tool (Higgins 2008). We used the following criteria.

- Was the allocation sequence adequately generated?
- Was the allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Were reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a high risk of bias?

We used these criteria for a judgement of high, low or unclear risk of bias for individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). A 'risk of bias graph' figure and 'risk of bias summary' figure are attached.

We assessed the impact of individual bias domains on study results at study and endpoint levels.

Measures of treatment effect

Dichotomous data—We expressed dichotomous data (for example stroke yes/no) as risk ratios (RR) with 95% confidence interval (CI). We planned to calculate the risk difference (RD) and number needed to treat to benefit (NNTB) in the analysis, if feasible. In case of adverse events we planned to calculate the number needed to treat to harm (NNTH), if possible. We would have calculated RD, NNTB and NNTH according to the guidelines referenced in the newest version of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

Continuous data—We expressed continuous outcomes (for example LDL-C) as mean differences (MD) with 95% CI.

Time-to-event data—We planned to express time-to-event data (for example time until death) as hazard ratios (HR).

Unit of analysis issues—We planned to take into account the level at which randomization occurred, such as cross-over trials, cluster-randomized trials and multiple observations for the same outcome.

Dealing with missing data—We obtained relevant missing data from authors, where possible and carefully performed evaluation of important numerical data such as the number of screened and randomized patients, intention-to-treat (ITT), as-treated and per-protocol (PP) population. We investigated attrition rates, for example drop-outs, losses to follow up

and withdrawals and critically appraised issues of missing data and imputation methods (for example, last-observation-carried-forward (LOCF)).

Assessment of heterogeneity—In the event of substantial clinical, methodological or statistical heterogeneity, we did not report study results as meta-analytically pooled estimations. We reviewed various study components such as patients, diseases, interventions, comparisons and outcomes in the included studies to decide if heterogeneity was substantially large. We identified heterogeneity by visual inspection of the forest plots, by using a standard Chi^2 test and a significance level of $\alpha = 0.1$, in view of the low power of such tests. We specifically examined heterogeneity with the I^2 statistic quantifying inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003), where an I^2 statistic of 50% and more indicates a substantial level of inconsistency (Higgins 2008).

Assessment of reporting biases—We planned to use funnel plots to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot (Sterne 2001). Therefore, we planned to carefully interpret the results (Lau 2006).

Data synthesis—We summarized data statistically if they were available, sufficiently similar and of sufficient quality. We performed statistical analyses according to the statistical guidelines referenced in the newest version of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

We performed meta-analyses of data using random-effects methods prior to fixed-effect models. In order to contrast absolute and relative measures, we also planned to express results as NNTB, NNTH; both NNTB and NNTH depend upon follow-up time and baseline risk. Therefore, we planned to adjust for follow-up time by annualising NNTH and NNTB as described previously (Mayne 2006). For discrete data we planned to adjust for baseline risk by analysing change in event rates; for continuous data if groups were not matched at baseline we only wanted to report results descriptively.

Subgroup analysis and investigation of heterogeneity—We wanted to carry out subgroup analyses if one of the primary outcome parameters demonstrated statistically significant differences between intervention groups. We tabulated adverse events and assessed with descriptive techniques, as they were likely to be different for the various interventions used.

Sensitivity analysis—We performed sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies;
- repeating the analysis excluding recruiting hypercholesteremic patients with hypertriglyceridemia;
- repeating the analysis taking account of risk of bias, as specified above;
- repeating the analysis taking account of different definitions of hypercholesterolemia;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;

- repeating the analysis excluding studies using the following filters: diagnostic criteria, source of funding (commercially funded versus non-(commercially) funded), and country.

We tested the robustness of the results by repeating the analysis using different measures of effect size (relative risk, odds ratio etc.) and different statistical models (fixed-effect model and randomeffects model).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

The initial search using the electronic search strategies listed in Appendix 1 yielded 5659 studies. We did not identify any unpublished studies. After we removed duplicates from different databases, we kept 5044 potentially relevant articles for further assessment. After scanning the studies identified, we identified 93 studies which could not be excluded by scrutiny of the title and abstract alone. Further investigation of the full articles revealed 22 included studies (28 publications) with six duplications. We excluded 60 studies and the reasons for exclusion are listed under Characteristics of excluded studies. We could not contact the authors of four studies by telephone or mail, the author of another study refused to answer any questions on the trial, and details of these five studies are shown under Characteristics of studies awaiting classification. We prepared a PRISMA flow diagram to describe the articles found from our searches (Figure 1). The review authors did not find any differences in their independent assessment of the eligibility of the studies.

Included studies

We included 22 RCTs (28 publications) in this review. Further details are given in the table Characteristics of included studies. Eighteen of the included trials (23 articles) were published in Chinese. Four trials (five publications) were published in English (Bundy 2008; Francini-Pesenti 2008; Jing 2009; Xu 2000). Of the 22 trials, 20 were conducted in China, and the other two trials were conducted in the UK (Bundy 2008) and Italy (Francini-Pesenti 2008). One study was a three-arm trial testing Xuezhikang versus simvastatin versus pravastatin (Li 2005). The remaining trials employed a parallel two-arm design. Two studies compared Chinese herbal medicines versus placebo and 20 trials compared Chinese herbal medicines versus conventional medicine. We were not able to do sensitivity analyses on language of publication, source of funding and country due to the limited number of trials. We did not conduct any sensitivity analysis on unpublished studies because we did not detect unpublished studies. We also did not conduct any sensitivity analyses on very long or large studies because there were none.

Participants

A total of 2130 participants with hypercholesterolemia were included in the 22 trials. Among the 2130 participants, 1987 were recruited in Chinese populations and 143 in the UK and Italy (Bundy 2008; Francini-Pesenti 2008). The average sample size of the trials was 97 participants (ranging from 28 to 232 participants per trial). The age of the participants ranged from 18 to 85 years. Three trials did not report the number of male and female participants (Francini-Pesenti 2008; Jing 2009; Qi 2004). Among the 1676 participants in 18 trials, the proportion of males to females was 1.5 (1075 to 703). Five trials included inpatients (Chen 2002; Francini-Pesenti 2008; Hua 2008; Wang 2006; Xu 2002); four trials

included outpatients (Lu 1998; Quan 2008; Tian 2007; Wang 2003); seven trials included both inpatients and outpatients (Deng 2006; Feng 2006; Jing 2009; Li 2005; Liu 2000; Qi 2004; Zhang 2005); and six trials did not specify trial settings (Bundy 2008; Ding 1999; Li 2006; Ma 2002; Wang 2004; Xu 2000).

Diagnosis

Twelve trials enrolled patients with hypercholesterolemia alone. Seven trials enrolled patients with hypercholesterolemia and hypertriglyceridemia. Three trials enrolled patients with hypercholesterolemia as well as patients with hypercholesterolemia combined with hypertriglyceridemia. We did a sensitivity analysis on the patients with or without hypertriglyceridemia (see Appendix 15). Among the 22 included trials, the participants of two trials (Quan 2008; Tian 2007) were diagnosed with the disorder hypercholesterolemia according to the Chinese national criteria (Fang 1997). The other 20 trials did not specify diagnostic criteria for hypercholesterolemia. We subjected the different diagnostic criteria to a sensitivity analysis but we did not detect any significant differences (see Appendix 16).

Interventions

There were large variations in the formulations, dosages, routes of administration, duration of treatments, and control interventions in the included trials among the herbal medicines tested (see Appendix 2 and Characteristics of included studies). In total, five different herbal medicines were tested and the compositions of the herbal medicines varied (Appendix 2). The formulations of herbal medicines were different, ranging from capsules, tablets to decoctions. Capsules containing artichoke leaf extracts (Bundy 2008), Xuezhikang (Chen 2002; Deng 2006; Ding 1999; Feng 2006; Hua 2008; Li 2005; Li 2006; Liu 2000; Lu 1998; Ma 2002; Qi 2004; Quan 2008; Wang 2003; Wang 2004; Wang 2006; Xu 2000; Xu 2002; Zhang 2005) and Daming (Jing 2009) were tested in 20 trials. No trial reported quality standards of the herbal preparations. Herbal tablets (Francini-Pesenti 2008) and decoctions (Tian 2007) were tested in one trial each. Xuezhikang was tested in 18 trials (Chen 2002; Deng 2006; Ding 1999; Feng 2006; Hua 2008; Li 2005; Li 2006; Liu 2000; Lu 1998; Ma 2002; Qi 2004; Quan 2008; Wang 2003; Wang 2004; Wang 2006; Xu 2000; Xu 2002; Zhang 2005). Artichoke leaf extracts (Bundy 2008), policosanol (Francini-Pesenti 2008), Daming capsules (Jing 2009) and Xiaozhiling decoction (Tian 2007) were tested in one trial. The control interventions included pravastatin, simvastatin, inositol nicotinate, atorvastatin, lovastatin, marine triglycerides and placebos. The duration of treatment varied from one month to six months. We grouped outcome data into those measured at one month (three trials), two months (including more than one month but less than two months, 14 trials), three months (three trials) and six months (two trials). We subjected the different treatment durations to a sensitivity analysis (16 trials) and we detected some significant differences between the subgroups (see Appendix 17).

Outcomes

All included trials reported serum cholesterol levels, such as TC, LDL-C, and HDL-C. No trial reported outcomes on cardiovascular events, such as myocardial infarction, angina pectoris, and stroke. Only one trial reported the outcome of health-related quality of life (Bundy 2008). The other outcomes that were reported included ALT, creatinine, apolipoprotein A1, apolipoprotein B, lipoprotein a, the ratios (TC-HDL-C)/HDL-C, LDL/HDL, body weight, body mass index (BMI), fasting blood glucose (FBG), post prandial glucose (PBG), glycosylated hemoglobin A1c (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), symptom scores, and adverse events. One trial reported health economic costs (Wang 2003). Nineteen of the 22 trials reported details of adverse events in the Chinese herbal medicine group (Appendix 14). Fourteen trials observed mild adverse events, i.e., upset stomach, abdominal distention, stomach-ache, and nausea

(Appendix 14). No serious adverse events were observed in the Chinese herbal medicines groups (Appendix 14). Five trials observed no adverse events in the Chinese herbal medicines groups (Deng 2006; Li 2005; Ma 2002; Wang 2004; Wang 2006). Three trials did not report adverse events in the intervention groups (Ding 1999; Lu 1998; Wang 2003). All trials measured outcomes at the end of treatment. No trial reported follow-up data.

Excluded studies

Sixty studies were excluded and the reasons for exclusion are listed under Characteristics of excluded studies. The major exclusion reason was that the participants did not meet the inclusion criteria. Other exclusion reasons included less than one month intervention time, improper control or intervention and, non-randomized clinical trials.

Risk of bias in included studies

All the trials provided very limited information about design and methodology. We identified two multicenter RCTs in our searches (Jing 2009; Xu 2000). One trial reported a sample size calculation (Francini-Pesenti 2008). All the trials had pre-specified inclusion criteria and 13 trials had pre-specified exclusion criteria. One trial stated that they performed an ITT analysis to evaluate the data (Bundy 2008). Six studies did not perform ITT analysis (Feng 2006; Francini-Pesenti 2008; Li 2006; Qi 2004; Wang 2006; Xu 2000). There was insufficient information to judge whether an ITT analysis was performed or not in one trial (Ding 1999). Thirteen trials did not state that they performed an ITT analysis, but missing data were not reported in these 13 trials (Chen 2002; Deng 2006; Hua 2008; Jing 2009; Li 2005; Liu 2000; Lu 1998; Ma 2002; Tian 2007; Wang 2003; Wang 2004; Xu 2002; Zhang 2005). Assessment of risk of bias is described for each included study in the Characteristics of included studies table. Review authors' judgements about each risk of bias item is presented as percentages across all included studies in Figure 2, and review authors' judgements about each risk of bias item for each included study is shown in Figure 3. The review authors found no difference in their risk of bias assessments of the included studies. We could only perform sensitivity analyses taking into account the risk of bias domains 'incomplete outcome data' and 'selective reporting'.

Allocation

Three studies reported an adequate sequence generation (Bundy 2008; Francini-Pesenti 2008; Tian 2007) and one study (Bundy 2008) reported allocation concealment. Detailed information is shown in Characteristics of included studies and Figure 3.

Blinding

Three studies reported blinding (Bundy 2008; Francini-Pesenti 2008; Jing 2009). Detailed information is shown in Characteristics of included studies and Figure 3.

Incomplete outcome data

Incomplete outcome data were adequately addressed in fifteen studies (Bundy 2008; Chen 2002; Deng 2006; Francini-Pesenti 2008; Hua 2008; Jing 2009; Li 2005; Lu 1998; Liu 2000; Ma 2002; Quan 2008; Tian 2007; Wang 2003; Wang 2004; Zhang 2005). Detailed information is shown in Characteristics of included studies and Figure 3. We performed a sensitivity analysis taking into account risk of bias on incomplete outcome data (see Appendix 18). We did not detect a significant influence on reported outcomes.

Selective reporting

None of the trials reviewed had published protocols of their study. According to the stated outcomes in the methods section and the reported outcomes in the results section of the

publication, we made judgements on this domain. We deemed five trials to be free of selective reporting (Bundy 2008; Chen 2002; Quan 2008; Wang 2004; Xu 2002). Detailed information is shown in Characteristics of included studies and Figure 3. We performed a sensitivity analysis taking into account risk of bias on selective reporting (see Appendix 19). We did not detect a significant influence on cholesterol outcomes.

Other potential sources of bias

We considered 16 of the included trials to be free of other potential sources of bias. Detailed information is shown in Characteristics of included studies and Figure 3. We performed a sensitivity analysis taking into account risk of bias on 'other bias' (see Appendix 20). We did not detect a significant influence on cholesterol outcomes.

Effects of interventions

See: Summary of findings for the main comparison Xuezhikang compared to simvastatin for hypercholesterolemia; **Summary of findings 2** Xuezhikang compared to pravastatin for hypercholesterolemia

There were no data on the primary outcome cardiovascular events and on the secondary outcomes death from any cause and WHR in any of the trials. No serious adverse events were reported (Appendix 11; Appendix 14). We were only able to perform metaanalyses on four outcomes in this review. We did not perform subgroup analyses due to lack of data.

Single herbs

Two trials investigated single herbs including artichoke leaf extract capsules and policosanol tablets (Bundy 2008; Francini-Pesenti 2008).

Artichoke leaf extract capsules

Artichoke leaf extract (ALE) capsule versus placebo—Artichoke leaf extract capsules were tested in one trial (Bundy 2008) and reported the following outcomes: TG, TC, HDL-C, LDL-C, and adverse effects. Compared with placebo, the trial did not show significant differences for TC, TG, HDL-C, LDL-C and well-being scores (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.6; Figure 4).

Policosanol

Policosanol versus placebo—Policosanol tablets were tested in one trial (Francini-Pesenti 2008) and outcomes of TG, TC, HDL-C, LDL-C, BMI and adverse effects were reported. Compared with placebo, the trial did not show significant differences for TG, TC, HDL-C, LDL-C and BMI (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4 Analysis 2.5 Figure 4).

Chinese proprietary medicines—Two Chinese proprietary medicines, Xuezhikang and Daming capsules were tested in 19 trials (Chen 2002; Deng 2006; Ding 1999; Feng 2006; Hua 2008; Jing 2009; Li 2005; Li 2006; Liu 2000; Lu 1998; Ma 2002; Qi 2004; Quan 2008; Wang 2003; Wang 2004; Wang 2006; Xu 2000; Xu 2002; Zhang 2005) with 1843 participants including 943 in the intervention and 900 in the control groups.

Xuezhikang capsules—Xuezhikang capsules were tested in 18 trials (Chen 2002; Deng 2006; Ding 1999; Feng 2006; Hua 2008; Li 2005; Li 2006; Liu 2000; Lu 1998; Ma 2002; Qi 2004; Quan 2008; Wang 2003; Wang 2004; Wang 2006; Xu 2000; Xu 2002; Zhang 2005) with 1783 participants including 913 in the intervention and 870 in the control groups. These trials reported outcomes for TG, TC, HDL-C, LDL-C, heart rate, apolipoprotein A1

(ApoA1), apolipoprotein B (ApoB), lipoprotein a (Lp(a)), the ratios (TC-HDL-C)/HDL-C and LDL/HDL, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), adverse events and costs. In total, 15 outcomes were reported. We performed meta-analysis on TG, TC, HDL-C, LDL-C and (TC-HDL-C)/HDL-C. Heart rate, ApoA1, ApoB, Lp(a), LDL/HDL, body weight, SBP, DBP, adverse events and costs are descriptively described .

Xuezhikang versus pravastatin—Three trials compared Xuezhikang with pravastatin in 314 participants including 176 in the intervention and 138 in the control groups (Li 2005; Wang 2003; Xu 2000). Compared with pravastatin, a meta-analysis of three trials (Li 2005; Wang 2003; Xu 2000) does not show significant differences of Xuezhikang capsules on TC, TG, HDL-C, LDL-C (Analysis 1.1; Analysis 1.2; Analysis 1.3 Analysis 1.4; Figure 5). One trial (Xu 2000) compared Xuezhikang with pravastatin on LDL/HDL and did not detect a significant difference (Analysis 1.23). One trial (Wang 2003) reported the cost-effectiveness ratio and incremental cost-effectiveness ratio and the data extracted are shown in Analysis 1.24 and Analysis 1.25. The results showed that Xuezhikang was more cost-effective than pravastatin. The cost-effectiveness ratios and incremental cost-effectiveness ratios were lower in the Xuezhikang group than in pravastatin group.

Xuezhikang versus simvastatin—Ten trials compared Xuezhikang with simvastatin in 885 participants including 448 in the intervention and 437 in the control group groups (Chen 2002; Deng 2006; Ding 1999; Hua 2008; Li 2005; Li 2006; Lu 1998; Qi 2004; Quan 2008; Wang 2004). For TC, LDL-C, HDL-C, and TG, there were no statistically significant differences between Xuezhikang and simvastatin (Analysis 1.1; Analysis 1.4; Figure 5). A meta-analysis of eight trials (Chen 2002; Deng 2006; Hua 2008; Li 2005; Li 2006; Lu 1998; Qi 2004; Wang 2004;) does not show significant effects of Xuezhikang capsules on TG (Analysis 1.2). A meta-analysis of nine trials (Chen 2002; Deng 2006; Ding 1999; Li 2005; Li 2006; Lu 1998; Qi 2004; Quan 2008; Wang 2004) does not show significant effects of Xuezhikang capsules on HDL-C (Analysis 1.3).

However, due to considerable unexplained heterogeneity pooled effect estimates for total cholesterol and LDL- as well as HDL-cholesterol are not reliable and are shown for illustrative purposes only.

In two trials (Lu 1998; Li 2006), a significant effect of Xuezhikang capsules on TC-HDL-C)/HDL-C was shown (Analysis 1.14). One trial (Lu 1998) compared Xuezhikang with simvastatin on ApoA1, ApoB, and Lp(a) and no significant differences were found (Analysis 1.11; Analysis 1.12; Analysis 1.13).

Xuezhikang versus inositol nicotinate—Two trials compared Xuezhikang with nicotinate in 254 participants including 127 in the intervention and 127 in the control groups (Feng 2006; Liu 2000). For TC, LDL-C, HDL-C, and TG, there were statistically significant differences between Xuezhikang and inositol nicotinate. Compared with inositol nicotinate, a meta-analysis of two trials (Feng 2006; Liu 2000) shows a significant effect in favor of Xuezhikang capsules on the following outcomes: for TC the MD was -0.90 mmol/L (95% CI -0.13 to -0.68); 254 participants, two trials (Analysis 1.1; Figure 5); for TG the MD was 0.24 mmol/L (95% CI 0.05 to 0.42); 254 participants, two trials (Analysis 1.2); for LDL-C the MD was -0.58 mmol/L (95% CI -0.93 to -0.23); 254 participants, two trials (Analysis 1.4); for HDL-C: the MD was 0.18 mmol/L (95% CI 0.09 to 0.27), Analysis 1.3.

Xuezhikang versus marine triglycerides—One trial compared Xuezhikang with marine triglycerides in 60 participants including 30 in the intervention and 30 in the control group (Ma 2002). Compared with marine triglycerides, significant effects were found on the following outcomes: for TC the MD was -0.80 mmol/L (95% CI -1.18 to -0.42); 60

participants, one trial (Analysis 1.1; Figure 5); and for LDL-C the MD was -0.40 mmol/L, (95% CI -0.80 to 0.00); 60 participants, one trial (Analysis 1.4). No significant effects were found on TG, HDL-C, heart rate, body weight, SBP, DBP (Analysis 1.2; Analysis 1.3; Analysis 1.5; Analysis 1.15; Analysis 1.6; Analysis 1.7).

Xuezhikang versus atorvastatin—Two trials compared Xuezhikang with atorvastatin in 202 participants including 98 in the intervention and 104 in the control groups (Wang 2006; Zhang 2005). For TC, LDL-C, and TG, there were no statistically significant differences between Xuezhikang and atorvastatin (Analysis 1.1; Analysis 1.2; Analysis 1.4; Figure 5). Compared with atorvastatin, a meta-analysis of two trials (Wang 2006; Zhang 2005) shows a significant effect on HDL-C with a MD of -0.15 mmol/L, (95% CI -0.23 to -0.06); 112 participants, two trials (Analysis 1.3).

Xuezhikang versus lovastatin—One trial compared Xuezhikang with lovastatin in 68 participants including 34 in the intervention group and 34 in the control group (Xu 2002). Compared with lovastatin, a significant difference was not found for TC, LDL-C, TG, and HDL-C (Analysis 1.1; Analysis 1.4; Analysis 1.2; Analysis 1.3; Figure 5).

Daming capsules—Daming capsules (DMC) were tested in one trial (Jing 2009).

DMC versus pravastatin—One trial compared DMC with pravastatin in 60 participants including 30 in each group (Jing 2009) and outcomes of TG, TC, HDL-C, LDL-C, heart rate, SBP, DBP, adverse effects, BMI, ALT, and creatinine were reported. No significant differences were found in favor of Daming capsules.

Herb mixtures (decoctions)—One herbal mixture named Xiaozhiling decoction was tested in one trial (Tian 2007).

Xiaozhiling versus simvastatin—One trial compared Xiaozhiling decoction with simvastatin in 68 participants including 32 in the intervention and 36 in the control group (Tian 2007). Outcomes of TG, TC, HDL-C, LDL-C, SBP, DBP, FBG, PBG, glycosylated hemoglobin A1c (HbA1c), symptom scores and adverse events were reported. Compared with pravastatin, the trial showed significant effects of Xiaozhiling on the outcomes: for HDL-C the MD was 0.52 mmol/L (95% CI 0.22 to 0.82), 68 participants, one trial (Analysis 1.1); for LDL-C the MD was -0.59 mmol/L (95% CI -0.92 to -0.26), 68 participants, one trial (Analysis 1.3). Significant effects were found on SBP, DBP, fasting blood glucose (FBG), post-prandial glucose (PBG), headache symptom scores, chest stuffiness symptom scores, vomiting and salivation symptom scores and numb limb symptom scores but not on TC, TG and HbA1c (Analysis 1.6; Analysis 1.7; Analysis 1.20; Analysis 1.21; Analysis 1.16; Analysis 1.17; Analysis 1.18; Analysis 1.19; Analysis 1.1; Analysis 1.2; Analysis 1.22).

DISCUSSION

Summary of main results

Twenty two RCTs (28 papers) with 2130 participants are included in this review. The mean duration of treatment was 2.3 months. The present systematic review suggests that some Chinese herbal medicines may have positive effects on hypercholesterolemia. Compared with inositol nicotinate, there was a significant difference in favor of Xuezhikang on total cholesterol (TC), low-density cholesterol (LDL-C), high-density cholesterol (HDL-C) and no significant difference for triglycerides (TG). Compared with marine triglycerides, Xuezhikang was significantly effective on TC and LDL-C. Compared with atorvastatin,

Xuezhikang showed no significant difference on HDL-C. Compared with pravastatin, Daming capsule showed a significant difference on TC and creatinine. Compared with pravastatin, Xiaozhiling showed significant differences on HDL-C, LDL-C, systolic and diastolic blood pressure, as well as fasting and post-prandial glucose, headache, chest stuffiness, vomiting and salivation and numb limb symptom scores.

Overall completeness and applicability of evidence

The age and gender of participants in the included trials was representative of hypercholesterolemic patients. Most of the participants were recruited from Chinese populations and this could impact on the applicability of the interventions to other populations. No long-term data on outcomes were reported in the included trials. The results of this systematic review can only be used to guide clinical practice for the tested Chinese herbal medicines we have evaluated. Many types of Chinese herbal medicines with possible lipid-lowering effects have not been investigated in RCTs. Therefore, the evaluation of these medicines should be addressed in future studies.

Quality of the evidence

All the randomized trials included in this review were of poor quality in terms of their design, reporting, and methodology. They provided only limited descriptions of study design, randomization, allocation concealment, and baseline data. We only identified two multicenter, large scale RCTs. Among the 22 studies, there was one moderate quality study and 21 low quality studies. Methodologically poorly designed trials show larger differences between experimental and control groups than those conducted rigorously (Kjaergard 2001; Moher 1998; Schulz 1995). However, the insufficient number of adequate trials prohibited us from performing meaningful sensitivity analyses to show how robust the results of the review are after restricting analyses to trials with adequate methodology. Moreover, the included trials were heterogeneous in the populations (adults or elderly patients, or hypercholesterolemia with or without hypertriglyceridemia), interventions (five herbal medicines tested only once), and the reported outcomes.

Diagnostic criteria

Among the 22 included trials, only two trials diagnosed participants with hypercholesterolemia based on the Chinese national criteria which also conform with the international recommended criteria. The remaining 20 trials did not describe exact diagnostic criteria. The sensitivity analysis on diagnostic criteria did not show significant differences.

Interventions

There are wide variations among the tested herbal medicines and control interventions. Two trials used placebo controls. Twenty trials compared herbal medicines with conventional medicine. The same herbal interventions were reported using different treatment regimens including the dosage and duration of treatment. We performed a sensitivity analysis on treatment duration and we did not find any significant differences.

Furthermore, there is still a lack of information about quality standards for the development of the herbal preparations or for the manufacture of the herbal products. Future trials should provide information about standardization including composition, quality control, detailed dose regimen, and duration of treatment.

Surrogate outcomes

The primary goal of the treatment for hypercholesterolemia is to prevent cardiovascular events. No trial reported cardiovascular events in patients with hypercholesterolemia. Other outcomes from the included trials are mainly surrogate outcomes, i.e. TC, TG, LDL-C, HDL-C. We excluded 60 randomized trials from this review. The main reasons were because they involved less than one month treatment duration, included ineligible participants in the trial, and were not true randomized trials.

Adverse outcomes

There was inadequate reporting on adverse events in the included trials (Appendix 11, Appendix 14). Three trials did not report results about adverse effects. Five trials did not observe adverse events. Twelve trials reported inconsistent mild adverse effects and thus we cannot come to firm conclusions about the safety of herbal medicines. The general perception that it is safe to use herbal medicines for various conditions is not supported by these data and more studies focusing on the adverse effects of Chinese herbal medicines are needed (Chen 2007; Gottlieb 2000; Ishizaki 1996; Liu 2006; Melchart 1999). Though there was inadequate reporting on adverse events in the included trials of this review, the proportion (19/22) of trials reporting adverse effects is higher than in the past (Liu 2004). In order to obtain more information on the adverse effects of Chinese herbal medicines, the safety of herbal medicines needs to be further monitored and reported in clinical trials and observational studies such as cohort studies.

Potential biases in the review process

Although we conducted comprehensive searches, we only identified and included 22 trials. Among the 22 trials, 20 were conducted and published in Chinese, and two were conducted and published in the UK and Italy. Most of the trials had small sample sizes. We tried to avoid language bias and location bias, but we could not exclude potential dissemination bias. We have undertaken extensive searches for unpublished material, few of the trials identified qualified for inclusion, but at the same time we cannot disregard the fact that trials with negative findings remain unpublished.

Agreements and disagreements with other studies or reviews

As far as we are aware, no systematic review has been done with a focus on Chinese herbal medicines for hypercholesterolemia. A systematic review on Chinese red yeast rice for dyslipidemia was published in 2006 (Liu 2006). The review (Liu 2006) included 93 trials with red yeast rice as the intervention and placebo as the control. Patients with primary hyperlipidemia were included in the review (Liu 2006). Meta-analyses were conducted by grouping different controls and the conclusion of the review was that current evidence from randomized trials shows short-term beneficial effects of red yeast rice preparations on lipid modification (Liu 2006). Seven trials (Chen 2002; Lu 1998; Quan 2008; Wang 2003; Wang 2004; Xu 2000; Xu 2002) of this review (Liu 2006) were also included in our review. The other included trials in the review (Liu 2006) were excluded in this review, mostly because the participants were not hypercholesterolemic individuals, and some other trials were excluded because they did not meet the inclusion criteria, or were duplicate publications. Though the two reviews did not focus on the same events, the conclusions of the review (Liu 2006) and this review are similar as hyperlipidemia and hypercholesterolemia are closely related.

AUTHORS' CONCLUSIONS

Implications for practice

Based on this systematic review, we cannot be certain of the effectiveness and safety of Chinese herbal medicines in the treatment of hypercholesterolemia. The evidence is inconclusive due to the high risk of bias of many of the included trials.

Implications for research

From the results of the present review, it would be interesting to test especially Xuezhikang more thoroughly and compare it with conventional medicine in patients with hypercholesterolemia. For herbal mixtures, rigorous description of the pharmacology of the interventions and clinical outcomes should be emphasized. Information about species, geographical origin of herbs, season for collecting the herbs and quality of the preparations should be provided (Gagnier 2006). Standardised monitoring and reporting should be used for assessment of adverse events.

With regard to methodology, international, multicenter, rigorously designed, high quality studies with a large sample size are required to provide more rigorous evidence. Attention should also be paid to the definition of outcome measures and the incidence of adverse events. In addition, the following methodological issues should be addressed: (a) methods of generating allocation sequence and allocation concealment; (b) blinding with the use of adequate placebo; (c) clear descriptions of withdrawals and drop-outs during the trial and use of an ITT analysis; and (d) reporting trials according to the updated CONSORT statement (<http://www.consortstatement.org/consort-statement/>) (Schulz 2010). To improve the quality of future trials, we suggest that all researchers should receive necessary training on clinical trials methodology before designing a trial and register the trial in an internationally recognized trial registry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Huihui Jiang: screening of papers, data extraction and translation.

Mengwei Wang: screening of papers, data extraction and translation.

Sitong Luo: screening of papers, data extraction and translation.

APPENDICES

Appendix 1

Search strategies

Search terms

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign (\$) or asterisk (*) stand for any character(s); the question mark (?) = to substitute for one or no characters; ab = abstract; adj = adjacent; ot = original title; pt = publication type; rn = Registry number or Enzyme Commission number; sh = MeSH; ti = title; tw = text word.

The Cochrane Library

- #1 MeSH descriptor Hypercholesterolemia explode all trees
- #2 MeSH descriptor Hyperlipoproteinemias explode all trees
- #3 MeSH descriptor Cholesterol explode all trees
- #4 (hypercholesterol?emia* in All Text or hyperlipoprotein?emia* in All Text)
- #5 (HDL in All Text near/6 elevat* in All Text)
- #6 (HDL in All Text near/6 ris* in All Text)
- #7 (HDL in All Text near/6 increas* in All Text)
- #8 (HDL in All Text near/6 improv* in All Text)
- #9 (LDL in All Text near/6 elevat* in All Text)
- #10 (LDL in All Text near/6 ris* in All Text)
- #11 (LDL in All Text near/6 increas* in All Text)
- #12 (LDL in All Text near/6 improv* in All Text)
- #13 (cholesterol in All Text near/6 elevat* in All Text)
- #14 (cholesterol in All Text near/6 ris* in All Text)
- #15 (cholesterol in All Text near/6 increas* in All Text)
- #16 (cholesterol in All Text near/6 improv* in All Text)
- #17 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)
- #18 MeSH descriptor Phytotherapy explode all trees
- #19 MeSH descriptor Medicine, traditional explode all trees
- #20 MeSH descriptor Medicine, chinese traditional explode all trees
- #21 MeSH descriptor Plants, medicinal explode all trees with qualifiers: TH,TU
- #22 MeSH descriptor Herbal medicine explode all trees
- #23 MeSH descriptor Plant preparations explode all trees with qualifiers: TH,TU
- #24 MeSH descriptor Drugs, chinese herbal explode all trees
- #25 (chinese in All Text near/3 medic* in All Text)
- #26 (chinese in All Text near/3 herb* in All Text)
- #27 (chinese in All Text near/3 drug* in All Text)
- #28 (chinese in All Text near/3 formul* in All Text)
- #29 (chinese in All Text near/3 plant* in All Text)
- #30 (chinese in All Text near/3 prescri* in All Text)
- #31 (phyto in All Text near/6 drug* in All Text)
- #32 (phyto in All Text near/6 therap* in All Text)
- #33 (phyto in All Text near/6 treatment* in All Text)
- #34 (phyto in All Text near/6 medicin* in All Text)

Search terms

- #35 (complementary in All Text near/3 therap* in All Text)
 #36 (complementary in All Text near/3 medicin* in All Text)
 #37 (complementary in All Text near/3 treatment* in All Text)
 #38 (alternativ* in All Text near/3 therap* in All Text)
 #39 (alternativ* in All Text near/3 medicin* in All Text)
 #40 (alternativ* in All Text near/3 treatment* in All Text)
 #41 (#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
 #42 (#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
 #43 (#41 or #42)
 #44 (#17 and #43)

MEDLINE

1. exp hypercholesterolemia/ or exp hyperlipoproteinemias/
2. exp Cholesterol/
3. (hypercholesterol?emi* or hyperlipoprotein?emia).tw,ot.
4. ((HDL or LDL or cholesterol) adj6 (elevat* or ascend* or ris* or increas* or improv*)).tw,ot.
5. or/1-4
6. exp Phytotherapy/
7. exp Medicine, traditional/
8. exp Medicine, Chinese Traditional/
9. exp Plants, Medicinal/th, tu [Therapy, Therapeutic Use]
10. exp Herbal Medicine/
11. exp Plant Preparations/tu [Therapeutic Use]
12. exp Drugs, chinese herbal/
13. (chines* adj6 traditional medicin*).tw,ot.
14. (chinese adj3 (medic* or herb* or drug* or formul* or plant* or prescri*)).tw,ot.
15. (phyto adj6 (drug* or pharmaceutical* or therap* or treatment* or medicin*)).tw,ot.
16. ((complementary or alternativ*) adj3 (therap* or medicine*)).tw,ot.
17. or/6-16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomi?ed.ab.
21. placebo.ab.
22. drug therapy.fs.
23. randomly.ab.
24. trial.ab.
25. groups.ab.
26. or/18-25
27. Meta-analysis.pt.
28. exp Technology Assessment, Biomedical/
29. exp Meta-analysis/
30. exp Meta-analysis as topic/
31. hta.tw,ot.

Search terms

32. (health technology adj6 assessment\$).tw,ot.
33. (meta analy\$ or metaanaly\$ or meta?analy\$).tw,ot.
34. ((review\$ or search\$) adj10 (literature\$ or medical database\$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content\$ or systemat\$)).tw,ot.
35. or/27-34
36. (comment or editorial or historical-article).pt.
37. 35 not 36
38. 26 or 37
39. 5 and 17 and 38
40. (animals not (animals and humans)).sh.
41. 39 not 40

EMBASE

1. exp hypercholesterolemia/
2. exp hyperlipoproteinemia/
3. exp cholesterol/
4. (hypercholesterol?emi* or hyperlipoprotein?emi*).tw,ot.
5. ((HDL or LDL or cholesterol) adj3 (elevat* or ascend* or ris* or increas* or improv*)).tw,ot.
6. or/1-5
7. exp phytotherapy/
8. traditional medicine/
9. exp Chinese medicine/
10. exp medicinal plant/
11. exp herbal medicine/
12. exp plant medicinal product/dt [Drug Therapy]
13. exp herbaceous agent/
14. (chines* adj3 (medicin* or herb* or drug* or plant* or formula* or prescri*)).tw,ot.
15. (phyto adj3 (drug* or pharmaceutical* or therap* or treatment* or medicin*)).tw,ot.
16. ((complementary or alternativ*) adj2 (therap* or treatment* or medicin*)).tw,ot.
17. or/7-16
18. 6 and 17
19. exp Randomized Controlled Trial/
20. exp Controlled Clinical Trial/
21. exp Comparative Study/
22. exp Drug comparison/
23. exp Randomization/
24. exp Crossover procedure/
25. exp Double blind procedure/
26. exp Single blind procedure/
27. exp Placebo/
28. exp Prospective Study/
29. ((comparativ\$ or prospectiv\$ or randomi?ed) adj3 (trial\$ or stud\$)).ab,ti.
30. (random\$ adj6 (allocat\$ or assign\$ or basis or order\$)).ab,ti.

Search terms

31. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj6 (blind\$ or mask\$)).ab,ti.
32. (cross over or crossover).ab,ti.
33. or/19-32
34. exp meta analysis/
35. (metaanaly\$ or meta analy\$ or meta?analy\$).ab,ti,ot.
36. ((review\$ or search\$) adj10 (literature\$ or medical database\$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content\$ or systematic\$)).ab,ti,ot.
37. exp Literature/
38. exp Biomedical Technology Assessment/
39. hta.tw,ot.
40. (health technology adj6 assessment\$).tw,ot.
41. or/34-40
42. (comment or editorial or historical-article).pt.
43. 41 not 42
44. 33 or 43
45. 18 and 44
46. limit 45 to human

Allied and Complementary Medicine Database

1. Randomized controlled trials/
2. (hypercholesterol?emi* or hyperlipoprotein?emia or HDL or LDL or cholesterol).mp. [mp=abstract, heading words, title]
3. 1 and 2

Chinese BioMedical Database

- 1 MeSH=="hypercholesterolemia /all subtitles/all trees"
- 2 MeSH=="hyperlipoproteinemias/all subtitles/all trees"
- 3 Hypercholesterolemia
- 4 MeSH=="cholesterol /BL/all trees"
- 5 Low density lipoprotein ascend or LDL ascend or High density lipoprotein reduce or HDL reduce or cholesterol ascend or TC ascend or high cholesterol
- 6 HDL
- 7 MeSH=="medicine, eastern tradition/all subtitles/all trees"
- 8 MeSH=="complementary medicine/"
- 9 MeSH=="plant extracts/all subtitles/all trees"
- 10 MeSH=="Plant, Therapeutic Use /All subtitles"
- 11 MeSH=="drugs, over the counter"
- 12 MeSH=="Phytotherapy/All subtitles/all trees"
- 13 Herbs or herbal or herb
- 14 Alternative medicine*
- 15 Complementary medicine*
- 16 Traditional medicine*
- 17 plant or plants
- 18 (China or The East) with medicine*

Search terms

- 19 Plant medicinal product * or medicinal materials or herbal medicine
- 20 Chinese herbal drugs * or Chinese medicine*
- 21 Traditional Chinese Medicine *
- 22 Traditional Chinese Medicine and Western Medicine*
- 23 MeSH=="animals/all trees"
- 24 not #23
- 25 MeSH="Chinese herbal drugs/all subtitles"
- 26 #6 or #5 or #4 or #3 or #2 or #1
- 27 #25 or #22 or #21 or #20 or #19 or #18 or #17 or #16 or #15 or #14 or #13 or #12 or #11 or #10 or #9 or #8 or #7
- 28 #27 and #26 and #24
- 29 Title: rats or rabbits
- 30 (not #29) and #28
- 31 #30 and (summary in MH or summary in PT)
- 32 (not #31) and #30

Traditional Chinese Medical Literature Analysis and Retrieval System

- 1 Low density lipoprotein ascend or LDL ascend or High density lipoprotein reduce or HDL reduce or cholesterol ascend or TC ascend or high cholesterol or hypercholesterolemia or hyperlipidemia
- 2 Chinese herbal medicine or Chinese medicine or Chinese and western or plants or herbs
- 3 1 and 2

China National Knowledge Infrastructure

- 1 Low density lipoprotein ascend or LDL ascend or High density lipoprotein reduce or HDL reduce or cholesterol ascend or TC ascend or high cholesterol or hypercholesterolemia or hyperlipidemia
- 2 Chinese herbal medicine or Chinese medicine or Chinese and western or plants or herbs
- 3 1 and 2

Chinese VIP Information

- 1 Low density lipoprotein ascend or LDL ascend or High density lipoprotein reduce or HDL reduce or cholesterol ascend or TC ascend or high cholesterol or hypercholesterolemia or hyperlipidemia
- 2 Chinese herbal medicine or Chinese medicine or Chinese and western or plants or herbs
- 3 1 and 2

Chinese Academic Conference Papers Database and Chinese Dissertation Database

- Cholesterolemia and (Chinese medicine or Chinese herbal medicine or Chinese and Western or plants or herbs) and randomization
-

Appendix 2

Description of interventions (part 1)

Characteristic	Bundy R, 2008	Chen LL, 2002	Deng YM, 2006	Ding W, 1999	Feng XY, 2006	Francini-Pesenti F, 2008	Hua D, 2008
Intervention [route, frequency, total dose/day]	I: Artichoke leaf extract (Cynara Scolymus) orally, daily, 1280 mg/day	I: Xuezhikang orally, 3 times a day, 3.6 g/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day	I: Xuezhikang orally, 2 times a day, 2.4 g/day	I: Policosanol orally, daily, 10 mg/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day
Control(s) [route, frequency, total dose/day]	C: placebo orally, daily, 1280 mg/day	C: simvastatin orally, daily, 10 mg/day	C: simvastatin orally, daily, 20 mg/day	C: simvastatin orally, daily, 10 mg/day	C: inositol nicotinate orally, 3 times a day, 0.6 g/day	C: placebo orally, daily, 10 mg/day	C: simvastatin orally, daily, 10 mg/day

Footnotes

C: control; I: intervention

Appendix 3

Description of interventions (part 2)

Characteristic	Jing A, 2009	Li KL, 2006	Li LH, 2005	Liu L, 2000	Lu GP, 1998	Ma YL, 2002	Qi MY, 2004
Intervention (s) [route, frequency, total dose/day]	I: DMC orally, 2 times a day, 4 g/day	I: Xuezhikang orally, 2 times a day, 1 g/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day	I: Xuezhikang orally, daily, 1.2 g/day	I: Xuezhikang orally, 3 times a day, 6 capsules/day	I: Xuezhikang orally, 2 times a day, 2.4 g/day
Control(s) [route, frequency, total dose/day]	C: pravastatin orally, daily, 10 mg/day	C: simvastatin orally, daily, 10 mg/day	C1: pravastatin orally, daily, 10mg/day C2: simvastatin orally, daily, 20 mg/day	C: inositol nicotinate orally, 2 times a day, 0.8 g/day	C: simvastatin orally, 2 times a day, 20 mg/day	C: marine triglycerids orally, 3 times a day, 9 capsules/day	C: simvastatin orally, daily, 10 mg/day

Footnotes

C: control; I: intervention

Appendix 4

Description of interventions (part3)

Characteristic	Quan SL, 2008	Tian X, 2007	Wang DG, 2003	Wang WH, 2006	Wang XL, 2004	Xu CB, 2000	Xu SG, 2002	Zhang G, 2005
Intervention (s) [route, frequency, total dose/day]	I: Xuezhikang orally, 2 times a day, 1.2 g/day	I: Xiaozhiling orally, 2 times a day, 600 ml/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day	I: Xuezhikang orally, daily, 2 capsules/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day	I: Xuezhikang orally, 2 times a day, 1.2 g/day
Control(s) [route, frequency, total dose/day]	C: simvastatin orally, daily, 20 mg/day	C: simvastatin orally, daily, 10 mg/day	C: pravastatin orally, daily, 10 mg/day	C: atorvastatin orally, daily, 10 mg/day	C: simvastatin orally, daily, 20 mg/day	C: pravastatin orally, daily, 1/2 tablet/day	C: lovastatin orally, daily, 20 mg/day	C: atorvastatin orally, daily, 10 mg/day

Footnotes

C: control; I: intervention

Appendix 5

Baseline characteristics (part 1)

Characteristic	Bundy R, 2008	Chen LL, 2002	Deng YM, 2006	Ding W, 1999	Feng XY, 2006	Francini-Pesenti F, 2008	Hua D, 2008
Intervention(s) & control(s)	I: Artichoke leaf extract C: placebo	I: Xuezhikang C: simvastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C: inositol nicotinate	I: Policosanol C: placebo	I: Xuezhikang C: simvastatin
Participating population	75	65	100	80	232	68	136
Sex [female% / male%]	./.	21.5%/78.5% (14/51)	38%/62% (38/62)	16.25%/83.75% (13/67)	43.1%/56.9% (100/132)	./.	34.6%/65.4% (47/89)
Age [mean years (SD)]	./.	I: 55.2 (3.8) C: 56.7 (3.1)	70.8 (4.6)	./.	I: 52.6 (10.4) C: 53.3 (10.8)	I: 48 (5) C: 53 (6)	./.
Duration of disease [mean years (SD)]	./.	1 week to 3 months	./.	./.	./.	./.	./.
Ethnic groups [%]	English: 100	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100	Italians: 100	Chinese: 100
Duration of intervention	12 weeks	4 weeks	8 weeks	4 weeks	8 weeks	8 weeks	8 weeks
Duration of follow up	./.	./.	./.	./.	./.	./.	./.

Footnotes

C./.: not reported

C: control; I: intervention.

Appendix 6

Baseline characteristics (part 2)

Characteristic	Jing A, 2009	Li KL, 2006	Li LH, 2005	Liu L, 2000	Lu GP, 1998	Ma YL, 2002	Qi MY, 2004
Intervention(s) & control(s)	I: DMC C: pravastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C1: simvastatin C2: pravastatin	I: Xuezhikang C: inositol nicotinate	I: Xuezhikang C: simvastatin	I: Xuezhikang C: marine triglycerids	I: Xuezhikang C: simvastatin
Participating population	60	80	60	118	28	60	224
Sex [female% / male%]	./.	31.25% / 68.75% (25/55)	46.7% / 53. (28/32)	43.2% / 56.8% (51/67)	35.7% / 64.3% (10/18)	53.3% / 46.7% (32/28)	./.
Age [mean years (SD)]	./.	./.	./.	./.	./.	./.	./.
Duration of disease [mean years (SD)]	./.	./.	./.	./.	./.	./.	./.
Ethnic groups [%]	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100
Duration of intervention	6 weeks	8 weeks	12 weeks	24 weeks	12 weeks	4 weeks	8 weeks
Duration of follow up	./.	./.	./.	./.	./.	./.	./.

Footnotes

C./.: not reported

C: control; I: intervention.

Appendix 7

Baseline characteristics (part 3)

Character- istic	Quan SL, 2008	Tian X, 2007	Wang DG, 2003	Wang WH, 2006	Wang XL, 2004	Xu CB, 2000	Xu SG, 2002	Zhang G, 2005
Intervention (s) & control (s)	I: Xuezhikang C: simvastatin	I: Xiaozhiling (herb mixture) C: simvastatin	I: Xuezhikang C: pravastatin	I: Xuezhikang C: atorvas- tatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C: pravastatin	I: Xuezhikang C: lovastatin	I: Xuezhikang C: atorvas- tatin
Partic- ipating pop- ulation	102	68	79	142	30	195	68	60
Sex [female% / male%]	31.4% / 68.6% (32/70)	45.6% / 54.4% (31/37)	41.8% / 58.2% (33/46)	43.7% / 56.3% (62/80)	33.3% / 66.7% (10/20)	39.0% / 61.0% (76/119)	35.3% / 64.7% (24/44)	48.3% / 51.7% (29/31)
Age [mean years (SD)]	60-80	./.	I: 52 (9) C: 56 (1)	./.	./.	./.	I: 52 (6.8) C: 56 (7.3)	./.
Duration of disease [mean years (SD)]	./.	./.	./.	./.	./.	./.	./.	./.
Ethnic groups [%]	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100	Chinese: 100
Duration of intervention	8 weeks	3 months	8 weeks	8 weeks	8 weeks	24 weeks	8 weeks	8 weeks
Duration of follow up	./.	./.	./.	./.	./.	./.	./.	./.

Footnotes

C/./: not reported

C: control; I: intervention.

Appendix 8

Matrix of study endpoints (part 1)

Characteristic	Bundy R, 2008	Chen LL, 2002	Deng YM, 2006	Ding W, 1999	Feng XY, 2006	Francini-Pesenti F, 2008	Hua D, 2008
Intervention(s) & control(s)	I: Artichoke leaf extract(ALE) C: placebo	I: Xuezhikang C: simvastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C: inositol nicotinate	I: Policosanol C: placebo	I: Xuezhikang C: simvastatin
Primary endpoint(s) ¹	plasma lipids (TC, LDL and HDL cholesterol, and triglycerides (TG))	/.	/.	/.	/.	/.	/.
Secondary endpoint(s) ²	anxiety, depressed mood, positive well-being, self-control, general health, vitality	/.	/.	/.	/.	/.	/.
Other endpoint(s) ³	/.	TC, LDL-C, TG, HDL-C	TC, LDL-C, TG, HDL-C	TC, LDL-C, HDL-C	TC, TG, HDL, LDL-C	body weight, body mass index (BMI), total cholesterol, HDL-C, LDL-C and TG	LDL-C, HDL-C, TC, TG

Footnotes

/.: not reported

ALT: alanine aminotransferase; BUN: urea nitrogen; C: control; CPK: creatine phosphokinase, HDL-C: high density lipoprotein cholesterol; I: intervention; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol.

¹ as stated in the publication² as stated in the publication³ not stated as primary or secondary endpoint(s) in the publication

Appendix 9

Matrix of study endpoints (part 2)

Characteristic	Jing A, 2009	Li KL, 2006	Li LH, 2005	Liu L, 2000	Lu GP, 1998	Ma YL, 2002	Qi MY, 2004
Intervention(s) & control(s)	I: Daming capsule(DMC) C: pravastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C1:Zocer C2: Mevalotin	I: Xuezhikang C: inositol nicotinate	I: Xuezhikang C: simvastatin	I: Xuezhikang C: Marine Triglycerids	I: Xuezhikang C: simvastatin
Primary ¹ endpoint(s)	./.	./.	./.	./.	./.	./.	./.
Secondary ² endpoint(s)	./.	./.	./.	./.	./.	./.	./.
Other ³ endpoint(s)	LDL-C, HDL-C, TC, TG	TC, TG, HDL-C, LDL-C, ALT, BUN, CPK, blood sugar, blood routine, urine routine.	TC, TG, HDL-C, LDL-C, blood pressure, liver function, renal func- tion, ck, heart rate.	TC, TG, HDL-C, LDL-C, CPK, liver function, renal function, blood routine, urine routine, electrocardio- gram.	TC, TG, HDL-C, LDL-C, ApoA1, ApoB, Lp(a), TC-HDL-/ HDL-C.	TC, TG, HDL-C, LDL-C, heart rate, blood pres- sure, weight.	TC, TG, HDL-C, LDL-C, TC-HDL-C/ HDL-C, plasma lipids, liver function, renal function.

Footnotes

./.: not reported

ALT: alanine aminotransferase; BUN: urea nitrogen; C: control; CPK: creatine phosphokinase; HDL-C: high density lipoprotein cholesterol; I: intervention; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol.

¹ as stated in the publication

² as stated in the publication

³ not stated as primary or secondary endpoint(s) in the publication

Appendix 10

Matrix of study endpoints (part 3)

Characteristic	Quan SL, 2008	Tian X, 2007	Wang DG 2003	Wang WH, 2006	Wang XL, 2004	Xu CB, 2000	Xu SG, 2002	Zhang G, 2005
Intervention (s) & control (s)	I: Xuezhikang C: simvastatin	I: Xiaozhiling (herb mixture) C: simvastatin	I: Xuezhikang C: pravastatin	I: Xuezhikang C: atorvastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C: pravastatin	I: Xuezhikang C: lovastatin	I: Xuezhikang C: atorvastatin
Primary ¹ endpoint(s)	/.	/.	/.	/.	/.	/.	/.	/.
Secondary ² endpoint(s)	/.	/.	/.	/.	/.	/.	/.	/.
Other ³ endpoint(s)	TC, TG, HDL-C, LDL-C, liver function, renal function, CK, blood sugar, blood and urine routine check, and electrocardiogram	TC, TG, HDL-C, LDL-C, blood pressure, weight, nutrition, liver function, renal function, electrocardiogram, blood routine, urine routine, stool routine.	TC, LDL-C, TG, HDL-C	TC, HDL-C, LDL-C, liver function, renal function, creatine, glucose, blood routine, urine routine, electrocardiogram	TC, HDL-C, LDL-C	TC, TG, HDL-C, LDL-C, LDL-C/HDL-C (L/H), and TC-HDL-C/HDL-C, ALT, ALP, AST, CPK, creatine kinase, BUN, blood glucose, routine blood, urine testing	TC, TG, HDL-C, LDL-C, blood sugar, SGPT, CPK, blood and urine routine check, physical examination, and electrocardiogram	TC, TG, LDL-C, HDL-C, fasting glucose, blood urea nitrogen, ALT, electrocardiogram, blood routine, creatine kinase, creatinine.

Footnotes

/.: not reported

ALT: alanine aminotransferase; BUN: urea nitrogen; C: control; CPK: creatine phosphokinase; HDL-C: high density lipoprotein cholesterol; I: intervention; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol.

¹ as stated in the publication

² as stated in the publication

³ not stated as primary or secondary endpoint(s) in the publication

Appendix 11

Adverse events (1) part 1

Characteristics	Bundy R, 2008	Chen LL, 2002	Deng YM, 2006	Ding W, 1999	Feng XY, 2006	Francini-Pesenti F, 2008	Hua D, 2008
Intervention(s) & control(s)	I: Artichoke leaf extract(ALE) C: placebo	I: Xuezhikang C: simvastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C: inositol nicotinate	I: Policosanol C: placebo	I: Xuezhikang C: simvastatin
Deceased participants [n]	I: 2 C: 2 Total: 4	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 3 C: 2 Total: 5	I: 0 C: 0 Total: 0
Adverse events [n / %]	I: 2.6%(1/38) C: 2.9%(1/35) Total: 2.7%(2/73)	I: 2.9%(1/34) C: 3.2%(1/31) Total: 3.1%(2/65)	I: 0 C: 1.9%(1/55) Total: 1%(1/100)	I: / C: / Total: /	I: could not calculated C: could not calculated Total: 2.35%	I: 5.9%(2/34) C: 2.9%(1/34) Total: 4.4%(3/68)	I: 5.7%(4/70) C: 7.6%(5/66) Total: 6.6%(9/136)
Serious adverse events [n / %]	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: / C: / Total: /	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Drop-outs due to adverse events [n / %]	I: 1(2.6%) C: 1(2.9%) Total: 2(2.7%)	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: / C: / Total: /	I: 0 C: 0 Total: 0	I: / C: / Total: /	I: / C: / Total: /
Hospitalisation [n / %]	I: / C: / Total: /	I: 100% C: 100% Total: 100%	I: / C: / Total: /	I: / C: / Total: /	I: / C: / Total: /	I: 0 C: 0 Total: 0	I: 100% C: 100% Total: 100%
Out-patient treatment [n / %]	I: / C: / Total: /	I: 0 C: 0 Total: 0	I: / C: / Total: /	I: / C: / Total: /	I: / C: / Total: /	I: 100% C: 100% Total: 100%	I: 0 C: 0 Total: 0
Symptoms [n / %]	I: flatulence (2); diarrhoea (1); constipation (3); tiredness (2); dry mouth (2); bloating (1); C: flatulence (3); headache(2); diarrhoea (2); tiredness (4); dry mouth (4); forgetfulness (1) Total: flatulence (5), headache (2), diarrhoea (2)	I: an upset stomach (1 case) C: an upset stomach (1 case) Total: an upset stomach (1 case)	I: NO C: ALT increased (1 case) Total: ALT increased (1 case)	I: / C: / Total: /	I: / C: / Total: /	I: gastrointestinal symptoms(2 cases) C: headache(1 case) Total: gastrointestinal symptoms(2 cases; 66.7%), headache (1 case, 33.3%)	I: nausea and mild abdominal distention (2 cases), increased AST(2 cases) C: nausea and mild abdominal distention (3 cases), CPK increased (1 case), AST increased (1 case) Total: nausea and mild abdominal distention (5 cases),

Characteristic	Bundy R, 2008	Chen LL, 2002	Deng YM, 2006	Ding W, 1999	Feng XY, 2006	Francini-Pesenti F, 2008	Hua D, 2008
	(3), constipation (3), tiredness (6), dry mouth (6), forgetfulness(1), bloating (1).						increased AST (3 cases), CPK increased (1 case)

Footnotes

./.: not reported

C: control; I: intervention; NO: not observed

Appendix 12

Adverse events (1) part 2

Characteristic	Jing A, 2009	Li KL, 2006	Li LH, 2005	Liu L, 2000	Lu GP, 1998	Ma YL, 2002	Qi MY, 2004
Intervention(s) & control(s)	I: DMC C: pravastatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C1 :Zocer C2: Mevalotin	I: Xuezhikang C: inositol nicotinate	I: Xuezhikang C: simvastatin	I: Xuezhikang C: Marine Triglycerids	I: Xuezhikang C: simvastatin
Deceased participants [n]	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C1 : 0 C2: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Adverse events [n / %]	I: 26.7%(8/30) C: 6.7%(2/30) Total: 16.7% (10/60)	I: 10%(4/40) C: 22.5%(9/40) Total: 16.25% (13/80)	I: 0 C1: 5%(1/20) C2: 5%(1/20) Total: 3.3% (2/60)	I: 11.7%(7/60) C: 27.6%(16/58) Total: 19.5% (23/118)	I: ./. C: ./. Total: ./.	I: 0 C: 0 Total: 0	I: 16.1%(18/112) C: 18.8%(21/112) Total: 17.4% (39/224)
Serious adverse events [n / %]	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C1: 0 C2: 0 Total: 0	I: 0 C: 0 Total: 0	I: ./. C: ./. Total: ./.	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Drop-outs due to adverse events [n / %]	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C1: 0 C2: 0 Total: 0	I: 0 C0 Total: 0	I: ./. C: ./. Total: ./.	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Hospitalisation [n / %]	I: ./. C: ./. Total: ./.	I: ./. C: ./. Total: ./.	I: ./. C1: ./. C2: ./. Total: ./.	I: ./. C: ./. Total: ./.	I: 0 C0 Total: 0	I: ./. C: ./. Total: ./.	I: ./. C: ./. Total: ./.
Out-patient treatment [n / %]	I: ./. C: ./. Total: ./.	I: ./. C: ./. Total: ./.	I: ./. C1: ./. C2: ./. Total: ./.	I: ./. C: ./. Total: ./.	I: 100% C: 100% Total: 100%	I: ./. C: ./. Total: ./.	I: ./. C: ./. Total: ./.
Symptoms [n / %]	I: Diarrhea (8 cases) C: myalgia(1 case), epigastric discomfort(1 case) Total: Diarrhea (80%), myalgia (10%), epigastric discomfort(10%)	I: increased ALT (2 cases), abdominal distention (2 cases) C: increased ALT (3 cases), abdominal distention(4 cases), dry mouth(2 cases) Total: increased ALT(5 cases, 38.5%), abdominal distention(6 cases, 46.2%), dry mouth(2 cases, 15.3%)	I: NO C1: CPK increased(1 case) C2: ALT increased(1 case) Total: CPK increased(50%), ALT increased (50%)	I: upset stomach and diarrhea (2 cases), muscular pain (3 cases), increased SGPT (4 cases) C: upset stomach and belching (9 cases), increased SGPT (6 cases) , erubescence and pruritus(8 cases) Total: upset stomach and diarrhea (2 cases), muscular pain (3 cases), increased SGPT (10cases) upset stomach and belching(9 cases) , erubescence	I: ./. C: ./. Total: ./.	I: NO CNO Total: NO	I: gastrointestinal symptoms (14 cases), increased ALT(4 cases) C: gastrointestinal symptoms(16 cases) , increased ALT(5 cases) Total: gastrointestinal symptoms (30 cases), increased ALT(9 cases)

Characteristic	Jing A, 2009	Li KL, 2006	Li LH, 2005	Liu L, 2000	Lu GP, 1998	Ma YL, 2002	Qi MY, 2004
				and pruritus(8 cases)			

Footnotes

./.: not reported
C: control; I: intervention; NO: not observed

Appendix 13

Adverse events (I) part 3

Character- istic	Quan SL, 2008	Tian X, 2007	Wang DG 2003	Wang WH, 2006	Wang XL, 2004	Xu CB, 2000	Xu SG, 2002	Zhang G, 2005
Interven- tion(s) & control(s)	I: Xuezhikang C: simvastatin	I: Xiaozhiling (herb mixture) C: simvastatin	I: Xuezhikang C: pravastatin	I: Xuezhikang C: atorvas- tatin	I: Xuezhikang C: simvastatin	I: Xuezhikang C: pravastatin	I: Xuezhikang C: lovastatin	I: Xuezhikang C: atorvas- tatin
Deceased partici- pants [n]	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: ./. C: ./. Total: ./.	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Ad- verse events [n / %]	I: 3.6%(2/ 56) C: 6.5%(3/ 46) Total: 4.9% (5/102)	I: 8.3%(3/ 36) C: 0 Total: 4.4% (3/68)	I: ./. C: ./. Total: ./.	I: 0 C: 6.8%(5/ 74) Total: 3.5% (5/142)	I: 0 C: 0 Total: 0	I: 2.5%(3/ 119) C: 17.2% Total: ./.	I: 5.9%(2/ 34) C: 11.8%(4/ 34) Total: 8.8% (6/68)	I: 10%(3/ 30) C: 10%(3/ 30) Total: 10% (6/60)
Serious ad- verse events [n / %]	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: ./. C: ./. Total: ./.	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0
Drop-outs due to ad- verse events [n / %]	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: ./. C: ./. Total: ./.	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 0 C: 1 Total: 1	I: 0 C: 0 Total: 0
Hospital- isation [n / %]	I: 100% C: 100% Total: 100%	I: 0 C: 0 Total: 0	I: 0 C: 0 Total: 0	I: 100% C: 100% Total: 100%	I: ./. C: ./. Total: ./.	I: ./. C: ./. Total: ./.	I: 0 C: 0 Total: 0	I: ./. C: ./. Total: ./.
Out-pa- tient treat- ment [n / %]	I: 0 C: 0 Total: 0	I: 100% C: 100% Total: 100%	I: 100% C: 100% Total: 100%	I: 0 C: 0 Total: 0	I: ./. C: ./. Total: ./.	I: ./. C: ./. Total: ./.	I: 100% C: 100% Total: 100%	I: ./. C: ./. Total: ./.
Symptoms [n / %]	I: mild symptoms (2 cases) C: nausea and anorexia (3 cases) Total : mild symptoms (2 cases) , nausea and anorexia (3 cases)	I: gastroin- testinal symptoms and mild di- arrhea (3 cases) C:No Total: gas- trointestinal symptoms and mild diarrhea (3 cases)	I: ./. C: ./. Total: ./.	I: NO C: GOT, GPT increased (3 cases), ab- dominal dis- tention(2 cases) Total: GOT, GPT increased (3 cases), ab- dominal dis- tention(2 cases)	I: NO C: NO Total: NO	I: ab- dominal dis- tention and constipation (2 patients) and rash 1 patient C: abdom- inal disten- tion(7.5%), constipation (4.3%) , nausea and tiredness	I: slightly in- creased SGPT (1 case), ab- dominal dis- tention (1 case) C: slightly increased SGPT (2 case) , slightly in- creased CPK (1 case)	I: ab- dominal dis- tention (2 cases), stom- achache (1 patient) C: ALT in- creased(1 patient) , anorexia(2 patients) Total: ab- dominal dis- tention (2 cases)

Character- istic	Quan SL, 2008	Tian X, 2007	Wang DG 2003	Wang WH, 2006	Wang XL, 2004	Xu CB, 2000	Xu SG, 2002	Zhang G, 2005
						(3.2%), in- somnia (2.2%) Total: ./.	, pruritus (1 case) To- tal: slightly increased SGPT (3 case), ab- dominal dis- ten- tion (1 case) , slightly in- creased CPK (1 case) , pruritus (1 case)	cases), stom- achache (1 pa-tient), ALT increased(1 patient) , anorexia(2 patients)

Footnotes

./.: not reported

C: control; I: intervention; NO: not observed

Appendix 14

Adverse events (2)

Herbs	Formulation	Compositions	Adverse events (n / %)	Study ID
Artichoke leaf extracts (Cynara scolymus)	capsule	320 mg of a standardised broad-spectrum aqueous extract (4-6: 1) of artichoke leaf, containing at least 2.5% total caffeoylquinic acids and at least 0.1% luteolin-7-O-glucuronide	flatulence (2); diarrhea (1); constipation (3); tiredness (2); dry mouth (2); bloating (1)	Bundy 2008
Xuezhikang	capsule	0.3 g/capsule	not reported (Lu 1998; Ding 1999; Wang 2003); not observed (Deng 2006; Li 2005; Ma 2002; Wang 2006; Wang 2004); an upset stomach (Chen 2002); abdominal distention (1.2%), stomachache (0.3%), rash (0.2%), increased SGPT (0.3%) and CPK (0.4%) (Feng 2006); nausea and mild abdominal distention (2 cases), increased AST (2 cases) (Hua 2008); increased ALT (2 cases), abdominal distention (2 cases) (Li 2006); upset stomach and diarrhea (2 cases), muscular pain (3 cases), increased SGPT (4 cases) (Liu 2000); gastrointestinal symptoms in 14 cases and increased ALT in four cases (Qi 2004); nausea and anorexia (3 cases), mild symptoms (2 cases) (Quan 2008); abdominal distention and constipation in two patients and rash in one patient (Xu 2000); slightly increased SGPT (3 cases), abdominal distention (1 case), slightly increased CPK (1 case), pruritus (1 case) (Xu 2002); abdominal distention in two cases and stomachache in one patient (Zhang 2005)	Lu 1998 Ding 1999 Liu 2000 Xu 2000 Chen 2002 Ma 2002 Xu 2002 Wang 2003 Qi 2004 Wang 2004 Li 2005 Zhang 2005 Deng 2006 Feng 2006 Li 2006 Wang 2006 Hua 2008 Quan 2008
Policosanol	tablet	10 mg of aliphatic primary alcohol mixture from Cuban sugar cane wax	gastrointestinal symptoms in two cases (Francini-Pesenti 2008)	Francini-Pesenti 2008
Daming	capsule	Cassia obtusifolia L.: Salvia miltiorrhiza: Panax ginseng CA. 12: 12: 6: 1.	diarrhea in three cases	Jing 2009

Herbs	Formulation	Compositions	Adverse events (n / %)	Study ID
Xiaozhiling	decoction	Aloe, Scutellaria, Cassia Oc- cidental, Fructus Crataegi, Folium Nelumbinis, Radix Salviae Miltiorrhizae, Spica Prunellae, Radix Polygoni Multiflori, Radix Astragali	gastrointestinal symptoms in two cases and mild diarrhea in 3 cases	Tian 2007

Appendix 15
Sensitivity analysis on hypercholesterolemic patients
with or without hypertriglyceridemia

Outcome	Sensitivity analysis on selective reporting	Result
1.1.4 TC	Exclude studies recruiting hypercholesterolaemic patients with hypertriglyceridemia (Deng 2006; Hua 2008; Li 2006) and studies recruiting hypercholesterolaemic patients and hypercholesterolaemic patients with hypertriglyceridemia (Li 2005; Qi 2004)	MD 0.25 (95% CI -0.45 to 0.94) I ² = 93%
1.1.3 TC	Exclude study recruiting hypercholesterolaemic patients and hypercholesterolaemic patients with hypertriglyceridemia (Li 2005)	MD 0.04 (95% CI -0.22 to 0.30) I ² = 50%
1.1.7 TC	Exclude study recruiting hypercholesterolaemic patients with hypertriglyceridemia (Zhang 2005)	MD 0.11 (95% CI -0.39 to 0.61) I ² = not applicable
1.2.4 TG	Exclude studies recruiting hypercholesterolaemic patients with hypertriglyceridemia (Deng 2006; Hua 2008; Li 2006) and studies recruiting hypercholesterolaemic patients and hypercholesterolaemic patients with hypertriglyceridemia (Li 2005; Qi 2004)	MD 0.04 (95% CI -0.29 to 0.38) I ² = 57%
1.2.3 TG	Exclude study recruiting hypercholesterolaemic patients and hypercholesterolaemic patients with hypertriglyceridemia (Li 2005)	MD -0.13 (95% CI -0.25 to -0.00) I ² = 29%
1.3.4 HDL-C	Exclude recruiting hypercholesterolaemic patients patients with hypertriglyceridemia (Deng 2006; Hua 2008) and studies recruiting hypercholesterolaemic patients and hypercholesterolaemic patients with hypertriglyceridemia (Li 2005; Qi 2004)	MD -0.04 (95% CI -0.24 to 0.16) I ² = 93%
1.3.3 HDL-C	Exclude study recruiting hypercholesterolaemic patients and hypercholesterolaemic patients with hypertriglyceridemia (Li 2005)	MD -0.05 (95% CI -0.12 to 0.03) I ² = 4%
1.4.4 LDL-C	Exclude studies recruiting hypercholesterolaemic patients with hypertriglyceridemia (Deng 2006; Hua 2008; Li 2006) and studies recruiting hypercholesterolaemic patients and hypercholesterolemia patients with hypertriglyceridemia (Li 2005; Qi 2004)	MD 0.29 (95% CI -0.35 to 0.93) I ² = 91%
1.4.3 LDL-C	Exclude study recruiting hypercholesterolaemic patients and hypercholesterolaemic patients with hypertriglyceridemia (Li 2005)	MD -0.05 (95% CI -0.30 to 0.20) I ² = 53%
1.4.7 LDL-C	Exclude study recruiting hypercholesterolaemic patients with hypertriglyceridemia (Zhang 2005)	MD 0.13 (95% CI -0.34 to 0.60) I ² = not applicable

Appendix 16

Sensitivity analysis on diagnostic criteria

Outcome	Sensitivity analysis on diagnostic criteria	Result
1.1.4 TC	Exclude 1997 national Suggestions on Prevention and Control of Dyslipidemia. (Quan 2008)	MD -0.01 (95% CI -0.09 to 0.08) $I^2 = 0\%$
1.3.4 HDL-C	Exclude 1997 national Suggestions on Prevention and Control of Dyslipidemia. (Quan 2008)	MD -0.00 (95% CI -0.13 to 0.12) $I^2 = 89\%$
1.4.4 LDL-C	Exclude 1997 national Suggestions on Prevention and Control of Dyslipidemia. (Quan 2008)	MD 0.01 (95% CI -0.17 to 0.19) $I^2 = 77\%$

Appendix 17

Sensitivity analysis on treatment duration

Outcome	Sensitivity analysis on treatment duration	Result
1.1.4 TC	Exclude one month (Chen 2002; Ding 1999)	MD 0.15 (95% CI -0.17 to 0.47) I ² = 90%
1.1.3 TC	Exclude six months (Xu 2000)	MD -0.03 (95% CI -0.22 to 0.15) I ² = 0%
1.1.5 TC	Exclude six months (Liu 2000)	MD -0.84 (95% CI -1.20 to -0.48) I ² = not applicable
1.2.4 TG	Exclude one month (Chen 2002)	MD -0.02 (95% CI -0.09 to 0.05) I ² = 52%
1.2.3 TG	Exclude six months (Xu 2000)	MD -0.06 (95% CI -0.17 to 0.06) I ² = 93%
1.2.5 TG	Exclude six months (Liu 2000)	MD 0.38 (95% CI 0.13 to 0.63) I ² = not applicable
1.3.4 HDL-C	Exclude one month (Chen 2002; Ding 1999)	MD 0.10 (95% CI 0.02 to 0.18) I ² = 71%
1.3.3 HDL-C	Exclude six months (Xu 2000)	MD 0.03 (95% CI -0.09 to 0.15) I ² = 57%
1.3.5 HDL-C	Exclude six months (Liu 2000)	MD 0.17 (95% CI 0.08 to 0.26) I ² = not applicable
1.4.4 LDL-C	Exclude one month (Chen 2002; Ding 1999)	MD 0.10 (95% CI 0.02 to 0.18) I ² = 84%
1.4.3 LDL-C	Exclude six month (Xu 2000)	MD -0.18 (95% CI -0.33 to -0.03) I ² = 0%
1.4.5 LDL-C	Exclude six months (Liu 2000)	MD -0.74 (95% CI -0.96 to -0.52) I ² = not applicable

Appendix 18
Sensitivity analysis taking into account risk of bias
(‘incomplete outcome data’)

Outcome	Sensitivity analysis on incomplete outcome data	Result
1.1.4 TC	Exclude studies biased on incomplete outcome data (Ding 1999; Li 2006; Qi 2004)	MD 0.17 (95% CI -0.29 to 0.62) I ² = 91%
1.1.3 TC	Exclude study biased on incomplete outcome data (Xu 2000)	MD -0.03 (95% CI -0.22 to 0.15) I ² = 0%
1.1.5 TC	Exclude study biased on incomplete outcome data (Feng 2006)	MD -0.94 (95% CI -1.22 to -0.66) I ² = not applicable
1.1.7 TC	Exclude study biased on incomplete outcome data (Wang 2006)	MD -0.02 (95% CI -0.44 to 0.40) I ² = not applicable
1.2.4 TG	Exclude studies biased on incomplete outcome data (Li 2006; Qi 2004)	MD -0.08 (95% CI -0.21 to 0.05) I ² = 62%
1.2.3 TG	Exclude study biased on incomplete outcome data (Xu 2000)	MD -0.06 (95% CI -0.17 to 0.06) I ² = 93%
1.2.5 TG	Exclude study biased on incomplete outcome data (Feng 2006)	MD 0.08 (95% CI -0.19 to 0.35) I ² = not applicable
1.3.4 HDL-C	Exclude studies biased on incomplete outcome data (Ding 1999; Qi 2004)	MD 0.08 (95% CI -0.03 to 0.19) I ² = 86%
1.3.3 HDL-C	Exclude study biased on incomplete outcome data (Xu 2000)	MD 0.03 (95% CI -0.09 to 0.15) I ² = 57%
1.3.5 HDL-C	Exclude study biased on incomplete outcome data (Feng 2006)	MD 0.24 (95% CI 0.01 to 0.47) I ² = not applicable
1.4.4 LDL-C	Exclude studies biased on incomplete outcome data (Ding 1999; Li 2006; Qi 2004)	MD 0.04 (95% CI -0.28 to 0.35) I ² = 88%
1.4.3 LDL-C	Exclude study biased on incomplete outcome data (Xu 2000)	MD -0.18 (95% CI -0.33 to -0.03) I ² = 0%
1.4.5 LDL-C	Exclude study biased on incomplete outcome data (Feng 2006)	MD -0.38 (95% CI -0.72 to -0.04) I ² = not applicable
1.14.1(TC-HDL-C)/HDL-C	Exclude study biased on incomplete outcome data (Li 2006)	MD 0.14 (95% CI -0.26 to 0.54) I ² = not applicable

Appendix 19
Sensitivity analysis taking into account risk of bias
(‘selective reporting’)

Outcome	Sensitivity analysis on selective reporting	Result
1.1.4 TC	Exclude studies with selective reporting (Deng 2006; Ding 1999; Hua 2008; Li 2005; Li 2006; Lu 1998; Qi 2004)	MD 0.45 (95% CI -0.66 to 1.55) I ² = 96%
1.2.4 TG	Exclude studies with selective reporting (Deng 2006; Hua 2008; Li 2005; Li 2006; Lu 1998; Qi 2004)	MD -0.10 (95% CI -0.49 to 0.30) I ² = 66%
1.3.4 HDL-C	Exclude studies with selective reporting (Deng 2006; Ding 1999; Hua 2008; Li 2005; Lu 1998; Qi 2004)	MD 0.04 (95% CI -0.18 to 0.27) I ² = 93%
1.4.4 LDL-C	Exclude studies with selective reporting (Deng 2006; Ding 1999; Hua 2008; Li 2005; Li 2006; Lu 1998; Qi 2004)	MD 0.21 (95% CI -0.77 to 1.18) I ² = 94%

Appendix 20

Sensitivity analysis taking into account risk of bias (‘other bias’)

Outcome	Sensitivity analysis on other bias	Result
1.1.3 TC	Exclude studies with other bias (Wang 2003; Xu 2000)	MD 0.09 (95% CI -0.31 to 0.49) I ² = Not applicable
1.1.4 TC	Exclude studies with other bias (Lu 1998)	MD 0.14 (95% CI -0.14 to 0.42) I ² = 89%
1.2.3 TG	Exclude studies with other bias (Wang 2003; Xu 2000)	MD 0.49 (95% CI 0.18 to 0.80) I ² = Not applicable
1.2.4 TG	Exclude studies with other bias (Lu 1998)	MD -0.03 (95% CI -0.10 to 0.04) I ² = 52%
1.3.3 HDL-C	Exclude studies with other bias (Wang 2003; Xu 2000)	MD 0.10 (95% CI -0.03 to 0.23) I ² = Not applicable
1.3.4 HDL-C	Exclude studies with other bias (Lu 1998)	MD 0.02 (95% CI -0.10 to 0.15) I ² = 91%
1.4.3 LDL-C	Exclude studies with other bias (Wang 2003; Xu 2000)	MD -0.22 (95% CI -0.46 to 0.02) I ² = Not applicable
1.4.4 LDL-C	Exclude studies with other bias (Lu 1998)	MD 0.14 (95% CI -0.11 to 0.38) I ² = 89%

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PLAIN LANGUAGE SUMMARY

Chinese herbal medicines for hypercholesterolemia

Hypercholesterolemia occurs when there is too much cholesterol in the blood. It is not a disease as such but a metabolic derangement. Elevated cholesterol in the blood is due to an increase in the amount of the so-called lipoproteins, particles that carry cholesterol in the bloodstream. There are two major types of cholesterol: HDL (high-density lipoprotein) cholesterol and LDL (low-density lipoprotein) cholesterol.

Hypercholesterolemia usually means elevated levels of total blood cholesterol or LDL-cholesterol with normal or low levels of HDL-cholesterol.

People with hypercholesterolemia have a higher risk of developing coronary artery disease, heart attacks, and stroke. Chinese herbal medicines have been commonly used and studied as cholesterol-lowering agents. To evaluate the effects of various herbal formulations (including single herbs, Chinese proprietary medicines, and mixtures of different herbs) for treating hypercholesterolemia, this review examined 22 randomized controlled trials of five different Chinese herbal medicines. The trials lasted from one to six months (average 2.3 months) and involved 2130 participants. There were no data on cardiovascular events and death from any cause. One trial each reported on well-being (no significant differences) and economic costs. No serious adverse events were observed. The available evidence suggests that several herbal medicines showed some cholesterol-lowering effect. However, due to considerable limitations in the quality of the included trials, further higher-quality and rigorously performed studies are required before any confident conclusions can be reached about the effects of Chinese herbal medicines for hypercholesterolemia.

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Internal sources

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- The "111" Project Number B08006, China.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of study selection

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

Figure 4. Forest plot of comparison: 2 Chinese herbal medicines versus placebo, outcome: 2.1 Total cholesterol (TC)

Figure 5. Forest plot of comparison: 1 Chinese herbal medicines versus conventional medicine, outcome: 1.1 Total cholesterol (TC)

Table 1

Overview of study populations

Study ID	Interven- tion(s) & control(s)	[n] screened	[n] ran- domized	[n] safety	[n] ITT	[n] finish- ing study	[%] of ran- dom- ized partici- pants finishing study	Comments
Bundy R, 2008	II: Ar- tichoke leaf extract (ALE) CI: placebo	II: ./. CI: ./. Total: ./.	II: 38 CI: 37 Total: 75	II: 38 CI: 35 Total: 69	II: 38 CI: 35 Total: 73	II: 37 CI: 34 Total: 71	II: 97.4 CI: 91.9 Total: 94.7	
Chen LL, 2002	II: Xuezhikang CI: simvas- tatin	II: ./. CI: ./. Total: ./.	II: 34 CI: 31 Total: 65	II: 34 CI: 31 Total: 65	II: ./. CI: ./. Total: ./.	II: 34 CI: 31 Total: 65	II: 100 CI: 100 Total: 100	
Deng YM, 2006	II: Xuezhikang CI: simvas- tatin	II: ./. CI: ./. Total: ./.	II: 45 CI: 55 Total: 100	II: 45 CI: 55 Total: 100	II: ./. CI: ./. Total: ./.	II: 45 CI: 55 Total: 100	II: 100 CI: 100 Total: 100	
Ding W, 1999	II: Xuezhikang CI: simvas- tatin	II: ./. CI: ./. Total: ./.	II: 40 CI: 40 Total: 80	II: 40 CI: 40 Total: 80	II: ./. CI: ./. Total: ./.	II: 40 CI: 40 Total: 80	II: 100 CI: 100 Total: 100	
Feng XY, 2006	II: Xuezhikang CI: inositol nicotinate	II: ./. CI: ./. Total: ./.	II: 116 CI: 116 Total: 232	II: 116 CI: 116 Total: 232	II: ./. CI: ./. Total: ./.	II: 116 CI: 116 Total: 232	II: 100 CI: 100 Total: 100	
Francini-Pesenti F, 2008	II: policosanol CI: placebo	II: ./. CI: ./. Total: ./.	II: 34 CI: 34 Total: 68	II: 34 CI: 32 Total: 66	II: ./. CI: ./. Total: ./.	II: 31 CI: 32 Total: 63	II: 91.2 CI: 94.1 Total: 92.6	
Hua D, 2008	II: Xuezhikang CI: simvas- tatin	II: ./. CI: ./. Total: ./.	II: 70 CI: 66 Total: 136	II: 70 CI: 66 Total: 136	II: ./. CI: ./. Total: ./.	II: 70 CI: 66 Total: 136	II: 100 CI: 100 Total: 100	
Jing A, 2009	II: DMC CI: pravas- tatin	II: ./. CI: ./. Total: ./.	II: 30 CI: 30 Total: 60	II: 30 CI: 30 Total: 60	II: ./. CI: ./. Total: ./.	II: 30 CI: 30 Total: 60	II: 100 CI: 100 Total: 100	
Li KL, 2006	II: Xuezhikang CI: simvas- tatin	II: ./. CI: ./. Total: ./.	II: 40 CI: 40 Total: 80	II: 40 CI: 40 Total: 80	II: ./. CI: ./. Total: ./.	II: 40 CI: 40 Total: 80	II: 100 CI: 100 Total: 100	

Study ID	Intervention(s) & control(s)	[n] screened	[n] randomized	[n] safety	[n] ITT	[n] finishing study	[%] of randomized participants finishing study	Comments
Li LH, 2005	I1: Xuezhikang C1: simvastatin C2: pravastatin	I1: ./. C1: ./. C2: ./. Total: ./.	I1: 20 C1: 20 C2: 20 Total: 60	I1: 20 C1: 20 C2: 20 Total: 60	I1: ./. C1: ./. C2: ./. Total: ./.	I1: 20 C1: 20 C2: 20 Total: 60	I1: 100 C1: 100 C2: 100 Total: 100	
Liu L, 2000	I1: Xuezhikang C1: inositol nicotinate	I1: ./. C1: ./. Total: ./.	I1: 60 C1: 58 Total: 118	I1: 60 C1: 58 Total: 118	I1: ./. C1: ./. Total: ./.	I1: 60 C1: 58 Total: 118	I1: 100 C1: 100 Total: 100	
Lu GP, 1998	I1: Xuezhikang C1: simvastatin	I1: ./. C1: ./. Total: ./.	I1: 15 C1: 13 Total: 28	I1: 15 C1: 13 Total: 28	I1: ./. C1: ./. Total: ./.	I1: 15 C1: 13 Total: 28	I1: 100 C1: 100 Total: 100	
Ma YL, 2002	I1: Xuezhikang C1: marine triglycerides	I1: ./. C1: ./. Total: ./.	I1: 30 C1: 30 Total: 60	I1: 30 C1: 30 Total: 60	I1: ./. C1: ./. Total: ./.	I1: 30 C1: 30 Total: 60	I1: 100 C1: 100 Total: 100	
Qi MY, 2004	I1: Xuezhikang C1: simvastatin	I1: ./. C1: ./. Total: ./.	I1: 112 C1: 112 Total: 224	I1: 112 C1: 112 Total: 224	I1: ./. C1: ./. Total: ./.	I1: 112 C1: 112 Total: 224	I1: 100 C1: 100 Total: 100	
Quan SL, 2003	I1: Xuezhikang C1: simvastatin	I1: ./. C1: ./. Total: ./.	I1: 56 C1: 46 Total: 102	I1: 54 C1: 43 Total: 97	I1: ./. C1: ./. Total: ./.	I1: 56 C1: 46 Total: 102	I1: 100 C1: 100 Total: 100	
Tian X, 2007	I1: Xiaozhiling (mixture of herbs) C1: simvastatin	I1: ./. C1: ./. Total: ./.	I1: 36 C1: 32 Total: 68	I1: 36 C1: 32 Total: 68	I1: ./. C1: ./. Total: ./.	I1: 36 C1: 32 Total: 68	I1: 100 C1: 100 Total: 100	
Wang DG, 2003	I1: Xuezhikang C1: pravastatin	I1: ./. C1: ./. Total: ./.	I1: 37 C1: 42 Total: 79	I1: 37 C1: 42 Total: 79	I1: ./. C1: ./. Total: ./.	I1: 37 C1: 42 Total: 79	I1: 100 C1: 100 Total: 100	
Wang WH, 2006	I1: Xuezhikang C1: atorvastatin	I1: ./. C1: ./. Total: ./.	I1: 68 C1: 74 Total: 142	I1: 68 C1: 74 Total: 142	I1: ./. C1: ./. Total: ./.	I1: 68 C1: 74 Total: 142	I1: 100 C1: 100 Total: 100	

Study ID	Intervention(s) & control(s)	[n] screened	[n] randomized	[n] safety	[n] ITT	[n] finishing study	[%] of randomized participants finishing study	Comments
Wang XL, 2004	I: Xuezhikang C: simvastatin	I: ./. C: ./. Total: ./.	I: 16 C: 14 Total: 30	I: 16 C: 14 Total: 30	I: ./. C: ./. Total: ./.	I: 16 C: 14 Total: 30	I: 100 C: 100 Total: 100	
Xu CB, 2000	I: Xuezhikang C: pravastatin	I: ./. C: ./. Total: ./.	I: 11 C: 76 Total: 195	I: 119 C: 76 Total: 195	I: ./. C: ./. Total: ./.	I: 119 C: 76 Total: 195	I: 100 C: 100 Total: 100	
Xu SG, 2002	I: Xuezhikang C: lovastatin	I: ./. C: ./. Total: ./.	I: 34 C: 34 Total: 68	I: 34 C: 34 Total: 68	I: ./. C: ./. Total: ./.	I: 31 C: 32 Total: 63	I: 91.2 C: 94.1 Total: 92.6	
Zhang G, 2005	I: Xuezhikang C: atorvastatin	I: ./. C: ./. Total: ./.	I: 30 C: 30 Total: 60	I: 30 C: 30 Total: 60	I: ./. C: ./. Total: ./.	I: 30 C: 30 Total: 30	I: 100 C: 100 Total: 100	
<i>Total</i>			<i>I: 1080 C: 1030 C2: 20 Total: 2130</i>			<i>I: 1075 C: 1026 C2: 20 Total: 2121</i>		

./.: not reported

C: control

I: intervention

ITT: intention-to-treat