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Food-based natural products for cancer management: Is the whole greater than the sum of the parts?

Suleman S. Hussain^{a,b}, Addanki P. Kumar^{a,b,c,d,e,#}, and Rita Ghosh^{a,b,c,d,*}

^aDepartment of Urology, School of Medicine, University of Texas Health Science Center, San Antonio, TX 78229, USA

^bDepartment of Pharmacology, School of Medicine, University of Texas Health Science Center, San Antonio, TX 78229, USA

^cDepartment of Molecular Medicine, School of Medicine, University of Texas Health Science Center, San Antonio, TX 78229, USA

^dCancer Therapy and Research Center, School of Medicine, University of Texas Health Science Center, San Antonio, TX 78229, USA

^eSouth Texas Veterans Health Care System, San Antonio, TX 78229, USA

Abstract

The rise in cancer incidence and mortality in developing countries together with the human and financial cost of current cancer therapy mandates a closer look at alternative ways to overcome this burgeoning global healthcare problem. Epidemiological evidence for the association between cancer and diet and the long latency of most cancer progression have led to active exploration of whole and isolated natural chemicals from different naturally occurring substances in various preclinical and clinical settings. In general the lack of systemic toxicities of most ‘whole’ and ‘isolated’ natural compounds, their potential to reduce toxic doses and potential to delay the development of drug-resistance makes them promising candidates for cancer management. This review article examines the suggested molecular mechanisms affected by these substances focusing to a large extent on prostate cancer and deliberates on the disparate results obtained from cell culture, preclinical and clinical studies in an effort to highlight the use of whole extracts and isolated constituents for intervention. As such these studies underscore the importance of factors such as treatment duration, bioavailability, route of administration, selection criteria, standardized formulation and clinical end points in clinical trial design with both entities. Overall lack of parallel comparison studies between the whole natural products and their isolated compounds limits decisive conclusions regarding the superior utility of one over the other. We suggest the

*Address for correspondence Rita Ghosh, PhD, Department of Urology, School of Medicine, University of Texas Health Science Center at San Antonio, 8403 Floyd Curl Drive, San Antonio, TX 78229, Tel: 210-562-4117, Fax: 210-562-4133, ghoshr@uthscsa.edu.

#Addanki P Kumar, PhD, Department of Urology, School of Medicine, University of Texas Health Science Center at San Antonio, 8403 Floyd Curl Drive, San Antonio, TX 78229, Tel: 210-562-4116, Fax: 210-562-4133, kumara3@uthscsa.edu

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critical need for rigorous comparative research to identify which one of the two or both entities from nature would be best qualified to take on the mantle of cancer management.

Keywords

Food-based extracts; active compounds; cancer prevention; cancer therapy; adjuvants

1. Introduction

The global map of cancer prevalence is rapidly changing. While the western world is witnessing a decrease in most cancer-related mortality, incidence and mortality continue to rise rapidly in developing and underdeveloped countries. The International Agency for Research on Cancer reported that 64.9% of cancer-deaths in 2012 occurred in less developed regions of the world [1]. About 97% of growth in world population in 2012 was also attributed to that of developing nations. Considering this unexpected growth, and higher life expectancies, it is projected that new cancer cases will dramatically increase from 14.1 million in 2012 to 19.3 million by 2025 [1, 2]. This crippling global cancer scenario raises immense concerns regarding accessibility to treatment due to excessive cost of modern cancer care in general and limited access to exorbitant therapeutics in developing countries in particular. Further, increased survival is also accompanied by increased healthcare costs to monitor many recurrent cancers. These devastating facts underscore the need for economical and novel interventions that may have a larger global reach. The ability to use naturally occurring materials to manage cancer is an appealing alternative to overcome these alarming statistics. Given the large numbers of starting materials in nature, the various isolated compounds, complexities of different cancers and the recapitulation of preclinical tumor models make it very clear that we have to ensure that the most commonly tested natural whole extract and/or their isolated compounds are fully and scientifically vetted to facilitate their use for cancer management. Chemoprevention in general and prevention with phytochemicals has been widely studied in 4 of the most common cancers including lung, colon, breast and prostate. In this review we focus largely on prostate cancer. Cell culture studies that reveal mechanistic aspects of the effects of these compounds and their parent extracts are also presented. As discussed here validation of these molecular mechanisms may facilitate their use as surrogate markers of efficacy in clinical trials.

2. Whole vs. isolated compound entities

An array of natural foods including tomatoes, grapes, green tea, soybeans, milk thistle, broccoli, pomegranate, black raspberries, and isolated compounds from them have been explored in various preclinical and clinical settings for their anti-cancer potential [3–8]. Clearly patients in developed countries are willing to explore botanicals/natural products as alternatives to manage cancers. In a study to assess interest in participating in a botanical chemoprevention trial for lung cancer prevention among heavy smokers 88% individuals were reported to express interest in participating in the trial [9]. However, one of the current dilemmas in natural product research is what is more beneficial the extract/natural product or its active phytoconstituent and whether they have utility in prevention or treatment (Fig.

1). Those in favor of the ‘whole’ compound argue that the therapeutic efficacy of an extract is the outcome of synergistic or additive effects of its various active components while those in favor of purified compounds argue that unlike isolated compounds several phytonutrients are not bioavailable and therefore less useful. There is merit to both sides of this argument and despite the fact that a large volume of research has been carried out, the literature does not proclaim a winning entity in this debate. We propose that numerous variables including but not limited to valid cancer models, end points such as prevention or therapy, bioavailability or lack thereof have to be compared head to head using whole vs. the isolated compounds to determine the most useful material for human use. To achieve this hypothesis-driven research is needed to determine whether targeting multiple cross-talking and redundant signaling pathways with whole extracts can standup to the beneficial outcomes claimed by isolated compounds [10]. To facilitate this discussion a brief summary (with a greater focus on prostate cancer) is presented of some of the available published studies that have examined the efficacy of whole natural product and isolated constituents (Table 1) and the known molecular targets (Table 2).

2.1 Tomatoes and lycopene

Lycopene is an antioxidant carotenoid abundant in tomatoes that is known to accumulate in the prostate [11]. In addition to lycopene, tomatoes have other polyphenols (quercetin, kaempferol, and naringenin), carotenoids (phytoene; phytofluene; and δ -, β -, and γ -carotene), folate, vitamins A, C, and E and potassium, which accumulate in the prostate [12]. While it is clear that these chemicals are available in the prostate the ability of each of these components to protect against cancer in a synergistic or additive manner has not been established. Further it is unclear why lycopene accumulates in androgen-sensitive tissues and more so in cancerous than non-cancerous prostate [11, 13]. A general paradigm regarding the anti-cancer protection afforded by these compounds is based on their antioxidant capability. The complexity of this antioxidant paradigm is the protection afforded to cancer cells that enables their survival. Preclinical studies with lycopene attenuated hepatocellular carcinoma (HCC) in several carcinogen-induced mouse models by reducing activation of pro-inflammatory molecules such as nuclear factor kappa B (NF κ B), signal transducer and activator of transcription 3 (STAT3) and interleukin 6 (IL-6) by deregulating protein kinase B/mechanistic target of rapamycin (AKT/mTOR) cascade and by increasing nuclear factor E2-related factor 2 (NRF2) expression to act as an anti-oxidant [14, 15]. Notably, lycopene (23 or 224 nmol/g diet) was less efficacious than powdered tomato in reducing tumor weight in a Dunning R3327-H prostate adenocarcinoma model [16]. Interestingly, comparison of lycopene vs. tomato powder in transgenic adenocarcinoma of the mouse prostate (TRAMP) mice from 4 to 10 weeks of age revealed that 26 prostatic genes were similarly affected by both dietary interventions with the exception of only 4 divergently expressed genes (nerve growth factor receptor; *Ngfr*; synaptophysin; *Syp*, *beta-2 microglobulin*; *B2m* and *vitamin D receptor*; *Vdr*) [17]. Tomato feeding altered expression of more genes (steroid-5-alpha-reductase, alpha polypeptide 2; *Srd5a2*, paxillin; *Pxn*, and sterol regulatory element binding transcription factor; *Srebf*) involved in androgen metabolism compared to lycopene (*Srd5a2*), while lycopene demonstrated a specific inhibition of genes related to neuroendocrine differentiation (*Ngfr* and *Syp*) [17]. These findings suggest that lycopene maybe useful in aggressive disease especially with the

emerging literature demonstrating an association of aggressive cancer with neuroendocrine phenotype [18]. On the other hand tomato powder may be useful in the setting of early stage localized disease. Remarkably, in a rat model of prostate carcinogenesis, prostate cancer (PCA)-specific mortality decreased only in the group fed with tomato powder with no differences observed after lycopene administration [19]. On the contrary, consistent with our interpretation above, a diet rich in lycopene decreased PCA incidence in TRAMP mice while tomato paste had no significant effect, although both similarly increased prostate lycopene levels [20]. The authors of the latter study noted that the tomato paste excluded skin and seeds, which could have eliminated some of the beneficial phyto constituents such as quercetin, keampferol and flavonoids. This suggests a possible synergistic or additive effect of the various chemicals present in tomato.

Twenty clinical trials are listed on clinicaltrials.gov with lycopene ranging from pre-surgery supplementation to adjuvant chemotherapy with 6 published reports from these clinical trials with varying results with respect to prostate specific antigen (PSA) reduction and PCA incidence [21, 22]. A prospective study of dietary lycopene in 50,000 male health professionals suggested that higher lycopene levels reduced risk of developing lethal PCA [21]. This effect was more prominent in early intake vs. recent intake of lycopene, which highlights the importance of duration to produce clinical effects. A dose-response meta-analysis of 26 clinical studies with 563,299 participants revealed that consumption of lycopene (9–21 mg/day) can reduce risk of developing PCA [23]. Similarly, consumption of lycopene (8 mg) for a year delayed progression to occult PCA in men with high grade prostatic intraepithelial neoplasia (HGPIN) lesions [24]. However, a higher dose of lycopene supplementation (30 mg) for a short time span (4 months) showed no PSA decline in HGPIN patients [25]. In contrast, PSA decline of 10.77% in patients with benign prostatic hyperplasia (BPH) was found following ingestion of 50 g of tomato paste for 10 weeks [26]. No clinical benefit was reported when lycopene was tested in castration resistant prostate cancer (CRPC) patients [27].

2.2 Grape seed extracts and resveratrol

Grape seed extract (GSE) contains several polyphenols and are particularly rich in proanthocyanidins. Orally administered GSE prevented the progression of prostatic intraepithelial neoplasia to adenocarcinoma in TRAMP mice by inhibiting cell cycle progression [28]. Although administration of gallic acid, (a major constituent of GSE), increased the incidence of low-grade prostate tumors it did decrease progression to poorly differentiated carcinoma [29]. GSE inhibited tumor growth and tumor angiogenesis in a breast cancer xenograft model that was associated with inhibition of vascular endothelial growth factor (VEGF) receptor kinase activity and VEGF-induced proliferation and migration of endothelial cells [30]. Interestingly, when the polyphenol components of GSE were removed, the extract lost its anti-angiogenic and anti-VEGF activity [30]. GSE also inhibited aromatase activity and expression in a breast cancer xenograft animal model [31]. In colorectal cancer (CRC), the anticancer activity of GSE was shown to be mediated by induction of endoplasmic reticulum stress and inhibition of the PI3K/AKT/mTOR pathway [32]. Strikingly, use of GSE supplements was associated with 41% reduction in risk of developing low-grade prostate cancer in 35,239 members of the VITamins And Lifestyle

(VITAL) cohort participants [33]. Resveratrol is a phytoalexin, which is produced by plants under environmental stress or microbial attack. Grapes, peanuts, red wine and mulberries are the main dietary sources of resveratrol [34, 35]. Interestingly, resveratrol was shown to have direct interactions with 20 proteins from diverse pathways involved in inflammation, metabolism, cell cycle [36]. Notably, resveratrol prevented hepatic tumorigenesis in rats by increasing Nrf2 and thus suppressing oxidative stress and inflammation [37]. Further, resveratrol decreased lung metastasis of CRC by suppressing TGF- β 1/Smad signaling-induced epithelial mesenchymal transition [38]. Further, mice receiving high-fat diet had greater reduction in tumor burden after low-dose resveratrol that was recapitulated in ex-vivo human samples as well as CRC patients [39]. Several studies including our own have established that resveratrol suppresses prostate cancer growth and metastasis by increasing the mammalian ortholog of yeast silent information regulator 2, (SIRT1) and inhibiting mTORC1 activity [7]. Resveratrol inhibits metastasis-associated protein 1 (MTA1), a chromatin modulator, which negatively regulates PTEN causing a decrease in proliferation index of PCA [40].

A recent clinical study of resveratrol in CRC patients showed that lower doses of resveratrol (correlative to chronic dietary consumption) was more effective than the 200 times higher supra-physiological dose usually administered in clinical trials of dietary supplements [39]. Low bioavailability, rapid metabolic clearance and gastrointestinal side effects of high doses of resveratrol have limited its clinical investigation and thus there are very few clinical trials of resveratrol in prostate cancer. Currently there are 4 clinical trials listed on clinical trials.gov for grape seed extract (all related to breast cancer) of which 2 have been completed yet no results are associated with these trials making it difficult to assess the comparative effectiveness of the whole extract with resveratrol. MPX, a formulation of pulverized muscadine grape skin containing ellagic acid, quercetin and resveratrol, given to biochemically recurrent PCA patients for 21–30 months was well tolerated and increased PSA doubling time (PSADT) by a median of 5.3 months [41].

2.3 Green Tea and epigallocatechin-3-gallate

Green Tea, a beverage commonly consumed in Asia, is rich in catechin polyphenols such as (–)-epigallocatechin-3-gallate (EGCG), (–)-epigallocatechin (EGC), (–)-epicatechin-3-gallate (ECG), and (–)-epicatechin (EC). It is also known to contain other polyphenols such as flavanols, their glycosides and depsides [42]. Although anti-cancer interactions between depsides and EGCG have not been published, depsides have been reported to be biologically active may possibly be involved in increasing the effectiveness of tea extracts compared to EGCG alone [43]. Combination of green tea infusion with soy phytochemical concentrate was shown to synergistically reduce metastasis and serum testosterone levels [44]. Green and black tea extracts decreased expression of multidrug-resistant gene (MDR-1), while EGCG alone increased MDR-1 expression suggesting the combination of compounds in the extracts maybe more competent in overcoming resistance than EGCG alone [45]. *Preclinical studies show that* TRAMP mice administered 1,000 mg/kg/day Polyphenon E[®], a mixture of GTP containing 800 mg EGCG, underwent a significant reduction in tumor metastasis [46]. Increased tumor-free survival was observed only when green tea infusions were given to TRAMP mice starting at 6 or 12 weeks [47]. The study also revealed that GTP-mediated

inhibition of insulin-like growth factor 1 (IGF-1) and downstream AKT/ERK signaling was detected only in early treatment groups. Additionally, EGCG was found to exert its anti-cancer activity by mobilizing increased copper generated in a carcinogen-induced rat model of HCC [48]. In an ovarian cancer xenograft, EGCG was shown to increase copper transporter 1 (*Ctr1*) expression and sensitize tumors to cisplatin [49]. Administration of EGCG suppressed VEGF levels and increased p-p38 levels to inhibit liver metastasis in a colon carcinoma xenograft model [50]. To address the problem of low bioavailability of EGCG, Khan and colleagues tested a slow-release chitosan nanoparticle encapsulated EGCG for anti-cancer activity in a xenograft model and reported a significant increase of various apoptotic markers associated with EGCG action compared with EGCG alone [51].

Evidence from *in vitro* studies regarding the inhibition of hepatocyte growth factor (HGF) and VEGF by green tea polyphenols (GTP) led to a clinical trial with Polyphenon E[®], which reduced PSA, VEGF, HGF and IGF after pre-surgery supplementation for about 35 days [52]. In a similar trial testing Polyphenon E[®] with the addition of a control arm, there was an insignificant decreased trend towards lowered serum PSA and IGF levels. Further, the authors reported low bioavailability of catechins in the prostate tissue [53]. Intake of Polyphenon E[®] containing 50–75% EGCG in HGPIN and atypical small acinar proliferation (ASAP) patients for 1 year was well tolerated but did not affect PCA incidence although there was a significant reduction in PSA levels [54]. While, daily ingestion of 600 mg GTP mixture containing 51.88% EGCG for a year had an incidence rate of 3% vs. 30% in the placebo arm [55]; GTP also improved the quality of life (QOL) score with patients having fewer lower urinary tract symptoms.

2.4 Soybeans and genistein

Soybeans are a rich source of isoflavones such as genistein and diadzein, which have weak estrogenic and anti-estrogenic activities [56]. Soy isoflavones have been one of the most widely studied compounds for anti-cancer effects. The anti-cancer effect of genistein in TRAMP mice was shown to be due to modulation of AKT/GSK-3 β signaling, reduction of cyclin D1 and by inhibition of osteopontin [57, 58]. Soy isoflavones increased lung metastasis in an experimental bone-metastasis breast cancer model [59]. Comparison between soy extracts and its individual components showed that the extract was more potent in inducing apoptosis without causing apoptosis in the BPH-1 non-cancerous prostate cell line [60]. Phytoalexins such as glyceollins are also present in soy and it has been reported to inhibit prostate cancer cell growth in vitro through an androgen-mediated pathway [61]. Comparison of isoflavone-depleted soy protein, soy phytochemical concentrate (containing genistein, diadzein and glycitein aglycone) and genistin (the glycoside form of genistein) for their abilities to inhibit prostate tumor growth and metastasis in mice showed that although all influenced tumor growth, the greatest reduction was for the soy phytochemical concentrate [62]. Dietary soy has been frequently tested in combination with other phytochemicals of dietary origin. For example the combination of soy and tea was shown to alleviate chronic inflammation in a rat model of prostate cancer [63]. Dietary intervention with soy protein supplement (40g soy protein/day) or tomato products (minimum dose of 25mg lycopene/day) and the combination in men diagnosed with PCA showed no grade II,

III and IV toxicities, was bioavailable as measured by serum and urine levels; however only 34% of men showing decreased PSA levels [64].

Consumption of soy protein isolates for six months reduced androgen receptor expression in high-risk PCA patients [65]. Strikingly, a highly concentrated genistein rich extract given to PCA patients for 6 months did not decrease PSA levels [66]. A recent trial using soy bread slices in recurrent PCA patients highlighted an immuno-modulatory function of soy isoflavones by decreasing T-helper cells and myeloid derived suppressor cells-associated cytokines [67]. Supporting this observation, a 20-week crossover randomized trial of soy bread in asymptomatic PCA patients established its safety and caused a three-fold prolongation in PSADT [68]. In contrast, a double-blind, randomized trial of soy isoflavones administered six weeks prior to radical prostatectomy showed no change in serum hormone levels or PSA [69]. Similarly, a mixture of soy isoflavones (genistein, diadzein, and glycitein) given for 12 weeks to PCA patients with Gleason Score 6 did not alter the serum levels of steroid hormones although there was an increase in plasma isoflavone levels [70]. A placebo controlled trial of soy proteins administered to early breast cancer patients between diagnosis and surgery (7–30 days) revealed an increase in cell cycle and proliferation genes, raising concerns over the efficacy of soy nutrients for breast cancer treatment [71].

2.5 Milk thistle extract and silibinin

Silymarin is a complex mixture of flavonolignans from the milk-thistle plant that belongs to the *Asteraceae* family and silibinin is the major active constituent of silymarin. Silibinin-mediated anti-tumor activity in a lung cancer xenograft model was mediated through decreased SIRT1 and increased p53 acetylation [72]. Notably, milk thistle extract overcame erlotinib resistance by inhibiting mesenchymal markers such as SNAIL, ZEB and N-cadherin [73]. Based on these observations, an ongoing Phase II trial is examining the combination of erlotinib and Siliphos® in EGFR mutant lung cancer patients (NCT02146118). In a prostate cancer model silymarin-mediated inhibition of tumor growth was associated with increased plasma insulin-like growth factor-binding protein-3 (IGFBP-3) levels [74]. Based on this evidence a clinical trial in PCA patients found that silibinin had poor bioavailability. In further work silibinin was made lipophilic by complexing with soy phospholipids such as phosphatidylcholine, making a phytosome-based formulation called Siliphos® [75]. Transient high plasma levels, low prostate accumulation of silibinin and no differences in IGF-1 and IGFBP-3 levels were noted after pre-surgery supplementation of Siliphos® in PCA patients [76]. Similarly, Siliphos® did not change IGFBP-3 and IGF-1 circulating levels when administered to CRC patients 7 days before surgery [77].

2.6 Broccoli Sprouts and sulforaphane

Cruciferous vegetables such as broccoli and Brussels sprouts are rich in glucosinolate and glucoraphanin, which are precursors of the isothiocyanate sulforaphane and indole-3-carbinol (I3C). Sulforaphane activates detoxifying enzymes such as quinone reductase and glutathione transferase [78]. Sulforaphane administration reduced tumor burden and decreased pulmonary metastasis in various prostate cancer models by inducing TNF-related apoptosis-inducing ligand (TRAIL)-R1/DR4 and caspase-mediated apoptosis as well as

inhibition of PI3K/AKT and NF κ B signaling [79–81]. Sulforaphane also inhibited VEGF and matrix metalloproteinases to modulate angiogenesis and metastasis and increased the lytic activity of natural killer cells [80, 81]. In a breast cancer xenograft model, sulforaphane administration drastically reduced aldehyde dehydrogenase (ALDH)-positive breast cancer cells and inhibited Wnt/ β -catenin pathway [82]. Preclinical evaluation in rats showed that both sulforaphane and glucoraphanin inhibited mammary carcinogenesis by reducing expression of NAD(P)H quinone oxidoreductase 1 (*Nqo1*) and heme oxygenase-1 (*Ho-1*) [83]. I3C and 3,3'-diindolylmethane (DIM) also exhibit anti-prostate cancer activity [84, 85]. Broccoli sprout extracts are being currently tested in clinical trials for prostate, pancreatic, and lung cancers [86–88]. Administration of sulforaphane for 6 months to post-surgery prostate cancer patients did not achieve the primary end point of decreasing log PSA slope by 0.012 log (ng/mL)/month. However, the intervention increased PSADT by 86% and mean changes in PSA after 6 months was significantly lower in the treatment group [88]. Further, consumption of 200 μ moles/day sulforaphane-rich broccoli sprout extract for 20 weeks by PCA patients with biochemical recurrence led to a < 50% decline in PSA in 7 out of 20 patients and increased PSADT with one patient showing 50% decline in PSA [89]. Additionally, consumption of 400 g broccoli by HGPIN patients for a year caused significant changes in androgen, TGF- β , IGF and EGF signaling and the mechanism suggested was a covalent interaction of sulforaphane with insulin, TGF- β and EGF peptides to form thiourea [90].

2.7 Pomegranate extract

Pomegranate contains a multitude of phytochemicals besides ellagic acid and anthocyanins, which contribute to its antioxidant activity in various ailments. Punicalagin, an ellagitannin polyphenol present in pomegranate husk is considered to be its major active phytoconstituent [91]. Interestingly, juice from the aril of the fruit that lacks punicalagin demonstrated significantly lower antioxidant activity compared to the whole fruit [91]. However, when pomegranate juice was compared to punicalagin or ellagic acid alone, the juice had superior antioxidant and anti-proliferative effects in oral, prostate and colon cancer cell lines [92]. Pomegranate extracts have shown anti-cancer activity in *in vitro* and *in vivo* models of colon, prostate, skin, lung, breast cancer and leukemia by impeding key processes such as metastasis, inflammation, proliferation and angiogenesis [93–95]. The extracts were also shown to inhibit tumor progression in various PCA xenograft models with decreased NF κ B signaling, and cell cycle proteins leading to apoptosis [96–98]. In TRAMP mice, oral infusions of pomegranate fruit extract increased survival and decreased metastasis by inhibition of IGF-1/AKT/mTOR pathways [99]. A clinical study using 8 ounces of pomegranate juice in men with rising PSA following surgery or radiotherapy showed enhanced PSADT [100]. A subsequent study tested 1 and 3 g pomegranate extract in the form of POMx capsules in a randomized double-blind dose exploration study in PCA patients with rising PSA using changes in PSADT as the primary endpoint. POMx was found to be well tolerated and increased PSADT irrespective of the dose [101]. However, this study also suffered from the same limitation since it did not include a placebo-control arm that was a drawback of the previous study. Strikingly, a recent multi-institutional randomized placebo-controlled trial of pomegranate extract showed no significant prolongation of PSADT in PCA patients with rising PSA after primary therapy [102].

2.8 Black raspberry extract

Anthocyanins and ellagitannins are major phyto-constituents of black raspberry extract [103]. Using different fractions of the extract, anthocyanins were shown to be essential components for the chemopreventive effect in rat esophageal tumors by inhibition of *Nfκb*, activator protein-1 (*Ap-1*) and Pentraxin-3 (*Ptx3*; a cytokine produced in response to interleukin-1β) and *Tnf-α* expression [104, 105]. Black raspberry extract delayed mammary tumorigenesis in rats by decreasing estrogen receptor-α (*Era*) expression and modulation of metabolic enzymes for estrogen such as CYP1A1 and CYP1B1 [106, 107]. Notably, topical application of the extract reduced cutaneous UV-B induced carcinogenesis in female SKH-1 hairless mice and reduced inflammation by decreasing CD3⁺ foxp3⁺ regulatory T-cells, neutrophil activation and oxidative DNA damage [108]. In a rat model of prostate cancer animals fed 10% black raspberry extract diet did not affect incidence or tumor multiplicity although in vitro experimentation showed a beneficial effect on prostate cancer cells [109]. Black raspberry extract is being extensively studied in clinical trials for Barrett's esophagus, oral, colorectal and prostate cancers. There was reduced polyp burden in familial adenomatous polyposis (FAP) patients when black raspberry extract was rectally administered, with no added-benefit in the oral-administration group [110]. The same group developed a bio-adhesive berry gel (containing 10% freeze dried black raspberry) for topical application that when applied to oral mucosa for 6 weeks after initial oral intraepithelial neoplasia (OIN) biopsy, caused histological regression of OIN (a precursor to oral squamous cell carcinoma) in 41% of study participants [135]. This finding was substantiated by a recent placebo-controlled trial in which 12 weeks of topical application of the gel reduced lesion size, histologic grade, and loss of heterozygosity events [111]. An on-going clinical trial (NCT01823562) is registered on clinical trial.gov using lyophilized black raspberry in men with prostate cancer undergoing surgery to determine safety and compliance.

3. Natural products as adjuvants in cancer therapy

The potential clinical benefits of phytochemicals from foods are becoming increasingly evident. The lack of systemic toxicity of these extracts makes them particularly promising as adjuvants in cancer therapy. The combination of natural products with the standard of care treatment is an emerging area of cancer therapeutics with a multitude of benefits such as dose reduction, synergistic effect and delay in development of drug-resistance. Along these lines, a recent meta-analysis of 29 different clinical trials with 2,547 non-small cell lung cancer (NSCLC) patients revealed that combination of radiation therapy (RT) with Astragalus containing Chinese herbal preparation improved performance status of patients, reduced radiation treatment-associated toxicity and increased survival compared to patients treated with RT alone [112]. Similarly, using EGCG as an adjuvant with RT in stage III lung cancer patients led to significant improvement of QOL of patients by decreasing acute radiation-induced esophagitis toxicity [113]. Oral administration of EGCG (400 mg *t.i.d*) for 8 weeks lowered serum levels of VEGF, HGF and MMP-9 in breast cancer patients undergoing RT [114]. EGCG also reduced TNF-α to alleviate bone cancer pain in an orthotopic bone cancer animal model, suggesting its potential as an adjuvant to improve QOL [115]. Oral administration of GTP was shown to mitigate chemotherapy-induced mucosal damage to the small intestine in mice [116]. Recently the combination of green tea

and quercetin was shown to sensitize prostate tumors to docetaxel [117]. Microencapsulated lycopene combined with docetaxel potentiated its anti-tumor efficacy by 38 % in a DU145 xenograft tumor model by inhibiting IGF-1 signaling [118]. No gastrointestinal side-effects were noted after tomato juice consumption during radiation therapy in men with localized prostate cancer, warranting further investigation of its role as an adjuvant to radiation therapy [119]. Lycopene supplementation prior to radical prostatectomy in prostate cancer patients reduced serum PSA and tumor volumes [120]. Milk thistle extracts act as hepatoprotectant by decreasing chemotherapy induced liver toxicity in acute lymphoblastic leukemia [121]. Silymarin potentiates doxorubicin cytotoxicity by inhibition of its P-glycoprotein mediated cellular efflux [122]. Combination of soy isoflavone extract with RT enhanced inhibition of tumor progression and protected the lung from radiation injuries such as pneumonitis in a NSCLC xenograft model [123]. Administration of fermented soybean extract MicrSoy-20 (MS-20) prior to and with chemotherapy caused a significant reduction in chemotherapy-associated fatigue and appetite loss, improving QOL for patients [124]. Recently, work from our laboratory demonstrated promising activity of *Phellodendron amurense* bark extract (Nexrutine®) in PCA patients. Patients received Nexrutine® (Nx) orally (500 mg *tid*) either one to two months pre-operatively or one to two months prior to and with RT. There was no grade 3 toxicity using common terminology criteria for adverse events in the combined Nx and radiation component. By the end of the neoadjuvant treatment, 81% of patients had a decline in PSA. This is the first report regarding the safety and tolerability of Nx in PCA patients. However, the limitations of this study were the lack of a placebo-controlled arm, small cohort of patients, and use of single dose of Nx for short period of time [125,126].

4. Challenges in clinical development of natural products

From the examples of studies listed above it is clear that we are far from concluding whether the whole natural extract or its most prominent chemical constituent should be the candidate anti-cancer agent for clinical testing. The examples above also highlight shortcomings such as lack of standard design including but not limited to duration of treatment, inclusion of proper control arms, choice of cancer stage, outcome measures and the nature of the natural product. For example from the tomato paste and lycopene studies it is clear that although lycopene is present in the whole extract the molecular pathways affected by each is distinctly diverse. It is not clear whether the higher dose of lycopene in the lycopene alone study than the amount of lycopene consumed as tomato extract was the reason for the different response. It is also possible that other components present in the tomato extract contributed to the different results. It is important to note that primary evidence to test diet-based natural compounds comes from low intake epidemiologic evidence therefore studies with larger doses should not be expected to produce greater anti-cancer effects. Many preclinical studies demonstrate the importance of the state of disease progression, a factor that is not always captured in the clinical setting. For example many clinical studies in prostate cancer are designed to examine natural agents given prior to standard of care treatment although the preclinical evidence is not necessarily obtained from the same setting. Given the dynamic changes that occur as cancer progresses the lack of a standard cancer state can also result in different outcomes between preclinical and clinical studies.

Assessment of pharmacokinetics and pharmacodynamics of natural products in various animal models with different genetic backgrounds is an essential entity to faithfully translate preclinical observations into the clinic. The importance of the target population selection in clinical trial design is elegantly demonstrated by the success of broccoli sprout extracts in pollutant over-exposed individuals who were at high risk for developing lung cancer [87]. The failure of selenium as a cancer prevention agent may also be attributed to the choice of target population since selenium deficiency is not associated with most areas of the US. Therefore supplemental selenium (a micronutrient) consumed over the doses required for proper systemic functioning may have contributed to the observed pro-cancer outcomes. While varied amounts of phytochemicals and their metabolites in foods consumed can be controlled relatively easily in preclinical studies it is more complicated in clinical trials and could be one factor in the observed differences in outcomes between preclinical and clinical models. Last but not the least the whole source of the compound vis-à-vis the isolated active ingredient should be tested extensively and simultaneously in preclinical studies. Future studies to assess the usefulness of natural compounds should take into consideration these criteria (Fig. 2) before candidate whole extracts and or isolated compounds can be made available as cancer management tools.

5. Future directions

The rationale adopted by scientists at the US National Cancer Institute in the 1950s to identify drugs from nature was based on the premise of ‘one active compound-one disease treatment’. This approach was driven by the state of the scientific understanding of cancer cell biology at that time. Further, the concept of synergy between different components within the whole botanical to affect cancer cell functions was not recognized. A better understanding of how cancer cells are wired (Fig. 3) coupled with the knowledge of synergy between phytochemical components should be used to guide modern cancer management using agents that can robustly detonate multiple pathways simultaneously. Whether the whole natural product or the isolated compound has the upper hand in such a scenario is still unclear. In our view a distinction has to be made between cancer prevention, and treatment. Evidence for the whole (especially diet-related agents) comes from epidemiological studies. Since these are consumed in low doses they may have best outcomes as cancer prevention agents for people without cancer. Preclinical models for this strategy would be non-transformed cells and animals models that develop cancer in response to carcinogen exposure. Target populations that have reduced access to these dietary sources would benefit most from such cancer prevention strategies. The isolated compounds may be more useful for therapy for people with cancer, which includes their use as secondary cancer prevention agents and as adjuvants with standard of care. Use of cancer cells and preclinical tumor models are well suited for such studies.

Another relatively unexplored area is clinical trials with a combination of natural products or dietary supplements. In support of this, a combination of tomato powder and soy germ significantly lowered prostate cancer incidence in the TRAMP model compared to each dietary intervention alone [127]. Administration of MB-6, a mixture of fermented soybean extract, green tea extract, *Antrodia camphorata* mycelia, spirulina, grape seed extract, and curcumin extract, for 16 weeks in metastatic CRC patients caused a significant reduction in

grade 4 toxicities compared to the placebo group [128]. Similarly, diet containing a mixture of tomato and broccoli caused greater reduction in tumor volume compared to tomato and broccoli alone in the Dunning R3327-H PCA model [16]. A blend of pomegranate, green tea, broccoli and turmeric extracts given for 6 months to localized PCA patients on active surveillance or watchful waiting caused significant delay in PSA rise [129]. Many low-grade prostate cancer patients are advised to be on active surveillance to avoid over-treatment of cancer. The use of natural products that are deemed safe, and can delay progression to advance disease, would benefit these patients. Similarly, the addition of a phytoconstituent or an extract to the standard of care treatment can have advantages such as reducing dose and toxicities, and targeting drug resistance. At the same time, caution is needed since drug-drug interactions can be antagonistic, wherein a natural product could inhibit the metabolism of certain drugs leading to dose-related toxicities or act as a competitive antagonist for certain receptors. For example, EGCG was shown to cause precipitation of the tyrosine kinase inhibitor sunitinib reducing its oral bioavailability [130]. Thus, it is imperative that extensive preclinical studies evaluating drug-drug interactions be performed to prevent adverse events.

Stringent research criteria are necessary to establish the anti-cancer activity of food-based chemicals. Overall there is a dearth of high quality studies that can provide guidance regarding the anti-cancer use of the isolated compounds/parental extracts/combination of compounds. A recent review of the literature for clinical trials that investigated phytochemical intervention in biochemically recurrent prostate cancer identified 23 full-length articles of which only 2 studies that were identified as having placebo-controlled, 2 were active control studies and one was a dose-response study [131]. Using the US Food and Drug Administration model these compounds must be evaluated for anti-cancer surrogate markers (identified and validated from cell culture models) or endpoints to establish risk reduction. Proper study design that includes placebo control, measurement of compounds/metabolites in the tissue of interest, quality of statistical analyses and sufficiently powered studies are needed for conclusive evidence regarding the utility of these compounds. Mimicking these criteria in cell culture models and adhering to them in preclinical models will allow evidence-based design of clinical trials. Since varied amounts of phytochemicals are present in different fruits and vegetables it is important to consider flush out periods to ensure adherence to doses in both preclinical and clinical studies. The shift in global cancer incidence places the burden on the cancer research community to develop affordable strategies for cancer management. Stringent research efforts focused on rigorous testing and standardization can establish the utility of naturally occurring chemicals present in foods and thus make affordable cancer management strategies available to the people who will need it most in times to come.

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Natural Product	Active Phytoconstituents
Soybeans	Genistein Diadzein
Grapes	Resveratrol
Tomatoes	Lycopene
Green tea	EGCG EGC ECG
Milk thistle	Silibinin Silychristin
Broccoli sprouts	Glucoraphan Sulforaphane
Pomegranate	Punicalagin
Black raspberry	Anthocyanins Ellagic Acid Urolithin A

Fig. 1.
Source of the natural product and its known active phytoconstituent

Fig. 2.

Factors to be considered for the successful development of natural products for cancer treatment.

Fig. 3.

Cancer signaling pathways targeted by isolated compounds from natural products. Each alphabet listed under the biological endpoint represents an isolated compound (a: lycopene, b: resveratrol, c: green tea polyphenols d: genistein, e: silibinin, f: sulforaphane, g: punicalagin, h: ellagic acid) and denotes signaling pathways targeted by the compound.

Table 1

Summary of clinical trials performed with natural products.

Natural Product	Dose & Constituent	Duration & Test population	End point	Outcome	Reference
Tomatoes & Lycopene	Lycopene (8 mg)	1 year- high grade prostatic intraepithelial neoplasia (HGPIN) patients	i) Prostate cancer incidence ii) Serum PSA and lycopene levels	i) Lower Prostate cancer incidence ii) Lower serum PSA & high serum lycopene levels	[24]
	Lycopene (30 mg)	4 months- HGPIN patients	Serum PSA and lycopene levels	ii) No difference in PSA levels ii) Higher serum lycopene levels	[25]
	Tomato oleoresin extract- (Lycopene - 30 mg)	21 days prior to prostate biopsy	i) Serum and prostate lycopene levels ii) DNA oxidation and lipid peroxidation in prostate tissues	i) Increased serum and prostate lycopene levels ii) No change in DNA oxidation and lipid peroxidation	[22]
	Lycopene (15 mg)	6 months - castration resistant prostate cancer (CRPC)	Serum PSA and clinical progression	No reduction in PSA and no improvement in clinical progression	[27]
	Lycopene (10 mg)	6 months - low risk PCA patients	PSA velocity slope	Reduces PSA velocity slope	[131]
	Tomato Juice (4, 8 or 12 oz)	During radiotherapy to PCA patients	Tolerance and serum lycopene levels	Well tolerated & increases serum lycopene levels	[119]
	Tomato paste (50g)	10 weeks- Benign prostatic hyperplasia (BPH) patients	Serum PSA levels	Significant decrease in PSA levels	[26]
Grapes	500–4000 mg MPX (pulverized muscadine grape skin containing 1.2 mg ellagic acid, 9.2 mg quercetin 4.4 mg trans resveratrol)	21–30 months to biochemically recurrent PCA patients	i) Recommend Phase II dose ii) PSA Doubling Time (PSADT)	i) 4000 mg MPX was well tolerated ii) Increase in PSADT by a median 5.3 months	[41]
	1.3 g polyphenols (800 mg EGCG)	34.5 days (median) prior to radical prostatectomy	Serum PSA, VEGF, HGH and IGF-1, IGFBP-3	Significant decrease in PSA, VEGF, HGH and IGF-1, IGFBP-3 levels	[52]
	0.65 g polyphenol (400 mg EGCG)	1 year- HGPIN and atypical small acinar proliferation (ASAP) patients	PCA incidence	No significant difference in PCA occurrence	[54]
	0.6 g polyphenol (311 mg EGCG)	1 year- HGPIN patients	PCA incidence	Significant decrease in prostate cancer incidence	[55]
Green Tea polyphenols	1.3 g polyphenols (800 mg EGCG)	3–6 weeks prior to radical prostatectomy	i) Bioavailability & PSA, IGF-1, IGFBP-3 levels ii) Leucocyte oxidative DNA damage iii) Tissue biomarkers of apoptosis, cell proliferation and angiogenesis	i, ii) Low Bioavailability and serum biomarkers decreased but not statistically significant iii) No difference in tissue biomarkers	[53]
	Soy protein isolate (107mg/d Isoflavones)	6 months - high risk prostate cancer (PCA) patients	i) IHC for Androgen receptor (AR) & Estrogen Receptor- β (ER- β)	Reduced AR and no difference in ER- β & circulating hormones	[65]

Natural Product	Dose & Constituent	Duration & Test population	End point	Outcome	Reference
Milk Thistle extract & Silibinin			ii) Circulating sex hormone levels		
	80 mg purified isoflavones (genistein, daidzein, glycerin)	12 weeks - PCA patients with Gleason Score 6	i) Plasma isoflavone levels ii) Serum Sex Hormone Binding Globulin (SHBG) and Steroid Hormone Levels	i) Increase in plasma Isoflavone level ii) No significant change in serum hormone levels	[70]
	450 mg genistein rich extract	6 months - histologically proven PCA patients	i) More than 50% reduction in Prostate Specific Antigen (PSA) levels	Only 1 men out of 52 had a PSA reduction > 50 %	[66]
	2 slices of soy bread (68 mg soy isoflavone)	56 days - PCA patients with asymptomatic biochemical recurrence	Serum cytokine and immune cell phenotype	i) Reduced TH1 and MDSC-associated cytokines ii) T reg cells & monocytic MDSC decreased	[67]
	Isoflavones (51 mg)	6 weeks prior to radical prostatectomy	Serum hormone levels, total cholesterol & PSA	No significant difference	[69]
	2.5, 5, 10, 15 & 20 g of Siliphos®	4 weeks - histologically confirmed adenocarcinoma of prostate	Assess toxicity & recommend a Phase-II dose	i) 13 g total daily dose was well tolerated ii) Hyperbilirubinemia (prominent adverse effect)	[132]
Broccoli sprout & Sulfuraphane	13 g Siliphos®	14–31 days prior to prostatectomy	i) Silibinin concentration in prostate ii) Serum levels of IGF-1 and IGFBP-3	i) Low prostate accumulation ii) No differences in serum IGF-1 & IGFBP-3 levels	[76]
	200 µM of sulfuraphane-rich broccoli sprout extract	20 weeks - biochemically recurrent prostate cancer	Safety and 50 % PSA decline	Only 1 out of 20 men had 50 % PSA decline, 7 men had < 50 % decline	[89]
	60 mg stabilized free sulfuraphane	6 months - men with rising PSA post-surgery	i) Primary end point: 0.012 log (ng/mL)/month decrease in log PSA slope ii) PSADT, Mean changes in PSA level	i) Primary end point not achieved ii) Mean changes in PSA significantly lower and PSADT was 86 % greater in Sulfuraphane group	[88]
	Broccoli sprout extract - 25/100 µmol glucosinolate or 25 µmol Sulfuraphane	7 days- healthy volunteers	Mean cumulative excretion of dithiocarbamates	Excretion of dithiocarbamates was similar in both doses of glucosinolate and about 4 fold higher in sulfuraphane	[133]
Pomegranate extract	Broccoli sprout beverage- 600 µmol glucoraphanin, 40 µmol sulfuraphane	12 weeks- airborne pollutants exposed individuals	Urinary excretion of the mercapturic acids of benzene, acrolein, and crotonaldehyde	Rapid and sustained increased excretion of benzene, acrolein and no change in crotonaldehyde excretion	[87]
	1 or 3 g POMx capsules (1g ~ 8 ounces of juice)	18 months - men with rising PSA and no metastasis after local therapy	Change in PSA Doubling Time (PSADT) and safety	No adverse effect and PSADT increased by atleast 6 months at both doses	[101]
	8 ounces pomegranate juice (570 mg polyphenol gallic acid equivalents)	33 months - men with rising PSA post-surgery or radiation	Safety and PSADT	Well tolerated and significant prolongation in PSADT from 15.6 month at baseline to 54.7 months after treatment	[100]
Black raspberry (BRB) extract	2 g of 10 % w/w freeze dried BRB bioadhesive topical gel	12 weeks after initial oral intraepithelial neoplasia (OIN) biopsy	Histologic grade, clinical size and Loss of heterozygosity (LOH)	Significant reduction in lesional size, histologic grades and LOH events	[111]

Natural Product	Dose & Constituent	Duration & Test population	End point	Outcome	Reference
	2 g of 10 % w/w freeze dried BRB bioadhesive topical gel	6 weeks after initial OIN biopsy	i) Light microscopic diagnosis ii) LOH indices	i) Histological regression in subset of patients ii) Reduced LOH loci	[134]
	2 BRB suppositories (1440 mg BRB powder) & 60g BRB oral powder	9 months- Familial adenomatous polyposis (FAP) patients	Rectal polyp counts and polyp sizes	Reduced polyp burden but no significant difference in polyp number	[110]
Nexrutine®	Nexrutine® (500 mg tid)	1–2 months pre-operatively/ prior to and with radiation therapy in PCA patients	i) Toxicity using common terminology criteria for adverse events (CTCAE) ii) Serum PSA levels	Well tolerated and decline in serum PSA levels	[125]
Fish Oil	2 g Fish oil -600 mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA)	9 weeks with chemotherapy in colorectal cancer patients	i) plasma levels of inflammatory markers ii) plasma fatty acid profile and nutritional status	i) Decreased C-Reactive Protein levels ii) Increased EPA & DPA plasma proportions iii) Prevents weight loss	[135]

Table 2

List of molecular targets and their functional outcomes targeted by natural products

Natural product	Targets	Functional Endpoint	References
Tomato & Lycopene	Akt/mTOR and IGF-1	Proliferation & Survival	[15,118]
	NFκB, STAT3, IL6, COX-2, TNF-α	Inflammation	[14]
	Nrf2	Oxidative stress	[15]
	CYP2E1, Androgen Metabolism	Metabolism	[17]
Grapes & Resveratrol	SIRT1, AMPK	Metabolism & Oxidative Stress	[7,39]
	mTORC1	Proliferation & Survival	[7,32]
	Metastasis associated protein 1, TGFβ-1/Smads	Metastasis	[38,40]
	Nrf2, NQO1	Oxidative stress and Inflammation	[37]
	Cyclin B1, A and E, Cdc2	Cell Cycle	[28,29]
	LC3-II	Autophagy	[7]
Green Tea & EGCG	PI3K/Akt, ERK, HGF, IGF-1	Proliferation & Survival	[47,52,53,114]
	VEGF	Angiogenesis	[50,52]
	TNF-α	Inflammation	[115]
	Copper transporter 1	Oxidative Stress	[48,49]
Soybeans & Genistein	AR, ER	Hormonal Regulation	[65,71]
	TH1 and MDSC-associated cytokines	Immunomodulatory	[67]
	Akt, GSK-3β	Proliferation & Survival	[57,58]
	Osteopontin	Metastasis	[58]
	Cyclin D1	Cell Cycle	[57,71]
Milk Thistle extract & Silibinin	IGFB-3, IGF, Akt	Proliferation & Survival	[74,76,77]
	STAT3, IκBα, COX-2	Inflammation	[138]
	CyclinD1	Cell Cycle	[137]
	SIRT1	Metabolism & Oxidative Stress	[72]
	p53 acetylation	DNA Repair	[72]
	Snail, ZEB, N-cadherin	Metastasis	[73]
Broccoli Sprout & Sulforaphane	Quinone reductase and glutathione transferase	Detoxification/Metabolism	[78]
	Wnt/β-catenin pathway, ALDH-positive cells	Cancer stem cells/Differentiation	[82]
	TRAIL, Caspase	Apoptosis	[79,80]
	PI3K/Akt, MEK/ERK	Proliferation & Survival	[79,80,81]
	NFκB, TGF-β	Inflammation, Metastasis	[80]
	VEGF	Angiogenesis	[80]
	Matrix metalloproteinases	Metastasis	[80,81]
	NQO1, HO-1	Oxidative stress and Inflammation	[83]
	Increased Natural Killer Cell Lytic activity	Immunomodulatory	[81]
	Increased Infiltration of T cells	Immunomodulatory	[81]
	EGF, IGF	Proliferation & Survival	[90]
Pomegranate	NFκB, COX-2, i-NOS	Inflammation	[97]

Natural product	Targets	Functional Endpoint	References
	Cyclin D1, E, p27, p21, Cdk4,6	Cell Cycle	[98]
	Bax, Bcl-2	Apoptosis	[98]
	IGF-I/Akt/mTOR	Proliferation & Survival	[99]
	VEGF	Angiogenesis	[93,94,95]
	Matrix metalloproteinases	Metastasis	[93,94]
Black raspberry	NFκB, COX-2, iNOS	Inflammation	[104,105]
	PI3K/Akt, AP-1	Proliferation & Survival	[105]
	VEGF, CD 105	Angiogenesis	[136]
	Pentraxin-3 (PTX3), Neutrophil activation	Immunomodulatory	[105]
	ER-α	Hormonal Regulation	[106,107]
	CYP1B1, CYP1A1	Metabolism	[106,107]
	CD3(+) foxp3(+) regulatory T-cells	Immunomodulatory	[108]