Green Cancer Prevention and Beyond

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ABSTRACT

The concept of green chemoprevention was introduced in 2012 by Drs. Jed Fahey and Thomas Kensler as whole-plant foods and/or extract-based interventions demonstrating cancer prevention activity. Refining concepts and research demonstrating proof-of-principle approaches are highlighted within this review. Early approaches included extensively investigated whole foods, including broccoli sprouts and black raspberries showing dose–responsive effects across a range of activities in both animals and humans with minimal or no apparent toxicity. A recent randomized crossover trial evaluating the detoxification of tobacco carcinogens by a broccoli seed and sprout extract in the high-risk cohort of current smokers highlights the use of a dietary supplement as a potential next-generation green chemoprevention or green cancer prevention approach. Challenges are addressed, including the selection of dose, duration and mode of delivery, choice of control group, and standardization of the plant food or extract. Identification and characterization of molecular targets and careful selection of high-risk cohorts for study are additional important considerations when designing studies. Goals for precision green cancer prevention include acquiring robust evidence from carefully controlled human studies linking plant foods, extracts, and compounds to modulation of targets for cancer risk reduction in individual cancer types.

Introduction

Since antiquity, plant-based food components have held great interest for their possible health-promoting and disease-preventing properties (1). Diets rich in plant-based products are associated with less environmental impact and a lower risk of chronic diseases (2). It is recognized that the term "green chemoprevention" implies a myriad of responses such as environmentally friendly, renewable, natural, safe, and healthy. A recent summary of the clinical trial and observational evidence concerning the association between plant-based diets and cancer risk reported an inverse association between diets and overall cancer risk (3). In their analysis of research on how consuming whole grains, vegetables, and fruits affects the risk of developing cancer, the expert panel for the Continuous Update Project Expert Report of the World Cancer Research Fund/American Institute for Cancer Research reported that much of the evidence for the consumption of fruits, vegetables, and whole grains and cancer risk was found to be limited (4). They did find, however, probable evidence that consuming whole grains or an intake of foods containing dietary fiber decreases the risk of colorectal cancer, and greater consumption of non-starchy vegetables or fruit probably protects against aerodigestive cancers (4).

The incorporation of whole grains, vegetables, and fruits in one's diet results in the potential bioavailability of thousands of bioactive phytochemicals. Many of these phytochemicals have been shown in preclinical studies to have cancer-preventive properties (5). These properties include stimulating the immune system, detoxifying carcinogens, reducing inflammation, preventing DNA damage, and enhancing DNA repair, reducing oxidative damage to cells, slowing cancer cell proliferation, inducing apoptosis and cell death, and helping to regulate hormonal pathways (5). In addition, phytochemicals from whole grains, vegetables, and fruits are thought to have none or few adverse effects at minimal levels typically consumed that also is a condition to be met for cancer prevention. Findings also suggest that some gene–nutrient interactions can modify detoxification enzymatic capacities (e.g., glutathione S transferase Mu1 or GSTM1 and glutathione S transferase theta 1 or GSTT1) to potentially alter phytochemical levels needed to reduce some cancer risks (6). Microbiome composition may alter levels of phytochemicals. One example is for Urolithin A, a colonic microbial metabolite, studied for its cancer prevention activity, is also produced by gut microflora from foods rich in ellagitannins [e.g., black raspberries (BRB), pomegranate, walnuts] and varies with gut microbiome composition (7, 8) (**Fig. 1**). Processing of foods, including plant foods, is another important consideration linking diet (e.g., ultra-processed plant foods) to disease. Compared with minimally or unprocessed plant foods, ultra-processed foods may have diminished levels of phytochemicals in addition to advanced glycation end products that are associated with increased chronic disease

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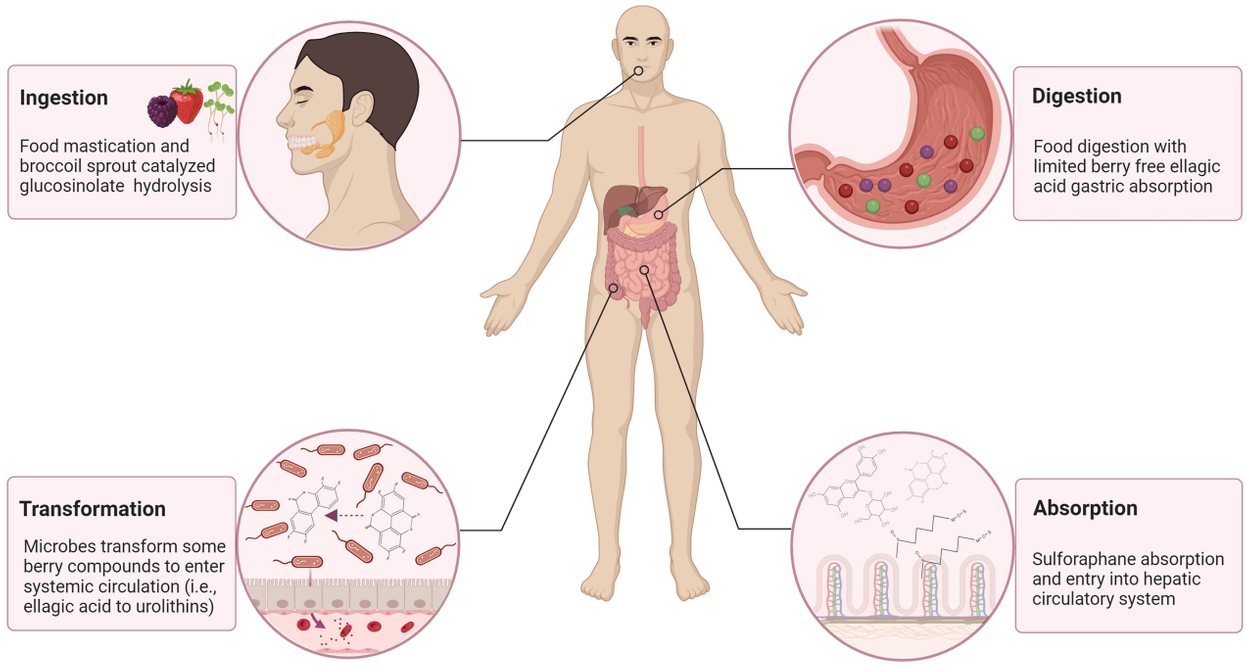

Figure 1.
Bioprocessing of select green cancer prevention food components. Created with BioRender.com. Legend, Human bioprocessing of select bioactive components in green cancer prevention. Ingestion, Food mastication reduces berries and broccoli sprouts to smaller food particles. Mastication of broccoli sprout cell walls releases its myrosinase catalyzing glucosinolate hydrolysis for sulforaphane release. Digestion, Masticated berry food particles release small amounts of free ellagic acid for limited gastric absorption. More complex berry ellagitannins are also released and undergo further digestion to ellagic acid. Masticated broccoli sprouts food particles enter the gastric compartment for continued sulforaphane processing and release. Gastric enzymes mix with both berry and broccoli sprout food particles forming chyme entering the small intestine. Absorption, Digested berry-derived food particles undergo limited absorption in the small intestine and move into the large intestine for further microbial bioprocessing. Sulforaphane, a major broccoli sprout glucosinolate, is primarily absorbed in the small intestine entering hepatic circulation for systemic distribution. Transformation, Berry-derived ellagic acid enters the large colon where resident microbiota metabolizes ellagic acid to urolithins for colonocyte absorption and transport into the systemic circulation. Little, if any, sulforaphane enters the colonic lumen as it was largely absorbed in the small intestine.

risk (9). Furthermore, a recent cross-sectional study found that higher consumption of fresh/minimally processed foods is accompanied by a higher intake of total polyphenols, whereas higher consumption of ultra-processed foods resulted in a lower intake of total polyphenols, suggesting consumption of plant foods, vegetables, and fruits are to be encouraged (10).

Because bioactive constituents are found in relatively low concentrations in bulk plant foods, a variety of efforts have been made to create concentrated extracts as dietary supplements. For some bioactive constituents, mechanistic studies of purified or synthetic derivative compounds revealed a range of underlying cancer-protective activities (11). Notable mechanisms included: "interceptor molecules" such as chlorophylls that can bind polycyclic aromatic carcinogens and prevent their activity (12); epigenetic modulators such as sulforaphane from broccoli and spinach (13); and homeostasis of cellular redox through regulation of nuclear transcription factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (KEAP1) by dietary flavones and other phytochemicals (14, 15).

Moreover, there are numerous other food-derived compounds that elicit cancer-protective effects, including resveratrol from grapes, betanins from beets, and diallyl sulfide from garlic and onions (16–18).

In contrast with interventions using isolated phytochemicals, micronutrients, or herbal pharmaceuticals for cancer prevention, another strategy is green chemoprevention or green cancer prevention, which was first described in 2012 as a food-centered approach to cancer prevention (19, 20). Green chemoprevention was defined as interventions based on whole-plant foods or their extracts that demonstrate cancer prevention activity (20). Although an isolated phytochemical may determine a plant food's effect in preclinical studies, it is likely that multiple compounds—micronutrients and phytochemicals—work together as a complex mixture to provide anti-carcinogenic effects in humans (21). In this regard, studies involving the administration of more than one plant food compound with different activities, for example, an inducer of phase II detoxification enzymes in conjunction with a strong anti-proliferative agent, might be one strategy for green cancer prevention. Furthermore, the matrix of the plant food (or extract) may also influence pharmacokinetics through effects on absorption, distribution, metabolism, and excretion (22), perhaps influencing biological activity *in vivo*.

The appeal for green cancer prevention is that well-tolerated, affordable, easily implemented plant food-based interventions have potential application in both poor and rich countries. In this article, we highlight preclinical and clinical studies examining plant foods, extracts, or phytochemicals in high-risk individuals for a specific duration and putative physiological response, including genetic response modifiers for cancer risk reduction and prevention. Going beyond original reports, we analyze recent examples of green cancer prevention and suggest future approaches for advancing this research.

Plant-Based Food Approach and Challenges

The utility of some plant-based extracts and isolated constituents of plant foods as green cancer prevention approaches are discussed below. Illustrative examples of green cancer prevention are also described in **Table 1**, including studies examining berries and berry preparations, extracts from broccoli seed and sprouts and green tea, as well as isolated compounds such as curcumin.

Table 1. Green cancer prevention research examining selected plant food or plant food extracts examined in this review.

Food/Extract	Active Ingredient/ Metabolite	Cohort/Population/ Model	Study Design	Study End Point	Outcome of the Study	Reference
BSSE[a]	Sulforaphane	Healthy smokers	Randomized, crossover trial	Detoxification of benzene, acrolein, and croton-aldehyde	BSSE significantly upregulated detoxification of benzene, acrolein, and crotonaldehyde	(46)
Polyphenon E (Green Tea Polyphenol extract)	EGCG[b]	Subjects had colorectal advanced adenomas and >5 rectal ACF[c]	Randomized trial	Rectal ACF at chromo-endoscopy	Polyphenon E for 6 months did not significantly reduce rectal ACF number	(54)
PFE[d]	Urolithin A	Men with favorable risk PCa[e]	Randomized placebo control phase II trial	8-OHdG[f] and androgen receptor expression	Reductions from baseline in 8-OHdG and androgen receptor expression in prostate tumor, no change in IGF1[g] axis	(90)
Tomatoes, red carrots, watermelon, grapefruit, papaya	Lycopene	Men with localized PCa	Phase II controlled, randomized	Serum PSA[h], free testosterone, total estradiol, Ki67[i]	No significant changes as compared with controls	(70)
Strawberry (lyophilized)	Anthocyanins, ellagic acid	Adult patients with esophageal dysplastic lesions in a high-risk area in China	Randomized (non-comparative) phase II trial	Changes in histologic grade of esophageal dysplastic lesions	Decrease in histologic grade of esophageal dysplastic lesions	(23)
Blackberry (lyophilized)	Dimethylellagic acid glucuronide, urolithin A-glucuronide, urolithin A-sulfate	Patients Barrett's esophagus	Phase I pilot study (6 month)	Urinary excretion of 8-PGF2α[j] and 8-OHdG	Mean urinary levels of 8-PGF2α were significantly reduced at 26 weeks; 8-OHdG no significant change from baseline	(28)
Turmeric	Curcumin	Adult patients with familial adenomatous polyposis with 5 or more adenomas	Phase II	Mean number and size of polyps	No significant difference in polyp size or number with placebo control	(59)

[a]Broccoli seed and sprout extract (BSSE).
[b]Epigallocatechin gallate (EGCG).
[c]Aberrant crypt foci (ACF).
[d]Pomegranate fruit extract (PFE).
[e]Prostate cancer (PCa).
[f]8-hydroxy-2′-deoxyguanosine (8-OHdG).
[g]Insulin-like growth factor 1 (IGF1).
[h]Prostate-specific antigen (PSA).
[i]Ki-67 proliferation marker (Ki67).
[j]8-epi-prostaglandin F2α (8-PGF2α).

Berries

An early example is lyophilized (freeze-dried) strawberry preparations, which provided a concentrated phytochemical preparation and permitted easier handling, dosing, shelf-life, and product uniformity for use in studies (20). Following preclinical observations testing freeze-dried strawberries, Chen and colleagues (23), conducted a randomized Phase II trial in China to investigate the effects of two doses of freeze-dried strawberries in patients with esophageal dysplastic lesions in a high-risk area for esophageal cancer. They reported that the higher dose of dietary strawberries (freeze-dried, 60 g/d for 6 months) significantly decreased the histologic grade of patients' precancerous esophageal lesions, with 80.6% of the participants consuming 60 g of strawberry powder daily experiencing a decrease in histologic grade of the precancerous lesions ($P < 0.0001$) (23). Moreover, fewer numbers of participating patients presented with mild dysplasia at baseline compared with six months after consuming 60 g of strawberry powder daily, reducing incidence from 31 (86.1%) to 5 (13.9%), respectively. These changes in the histologic grade were associated with the downregulation of genes involved in the inflammatory response, cell proliferation, and gene transcription, including *COX-2,* inducible NO synthase (*iNOS)*, *NFkB*, and *mTOR*; however, the report suggested that the mechanism of this beneficial effect required further study. Both iNOS and COX-2 enzymes have been shown to be upregulated in rat esophageal tumorigenesis in studies from this laboratory (24, 25).

Strawberries, as well as other edible berries, continue to be studied for their cancer prevention properties in preclinical and clinical settings (26, 27) (**Fig. 1**). Anthocyanins and ellagic acid are among the active cancer prevention constituents in berries (26, 28–30) and several anticancer activities have been described for both, including anti-inflammatory effects, inhibition of oxidative stress, and beneficial impacts on metabolism (31, 32). BRBs are of interest because they are particularly high in anthocyanin content (i.e., cyanidin-3-rutinoside, cyanidin-3-xylosylrutinoside, and cyanidin-3-glucoside) (26, 33). Several studies have been conducted with either lyophilized BRB or BRB extracts to test their activity in oral, esophageal, and colorectal cancer prevention (26, 27). Lyophilized BRB has been found to inhibit chemically induced esophageal, colorectal, and oral carcinogenesis, with reduced oxidative stress, altered cytokine expression and innate immune cell trafficking, decreased DNA damage, and inhibition of cellular proliferation rates among the activities observed in these studies (34–37). The most definitive evidence for anthocyanins as inhibitors of cancer *in vivo* was observed in nitrosamine-induced tumors in the rat esophagus (38). The authors found that an anthocyanin-enriched extract of BRB was nearly as effective in reducing esophageal tumors as whole BRB powder containing the same level of anthocyanins. In addition, the "residue" (fiber) fraction of the extract was almost as effective as the anthocyanins suggesting that fiber is also important and, unlike the anthocyanins, the fiber fraction in different batches of BRB powder is quite constant (about 40%–50% of the dry weight of BRB). These results suggest that when investigating the cancer-preventive effects of plants and their extracts, the fiber fraction should be taken into consideration. Furthermore, a phase I clinical trial was conducted to evaluate the toxicity and uptake of anthocyanins and ellagic acid in humans following the consumption of BRB powder (39). The BRB powder was well tolerated, but the uptake of anthocyanins into blood was less than 1% of the administered dose and the uptake of ellagic acid was even less. These observations support the concept that localized absorption of these compounds into tissues of the oral cavity, esophagus, and colon is likely important for cancer prevention activity. These findings supported further study of berries in high-risk cohorts, including patients with Barrett's esophagus, a premalignant esophageal condition. A single-arm pilot trial in 20 patients with Barrett's esophagus was conducted to examine the effect of lyophilized BRB (45 g daily for males/32 g daily for females) on urinary metabolites and markers of lipid peroxidation, DNA damage, and tissue markers of cellular proliferation, detoxification, and inflammation (28). After 6 months of lyophilized BRB consumption mean urinary excretion of the lipid peroxidation marker 8-epi-prostaglandin F2α was reduced from a total of 1.6×10^{-10} at baseline to 1.4×10^{-10} at week 12 and 1.3×10^{-10} at week 26 ($P = 0.044$). Urinary levels of the BRB metabolites (i.e., urolithin A-glucuronide, urolithin A-sulfate) were increased following 12 and 26 weeks of lyophilized BRB consumption, suggesting adherence to the intervention. Because these are microbially produced metabolites, some variability may be due to individual differences in the microbiome (**Fig. 1**). The authors also reported that immunohistochemical staining of Barrett's esophagus biopsy tissue showed significant increases in glutathione S-transferase Pi (GST-Pi) levels, a marker of detoxification, following lyophilized BRB consumption. Lyophilized BRB treatment, however, did not significantly alter the Ki67 proliferation labeling index. This study reported changes in some biomarkers, but not all that were evaluated, following lyophilized BRB consumption and authors stated that BRB may need to be formulated differently, administered at higher concentrations, or multiple times a day to increase efficacy (28). *GST-Pi* (*GSTP1*) SNPs could decrease cell detoxification capacity thereby altering cancer risk (40). As stated above, complex interactions between individuals and the natural milieu of a plant-based diet may be a critical factor for biomarker modulation and resultant beneficial effects.

In this regard, one pilot study administering BRB to target colon cancer reported significant decreases in tissue Ki67 proliferation marker staining with BRB consumption 3 times daily (60 g total) for 1–9 weeks in patients with colon cancer (41). In another study evaluating two BRB rectal suppositories (each containing 720-mg BRB powder) administered daily at bedtime to familial adenomatous polyposis (FAP) patients, allowing for relatively direct delivery, there was a suggestion that the BRB rectal suppository decreased Ki67 and regressed rectal polyps in those that showed biomarker

response, but not in all patients (42). These results support that a higher cumulative dose, a longer duration of BRB treatment, or more direct tissue exposure may be required for a response in tissue markers compared with circulating markers.

The inconsistent outcomes from these investigations may be linked to differences in the mode, concentration, and frequency of BRB delivery as well as the duration of the intervention. As for mode, BRBs have been administered as a slurry of freeze-dried powder suspended in water, as rectal suppositories, as topical agents delivered in a bio-adhesive gel, or as dissolvable slow-release BRB troches (26). Research targeting sites that permit direct delivery, such as the oral cavity, appear to have the advantage of requiring less product, increasing direct contact time with the lesion, and taking advantage of local metabolism. In fact, a current BRB clinical trial is ongoing (NCT04372914) to study the effect of BRB lozenges on tobacco-induced DNA damage in the buccal cells of smokers. Furthermore, there are factors that influence the efficacy of a plant extract that may not be predictable, such as variation in host tissue metabolism of the phytochemical. An example concerns a Phase II trial testing the topical treatment of oral leukoplakic lesions with a 10% BRB gel. Differences in the regressive effects of the gel on lesions in different patients were reported (43). These differing results may have been due to varying levels of enzymes involved in the intraoral metabolism and bioactivation of BRB anthocyanins as they previously reported (44). Although the optimum dose, duration, and mode of berry delivery for cancer inhibition remains to be clarified, results to date suggest higher concentrations and longer durations of exposure may be required for tissue-specific effects (28). The prevention effects of BRB are not likely due to a single BRB compound but collectively from anthocyanins, ellagic acid, flavonoids, fiber, other antioxidants, phytochemicals, and BRB metabolites that may individually influence specific cellular processes or work together to modulate signaling pathways for tumor inhibition. This suggests that one needs a formulation or a delivery system that mimics the plant-based food product in its natural state. The role of precision nutrition in these discrepancies should also be considered as it can significantly influence study outcomes.

Cruciferous

Another example of green chemoprevention is for broccoli sprout beverages, enriched for either sulforaphane or glucoraphanin (GR), which were evaluated for detoxification activity in a population of healthy volunteers from Qidong, China exposed to high airborne pollutants using a crossover clinical trial design (45). The broccoli sprout beverages were prepared using lyophilized broccoli sprout powders rich in either GR or sulforaphane that were rehydrated in diluted mango juice just before dosing. Both beverages produced significant and sustained detoxification of air pollutants as measured by urinary excretion of glutathione-derived conjugates of acrolein, crotonaldehyde, and benzene, suggesting the ability to reduce cancer risk (45).

One recent study evaluated consuming a broccoli seed and sprouts extract (BSSE), enriched in GR and myrosinase, for risk reduction of tobacco-related head and neck squamous cell carcinoma (46). In this open-label, randomized, crossover design participants were treated for 2 weeks with both low (148 μmol GR) and higher-dose (296 μmol GR) BSSE Avmacol separated by a 2-week washout. The primary endpoint was the detoxification of benzene, as measured by a change in urinary excretion of the mercapturic acid of benzene, S-phenyl mercapturic acid (SPMA). Secondary objectives included evaluating additional urinary carcinogen metabolites, bioavailability of the BSSE Avmacol as measured by urinary sulforaphane metabolites, buccal expression of Nrf2 target genes, as well as dose–response and toxicity evaluation comparing the low and higher-dose BSSE.

Avmacol significantly increased urinary excretion of SPMA suggesting enhanced detoxification of the tobacco carcinogen benzene, as well as increased detoxification of acrolein and crotonaldehyde, in otherwise healthy smokers when administered at the higher dose over a 2-week exposure period. It is unclear if this enhanced detoxification of environmental pollutants or tobacco carcinogen by BSSE is clinically significant. The authors reported low toxicity and high compliance suggesting the possibility of a tolerable, long-term chemoprevention strategy against environmental carcinogenesis. A multicenter, randomized, placebo-controlled trial evaluating benzene and acrolein detoxification by higher-dose BSSE over 12 weeks is now planned in healthy, heavy tobacco smokers (NCT05121051). Using multiple centers should assist in attaining the racial and ethnic diversity of North America for a more representative and generalizable result.

The Avmacol study highlights the use of a commercially available dietary supplement as a next-generation green cancer prevention approach. In contrast with some of the challenges of green cancer prevention using plant foods, which includes standardization of the bioactive constituent in the plant food, dietary supplements can be manufactured with predictable concentrations of bioactive constituents, acceptable bioavailability, and produced in accordance with good manufacturing practice standards with a long shelf life at ambient temperature.

An important question in green cancer prevention is whether an efficacious dose of protective phytochemicals can be achieved by normal dietary intake. For the example here, the GR content of broccoli is highly variable due to genotype as well as field location, year, drought conditions, disease pressure, and other environmental conditions (47). Furthermore, the whole plant may contain additional bioactive compounds that may modify effectiveness. Clinical studies to understand factors influencing variation in response to consumption of plant foods are appropriate avenues of investigation. The authors estimate that roughly 28 ounces of market-stage broccoli would contain a similar GR content as the higher-dose Avmacol used in this study (46). Broccoli sprouts, however, contain 10–100 times the level of GR as mature plants and are a rich

source of myrosinase activity (48). Thus, the consumption of broccoli sprouts over broccoli seems more practical for the green cancer prevention approach.

Tea polyphenol

Although the epidemiological evidence for green tea beverage consumption and cancer is generally inconsistent, green tea polyphenols have shown cancer prevention activity in animal models of various tumor sites (49, 50). The major and most biologically active tea polyphenol is epigallocatechin-3-gallate (EGCG) that has demonstrated activity in several cancer processes and signaling pathways (51). Polyphenon E is a preparation with a defined polyphenol content, containing EGCG (55%–77%) and other catechins (∼25%) with minimal amounts of caffeine and theobromide and gallic acid (52, 53) that has been formulated for experimental studies. For example, a phase I trial supported by the Division of Cancer Prevention (DCP; NCT03278925) to examine the side effects and best dose of a defined green tea catechin extract for preventing liver cancer in participants with cirrhosis is currently ongoing.

A randomized phase II trial of Polyphenon E versus placebo in individuals at high-risk for colon cancer was recently reported (54). Participants ($N = 39$) with prior colorectal advanced adenomas or cancers and who had ≥5 rectal aberrant crypt foci (ACF) measured by chromoendoscopy at baseline were enrolled for the study. Subjects were randomized to receive either Polyphenon E (two 300-mg capsules twice daily containing 65% EGCG, 25% other catechins, and less than 0.6% caffeine) or matched placebo for 6 months. The primary outcome measure was chromoendoscopy with quantification of rectal ACFs, a potential surrogate endpoint biomarker of colorectal cancer. Eighty-two percent of subjects who participated in this study completed six months of Polyphenon E ($N = 15$) or placebo ($N = 17$) treatment. Among these participants, the change in percentage rectal ACF did not significantly differ between arms, and secondary outcomes of total burden and adenoma recurrence ratio were similar in both arms. The results suggest that Polyphenon E is well tolerated but not effective in reducing rectal ACF within a 6-month period.

Limitations of the study include the short duration and small sample size due to the pending expiration of Polyphenon E capsules (54). In addition, a modified intent-to-treat analysis, including only those participants with baseline and 6-month ACF data rather than the entire study population, was reported. The choice of dose and tea polyphenol composition as well as the primary endpoint, which has not been validated as a surrogate biomarker for rectal cancer, are features that may have influenced the study outcomes.

Future studies of Polyphenon E/tea polyphenols may benefit from using a biomarker to monitor exposure. The utility of long-term treatment with a concentrated form of green tea polyphenols is an issue as exposure must be carefully monitored for adverse effects by monitoring liver transaminase activity over time. In fact, the benefit of long duration of exposure to certain plant food extracts or single and combination plant food constituents needs to be carefully weighed against any risks.

Curcumin

Curcumin is chemically classified as a polyphenol and is isolated from the rhizomes of *Curcuma longa L.* (known as turmeric). Curcumin has shown potential therapeutic and chemopreventive benefits in preclinical studies against several cancers mostly due to its antioxidant and anti-inflammatory effects (55). Despite the promising anticancer potential of curcumin, its clinical application is limited due to poor aqueous solubility and low bioavailability because of high hepatic metabolism (56–58). A double-blind randomized clinical trial (RCT; NCT00641147) using 3 g/d of pure curcumin orally for 12 months in patients with familial adenomatous polyposis did not result in any significant regression of polyp number or sizes compared with the placebo group (59). In clinical trials of curcumin as a potential anticancer agent, plasma curcumin levels remain low even after administration of more than 8 g of curcumin a day (60). Poor bioavailability of orally administered pure curcumin in this and other similar trials appears to be a major reason for the lack of efficacy.

To increase concentrations of curcumin in serum different strategies have been tested, including innovative drug delivery systems (nanoparticle, liposome, and phytosome), the use of different chemical analogs of curcumin, and curcumin combined with other natural compounds like piperine, quercetin or silibinin (57, 61–66). Different innovative drug delivery systems either shield curcumin from metabolizing enzymes or increase solubility, thereby increasing bioavailability. Natural curcuminoids formulated with phospholipids (i.e., Meriva) increased bioavailability by improving the hydrolytic stability of curcuminoids and increasing intestinal absorption compared with uncomplexed curcuminoids (67). Currently, one phase IIb RCT is underway using a phospholipid formulation of curcumin (Meriva) to test the efficacy of curcumin in preventing gastric cancer in patients with chronic atrophic gastritis and/or gastric intestinal metaplasia (NCT02782949). In this RCT, patients either receive curcumin (Meriva) or placebo orally twice daily for 180 days in the absence of unacceptable toxicity and after completion of study treatment patients are followed up at 30 days and 7 months. Patients are evaluated for the changes in gastric mucosal IL1ß, IL8, TNF-alpha, and inducible protein 10 as well as gastric mucosal DNA damage and Histology Gastric Score from baseline to 6 months for placebo versus Meriva. Structural analogs of curcumin have also been generated to slow down its metabolism and increase anticancer efficacy and potency (65). Research on enhancing the bioavailability of curcumin (68) has had variable success, but more recent evidence suggests third-generation curcumin formulations, including curcumin galactomannan formulation or CurQfen (noncovalent complex

between curcumin and fenugreek galactomannans), curcuRouge (Starch and curcumin formulation), Curcuwin Ultra (cellulosic derivatives and curcumin formulation), and Longvida (soy lecithin and curcumin formulation) may be worthy of continued study (69).

Other considerations in green cancer prevention

Tomato products and the putative active constituent in tomatoes, lycopene, have also been examined for cancer prevention activity in clinical trials, including in men with recurring prostate cancer and in women at a high risk for breast cancer (20, 70). For many of these studies, a standardized preparation of tomatoes has not been delivered, but rather participants are instructed to consume a minimum quantity of tomato products per day. In such studies, the amount of plant food products and active constituents are determined post facto (20). Additional considerations for green cancer prevention include choice of placebo/control/comparison group and standardization of the plant food for study. For example, the concentration of a bioactive compound in the plant food (i.e., BRB) is likely dependent on many issues, including the cultivar, growing conditions (e.g., amount and quality of sunlight, soil composition, salinity, and temperature among other things) and season that leads to batch-to-batch variability (71). Other factors include determining the dose and duration of exposure to the plant food or extract, the regulatory context of the plant-based product, and the production and standardization of the plant-based product for a larger, individual trial, as well as for dissemination and implementation research efforts (20). In addition, participant compliance is likely a rate-limiting step for the success of a green cancer prevention strategy, so it is important that the approach be easy to follow and adhere to. Results from clinical trials/interventions using whole-plant products are often inconsistent. Studies show that some participants respond, but others do not, perhaps reflecting the heterogeneity between subjects as well as the complexity of each cancer or precursor lesion (26). Biological aspects that may explain inconsistent results include tumor heterogeneity, differences in molecular signaling and enzyme activity within tumors, and variations in individuals' microbiota, metabolism, and epigenetic status.

It should also be noted that food preparations and extracts of fruits or vegetables should be evaluated for microbial, fungal, and other pathogenic contamination. Furthermore, the evaluation of chemicals, including herbicides, pesticides, and fungicides that may be present in these plant foods, extracts, and phytochemicals should also be assessed as a food safety measure (72).

It is thought that the benefit of a plant-food approach to cancer prevention is that a complex mixture of bioactive components is simultaneously targeting multiple processes in carcinogenesis. Further research is warranted to test this possibility to increase our knowledge of the cancer inhibitory mechanisms of plant foods and to improve our understanding of which subgroup populations are most likely to benefit.

Physiologically driven human factors

Recently, the National Institutes of Health announced interest in a precision nutrition initiative to better understand this complex and dynamic interplay across foods, human microbiome, metabolism, food environment, and physical activity, as well as economic, social, and other behavioral characteristics across individuals and subgroup populations (73). Increasing evidence suggests that genetic factors (e.g., SNPs, genetic variants, altered DNA repair gene(s), copy number) can underpin some human responses to foods (responders vs. non-responders), and their extracts influencing health and disease risks, including cancer. Understanding these complex interrelationships may be particularly useful for distinguishing not only genetically based physiologic nutrient requirements, but also assessing response ability, especially in higher-risk individuals and populations. Individual and subpopulation genetic differences can modify particular physiological processes altering nutrient requirements and levels of phytochemicals required to reduce some cancer risks [e.g., 30% reduction in 5,10-methylenetetrahydrofolate reductase enzymatic function in heterogenous CT individuals, while reducing function by 60% in homozygous TT carriers (74) increasing nutrient requirements as well as risk for disease; refs. 75, 76]. Similar perturbations are known for peroxisome proliferator-activated receptor-γ2 gene Pro12Ala allele polymorphism (*PPARG2* Pro12Ala) that reduces cancer risk when minor allele carriers consume high levels of dietary carotenoids (77). However, pilot subgroup population risk stratification studies are more challenging when a genetic variation is not identified differentiating potential responding from non-responding human participants. For those in average-risk populations, green cancer prevention studies may require very large sample sizes to detect the levels of effect expected with a nutritional intervention. Additional stratification factors might also include existing or histories of premalignancies or malignant cancers, occupational or environmental carcinogen exposures, or of immunosuppression. Such interventions are multi-targeted due to a complex combination of bioactive food components and likely affect multiple pathways and genetic targets, especially if isolated phytochemicals or plant extracts are being investigated. Furthermore, plant foods provide a dietary role due to their nutrient profile and activity in the maintenance of optimum health through long-term consumption, whereas short- or long-term administration of plant extracts or isolated phytochemicals for green cancer prevention are intended to exert preventive and sometimes pharmacological properties without necessarily serving a nutritional purpose.

Green Cancer Prevention: Opportunities Going Forward

Although the concept of green chemoprevention in cancer prevention is appealing and has universal applicability, green chemoprevention trials are challenging, given the various hurdles discussed in previous sections. It is time to move

beyond traditional chemoprevention by applying strategies that would be more appropriate to the specific populations at the highest risk of developing cancer and to establish cancer prevention and interception as a global priority. Certain plant foods and extracts that offer benefits beyond their nutritional values may be among the first lines of defense against cancer for prevention and interception. The development of cancer interception strategies may be feasible using appropriate foods/extracts. Approaches like precision green cancer prevention strategies for high-risk cohorts such as individuals with predisposed hereditary syndromes (Lynch syndrome, FAP; breast cancer gene 1, *BRCA1;* breast cancer gene 2, *BRCA2;* and *BRCA1/2* mutation carriers), diagnosed premalignancy (ductal carcinoma in situ, colonic polyps, oral leukoplakia, and Barret's esophagus), metabolic risk (diabetes, obesity), and environmentally or occupationally exposed individuals (smokers, asbestos workers) may be explored as precision prevention. A detailed approach to the baseline assessment of nutritional status and susceptibilities with consideration of the above factors, will likely increase efficacy of green cancer prevention interventions. Precision nutrition may also shed light on how differences in human microbiome impact alone or in partnership with individual genetics influence cancer prevention strategies across high-risk subpopulations.

Future efforts to develop biomarkers of nutritional status are needed to identify and target subpopulations with unique genetically based requirements. The current lack of reliable biomarkers and a clear understanding of the outcome makes this undertaking challenging. Yet, artificial intelligence (AI) and its sub-branch machine learning (ML) may offer critical advancements needed to enhance predictive developmental models suitable for precision nutrition and perhaps for green cancer prevention. Machine learning advances (e.g., algorithms, tools, and techniques) when applied to precision nutrition can stimulate a diverse array of advancements in nutrition research and clinical nutrition (78). Incorporating advanced ML approaches enabled clinical researchers to identify dietary-genetic variant interactions predictive of increased colorectal cancer while also providing risk reduction dietary and therapeutic strategies for colorectal cancer (78, 79). Newer ML approaches and other strategies should also be explored (e.g., forward, and reverse translation studies with robust and relevant preclinical models, molecular chemoprevention studies for biomarker discovery, omics technologies, and precision medicine) to examine plant foods and their extracts for green cancer prevention and cancer interception efficacy going forward.

In addition, it may be advantageous to conduct more abbreviated clinical trials (e.g., Phase 1b) with a plant food, extract, or phytochemical before embarking on the more expensive Phase II trials. This would provide information as to whether the test product/agent is likely to have positive effects in larger trials. Moreover, in some cohorts such as patients with FAP and even oral leukoplakia, it may be difficult to accrue enough subjects for an expanded Phase II trial. One example of the precision green cancer prevention approach is the recent randomized crossover trial evaluating the detoxification of tobacco carcinogens such as benzene, acrolein, and crotonaldehyde by broccoli seed and sprout extract in the high-risk cohort of current smokers (46). However, systematic studies are needed to overcome certain challenges such as the variation in responses (responders vs. non-responders), and the development of safer, more convenient, and affordable agents for administration over long periods. Applying multi-dimensional precision medicine approaches to green cancer prevention may overcome some of the stated challenges.

Integrated nutritional/dietary studies using preclinical animal models, for example, could focus on the complex interrelation between the microbiome, obesity, and cancer with respect to aging for precision nutrition approaches. Such follow-up clinical with supportive preclinical studies will help better understand the interplay between diet–obesity–microbiome. Importantly, well-defined biomarkers of predictive clinical efficacy need to be developed using preclinical systems that would be applicable to determine the effects of well-characterized plant food products. Studies to overcome challenges such as agent quality, purity, and batch-to-batch variations require the utmost attention. The use of infrared spectrum fingerprinting and hyperspectral imaging techniques to create standards will assist to overcome potential batch variations of plant foods and their extracts, including herbal extracts and/or dietary supplements. The generation of standard data analysis flow charts by applying multivariate calibration models and machine learning AI models presents opportunities to overcome these challenges and will significantly improve the accuracy and enhance the universality and stability of the plant extract/compounds.

The aberrant regulation of epigenetic mechanisms such as DNA methylation and histone modifications in high-risk cohorts (e.g., *BRCA* mutation carriers, Lynch syndrome) may be restored by several plant foods and their components as supported by several preclinical proof-of-principle studies (80, 81). DNA methylation frequently inactivates tumor-suppressor genes such as *BRCA1/2*, *cyclin-dependent kinase inhibitor 2A,* and *cyclin-dependent kinase inhibitor 2B,* and DNA mismatch repair genes like *MutL homolog 1, MutS homolog 2*, *MutS homolog 6*, and *postmeiotic segregation increased 2*. Furthermore, the modulation of epigenetic activities by green cancer prevention dietary components will allow the discovery of novel biomarkers and molecular targets for cancer intervention/prevention. For example, dietary flavones and flavonols are known to inhibit poly(ADP-ribose) polymerase-1 (PARP1) and promote (directly or indirectly) epigenetic modifications (82–87). Therefore, modulating epigenetic alterations may reduce cancer risk if appropriate targets are identified and validated and modulation is achieved using potential plant foods/extracts/dietary supplements.

Applying recent omics technologies will improve the prospect of precision nutrition for the prevention and management

of early stage precancers in high-risk cohorts. As an example, the development of the Human Tumor Atlas Network Precancer Atlas, and other high-throughput next-generation sequencing data produced extensive new knowledge about the genetic architecture of the early-stage cancers and precancerous lesions has underpinned studies of biological axes beyond the genome, such as the transcriptome, epigenome, and microbiome. The precision nutrition approach combined with the early-stage genomic information can potentially result in a comprehensive plant-based diet approach to the prevention and management of precancers in high-risk populations.

Summary

The green cancer prevention approach where interventions are based on whole foods or their extracts that demonstrate prevention activity offer promise as described above, especially with broccoli sprouts and BRBs (29, 88). However, many of the studies conducted are pilot or single-arm studies without placebo comparisons (**Table 1**). Continuing refinement of the science for optimizing formulations, doses, study cohorts, and endpoints in RCTs is likely to define clear directions for the use of plant foods and their extracts for green cancer prevention. With stronger clinical signatures of efficacy from carefully designed, conducted, and analyzed clinical trials it is likely that patient and consumer acceptance will follow.

Going beyond the original concept of green chemoprevention includes applying precision (-nutrition, -prevention, -medicine) strategies, discovery/building preclinical evidence for clinical studies, and identifying and characterizing clinically relevant targets. Exploring new formulations and methods to improve the bioavailability of isolated phytochemicals as well as discovery of new phytochemical extracts and their active constituents with cancer prevention activity are some additional research considerations on the horizon. Furthermore, with the advent of omic technologies and their integration and other systematic approaches, it may be possible to determine biomarker-based variation in responses (responders vs. nonresponders) to green cancer prevention. This would likely provide feasibility for the development of safer regimens for administration over long periods.

Recently, DCP, NCI announced a new program and accompanying Request for Applications, entitled "Discovery and Development of Natural Products for Cancer Interception and Prevention (DDNP-CIP)," for the discovery, screening and development of novel, natural occurring agents with specific biological targets for cancer interception and prevention, which may be one approach for discovery of green cancer prevention agents (89).

Further research toward identifying novel and effective biomarkers for predicting risk reduction and green cancer prevention agent efficacy, identifying novel targets for green cancer prevention and nutritional interventions, and identifying susceptible or responsive individuals through gene–diet interactions are needed for developing effective green cancer prevention and interception strategies as primary tools to reduce the incidence of cancer.

Authors' Disclosures

No disclosures were reported.

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