Spicing up a vegetarian diet: chemopreventive effects of phytochemicals[1–4]

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ABSTRACT Thousands of chemical structures have been identified in plant foods. Many are found in spices. Typically, spices are the dried aromatic parts of plants—generally the seeds, berries, roots, pods, and sometimes leaves—that mainly, but not invariably, grow in hot countries. Given the wide range of botanical species and plant parts from which spices are derived, they can contribute significant variety and complexity to the human diet. In the past, the medicinal uses of spices and herbs were often indistinguishable from their culinary uses, and for good reason: people have recognized for centuries both the inherent value, as well as the potential toxicity, of phytochemicals in relation to human health. Plants have the capacity to synthesize a diverse array of chemicals, and understanding how phytochemicals function in plants may further our understanding of the mechanisms by which they benefit humans. In plants, these compounds function to attract beneficial and repel harmful organisms, serve as photoprotectants, and respond to environmental changes. In humans, they can have complementary and overlapping actions, including antioxidant effects, modulation of detoxification enzymes, stimulation of the immune system, reduction of inflammation, modulation of steroid metabolism, and antibacterial and antiviral effects. Embracing a cuisine rich in spice, as well as in fruit and vegetables, may further enhance the chemopreventive capacity of one's diet. *Am J Clin Nutr* 2003;78(suppl):579S–83S.

KEY WORDS Antioxidants, cancer prevention, herbs, intervention studies, phytochemicals, spices

INTRODUCTION

Spices are defined by the US Food and Drug Administration as "aromatic vegetable substances, in the whole, broken, or ground form, whose significant function in food is seasoning rather than nutrition. They are true to name, and from them no portion of any volatile oil or other flavoring principle has been removed" (1). By this definition, onions, garlic, and celery, even dried, and seeds such as poppy and sesame seeds are typically regarded as foods, not spices. Some spices, such as paprika, turmeric, and saffron, are used for color as well as flavor and when used as ingredients in foods are designated as "spice and coloring." Most spices are derived from bark (eg, cinnamon), fruit (eg, red and black pepper), and seed (eg, nutmeg). In contrast, herbs used in cooking are typically composed of leaves and stem. This review is limited to discussion of spices and their constituents.

Population-wide average dietary intake of common spices has been estimated at 0.5 g/person per day in Europe and 1.0 g/person per day in New Zealand (2). According to the American Spice Trade Association, per capita spice consumption in the United States was ≈4 g/person per day (3.6 lb/person per year) in 1998, and hot spices such as black and white pepper, red pepper, and mustard seed account for 41% of US spice usage (3). In contrast, on the Indian subcontinent, turmeric consumption alone has been estimated at 1.5 g/person per day (4). Generally, cuisines that traditionally do not include much meat use a wider variety of spices for seasoning. These include cuisines in areas of the world where vegetarianism has existed for centuries, such as among followers of Hinduism and Buddhism. Nearly all spices important in cooking today are of Asian origin, with the exception of allspice, vanilla, and chili (5). Thus, globally, the amounts and types of spices used vary widely.

Given the wide range of botanical species and plant parts from which spices are derived, spices can contribute significant variety and complexity to the human diet. In the past, the medicinal uses of spices and herbs were often indistinguishable from their culinary uses; people have recognized for centuries both the inherent value, as well as potential toxicity, of phytochemicals in relation to human health. Today, in the area of cancer prevention, the use of spices and their constituents as potential chemopreventive agents remains a topic of intense research.

PHYTOCHEMICALS IN SPICES

Over millions of years, plants have developed the capacity to synthesize a diverse array of chemicals. In general, these phytochemicals function to attract beneficial and repel harmful organisms, serve as photoprotectants, and respond to environmental changes. For example, numerous classes of phytochemicals, including the isoflavones, anthocyanins, and flavonoids, function as phytoalexins, substances that assist a plant to resist pathogens. Various glycosides of these also render plants unpalatable and thereby reduce intake by animals. Carotenoids aid in light collection under conditions of low light or help to dissipate excess absorbed energy as heat under conditions of high sun exposure; most plants have the flexibility to alter their carotenoid composition

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TABLE 1
Major classes of phytochemicals that contribute to the aroma of spices and examples of their sources[1]

Class of phytochemicals	Source
Terpenes	
Monoterpenes	Apiaceae family (eg, cumin, fennel, caraway)
Tetraterpenes (eg, carotenoids)	Paprika, saffron
Sesquiterpenes	Cinnamon, juniper, ginger, turmeric, galangal
Terpene derivatives	Coriander
Phenylproponoids	
Cinnamic acid	Cinnamon
Eugenol	Cloves
Vanillin	Vanilla bean
Diarylheptanoids	
Curcumin	Turmeric
Isothiocyanates	
Allyl isothiocyanate	Mustard seed, wasabi
6-Methylsulfinylhexyl isothiocyanate	Wasabi
Sulfur compounds	
Thiols, sulfides, di- and polysulfides	Garlic, asafetida

[1] Adapted from reference 5.

in response to growth under deep shade or full sunlight (6). Understanding how phytochemicals function in plants may further our understanding of mechanisms by which they may benefit humans. Paradoxically, spices are grown as food enhancers, despite the intention of these tasty constituents to discourage consumption of the plant.

Only a small number of primary compounds serve as precursors of the large array of phytochemicals produced by higher plants, and most of these are obtained from the early products of photosynthesis (7). The constituents responsible for the flavor properties of spices are products of secondary metabolism in plants: that is, they are not vital for plant tissue synthesis or energy production and storage, but their production is essential to the viability of the plant. Most known phytochemicals arise from 3 well-recognized metabolic pathways: the shikimate pathway, the cinnamic acid pathway, and the isoprenoid pathway. The shikimate pathway is a major source of carbon for many compounds (8), in part because the 3 aromatic amino acids formed as end products—phenylalanine, tryptophan, and tyrosine—are important precursors that feed into several synthetic pathways. For example, phenylalanine is the starting material for the cinnamic acid pathway, which produces numerous phenolic acids, coumarins, flavonoids, isoflavonoids, and lignans. These 3 amino acids, in addition to others, also provide the carbon atoms for production of glucosinolates in Brassicaceae. Pyruvic acid, an early product of photosynthesis, is the starting point for the isoprenoid pathway, from which families of carotenoids, terpenes, saponins, and so forth are derived.

Despite the large number of phytochemical classes, most plants contain only a few of them, and botanically related plants often contain similar or even the same constituents. As a result, spices tend to cluster in certain plant families, while other families do not contain any aromatic plants (5). The major phytochemical classes associated with spices are outlined in **Table 1** and include a diverse array of compounds of varying molecular weight and structure. The terpenes and terpene derivatives are probably the most important class of aroma compounds, with monoterpenes contributing to the fragrance of 90% of spices (5). Monoterpenes occur in many different plants, and the characteristic aroma of a spice results from a specific mixture of monoterpenes, not a specific compound (5).

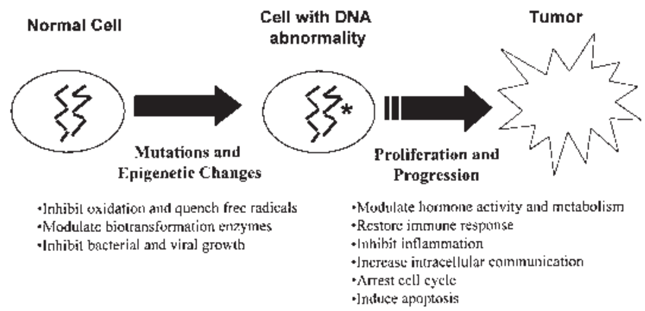

FIGURE 1. Possible mechanisms for chemoprevention by spices and their constituents. Adapted from references 9 and 10.

Many phytochemicals are present in plants as glycosides (ie, with a sugar moiety attached). Generally, glycosides are nonvolatile and lack fragrance. Cleaving the glycosidic bond yields the aglycon, which itself may be volatile and fragrant. For example, glucosinolates of the cabbage family (Brassicaceae) are hydrolyzed by the plant enzyme thioglucosidase (myrosinase) when cells are damaged (eg, cut or chewed), yielding the pungent isothiocyanates, and vanillin is released from a glycoside precursor during drying, a step in the processing of vanilla beans. Thus, how a spice is processed will also determine the amount and form of its constituents.

Potential mechanisms of action

Many of the phytochemicals in spices are potent biologic agents that can influence cancer risk via several complementary and overlapping mechanisms. Mechanisms related to inhibition of mutagenesis and epigenesis of DNA include antioxidant activity, alteration of biotransformation enzyme activity, and antibacterial and antiviral effects. Mechanisms that affect the proliferation and progression of cancer include alteration of immune function, reduction of inflammation, modulation of steroid hormone concentrations and hormone metabolism, arrest in cell cycle progression, and stimulation of apoptosis. The combination of these biologic processes, rather than any one specific mechanism, most likely alters the risk and course of cancer. The mechanisms are outlined in **Figure 1**, and in vitro and animal studies that have tested the effect of spices on some of these mechanisms are described below. Studies in humans are described in the section "Intervention studies in humans."

Antioxidant activity

Processes that prevent free radical formation, remove radicals before damage can occur, repair oxidative damage, eliminate damaged molecules, or prevent mutations are important mechanisms in cancer prevention (11). Systematic determination of total antioxidant concentration of a variety of spice extracts has been conducted using in vitro assays. Ginger (*Zingiber officinale*) has been identified in several studies as a plant with a high antioxidant content (12, 13). Extracts of several commonly used Indian spices also have been shown to inhibit lipid peroxidation; in one study, relative antioxidant activities from highest to lowest were found in cloves, cinnamon, pepper, ginger, and garlic (12). Interestingly, the antioxidant activity of the extracts was retained even after boiling for 30 min, suggesting that, unlike many antioxidants, the antioxidants in these spices were heat stable. In addition, synergistic antioxidant effects were observed with combinations of spices.

Antioxidant activity of isolated compounds from spices has also been tested. Linalool, a terpene tertiary alcohol and major phytochemical in coriander seeds, is an antioxidant at high concentrations (14). Curcumin (diferuloylmethane), the active ingredient of the spice turmeric (*Curcuma longa*), is a strong antioxidant [reviewed in (4)] and reportedly several times more potent than vitamin E as a free radical scavenger (15).

Numerous studies have also tested the antioxidant capacity of spices or their constituents in vivo. The antioxidant capacity of ginger has been reported in relation to LDL cholesterol oxidation in apolipoprotein E–deficient mice (16). Coriander, cinnamon, and cardamom have also been shown to have antioxidant effects in rodents, in part through activating antioxidant enzymes in various tissues (17, 18).

Alteration of biotransformation enzyme activity

Biotransformation enzymes, also referred to as xenobiotic- or drug-metabolizing enzymes, play a major role in regulating the toxic, mutagenic, and neoplastic effects of chemical carcinogens. The unique efficacy of Brassicaceae to protect against neoplastic disease through modulation of biotransformation enzymes is attributed to the glucosinolate, and ultimately isothiocyanates, content of these plants. To date, much of this research has focused on effects of vegetables in this botanical family [reviewed in (19, 20)], but 6-methylsulfinylhexyl isothiocyanates in wasabi (*Wasabia japonica*, Japanese domestic horseradish) also increases glutathione *S*-transferase (GST) activities (21). Other spices that have been shown to alter biotransformation enzyme activities include coriander, which increases hepatic superoxide dismutase, catalase, GST, glucose-6-phosphate dehydrogenase, and glutathione-disulfide reductase activities (18); curcumin, which up-regulates hepatic GST in rodents (22–24); and cinnamon, which decreases cytochrome P450 content but increases GSH content and the activity of glutathione-dependent antioxidant enzymes (25).

Antibacterial and antiviral effects

Several bacterial infections are associated with the risk of certain cancer, and viruses are now recognized as the second most important cause of human cancer. Given that many chemicals are produced in plants as antimicrobial and antiviral agents, these compounds are being examined for their potential to inhibit human pathogens. A preliminary screening of 35 different Indian spices and herbs indicated that clove, cinnamon, bishop's weed, chili (*Capsicum annum*), horseradish, cumin, tamarind, black cumin, pomegranate seeds, nutmeg, garlic, onion, tejpat, celery, and cambodge had potent antimicrobial activities against the test organisms *Bacillus subtilis* (ATCC 6633), *Escherichia coli* (ATCC 10536), and *Saccharomyces cerevisiae* (ATCC 9763) (26). Garlic and cloves also possess antimicrobial activity against some human pathogenic bacteria and yeasts in vitro; some bacteria that showed resistance to certain antibiotics were sensitive to extracts of both garlic and clove (27). In vitro, garlic extracts are also potent inhibitors of *Helicobacter pylori*, the bacteria associated with gastric cancer risk (28); however, interventions in *H. pylori*–infected humans have been ineffective (*see* "Interventions studies in humans").

Antiinflammatory action

Prostaglandins and other eicosanoids are hypothesized to influence carcinogenesis through action on nuclear transcription sites and downstream gene products important in the control of cell proliferation (29). Nonsteroidal antiinflammatory drugs, potent inhibitors of cyclooxygenase (COX), the enzyme responsible for prostaglandin synthesis, are associated with reduced risk of several cancers (29). Thus, natural products, including spices, have been examined for their capacity to inhibit COX or other parts of the inflammation pathway. Ginger (30) and curcumin (31, 32) have been reported to interfere with inflammatory processes.

Chemoprevention studies with spices

Several spices and their constituents have been evaluated in animal carcinogenesis models, with positive results (33). Extracts of saffron (*Crocus sativus*) have been shown to inhibit and/or retard formation of skin, colon, and soft tissue tumors, and, in combination with cysteine and vitamin E, to protect against cisplatin-induced toxicity in mice and rats [reviewed in (34)]. The mechanisms of saffron's anticarcinogenic effect have not been elucidated. Crocetin (a polyene dicarboxylic acid in saffron) has a dose-dependent inhibitory effect on cellular DNA and RNA synthesis in tumor cells in vitro (34). Similarly, crocin (a glycosyl ester of crocetin) has antitumor activity that is sex dependent in rats, suggesting that there may be a hormonal component to the mechanism (35). Curcumin also has been shown to have chemopreventive effects against cancers of the skin, forestomach, colon, oral cavity, and liver in mice (36). In the colon, it inhibited the incidence and multiplicity of invasive and noninvasive adenocarcinomas as well as decreased tumor volume (37). Ginger and capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide), a pungent ingredient of hot chili pepper, also protected against experimentally induced mutagenesis and tumorigenesis (33, 38).

Intervention studies in humans

Study of spice extracts or isolated phytochemicals in cell culture systems and animal models has provided a wealth of information on the individual mechanisms by which constituents of spices might contribute to lower risk of cancer in humans. However, it is not clear whether the biology that appears to influence disease risk in animals, fed compounds often at high levels, is functional to the same degree or in the same manner in humans consuming doses that are part of a habitual diet or part of a chemopreventive regimen. Furthermore, studies in cell culture are often conducted without knowledge of how the phytochemicals are processed in vivo, how they are absorbed, how they are metabolized in the body, or if they are even available to tissues of interest.

Interventions in humans using spices or spice extracts are extremely limited; however, they are key to answering questions about absorption, metabolism, and tissue availability. For example, doses of 180 mg curcumin/d resulted in no detectable curcumin or its metabolites in blood or urine (4). Even a single oral dose of 2 g curcumin raised serum concentrations to only transiently detectable concentrations (39), suggesting that the compound's systemic bioavailability is limited. These data also raise questions about the chemopreventive potential of curcumin in target tissues that rely on systemic delivery.

Other studies have attempted to reproduce in humans what has been observed in vitro or in animal models. Following up on the in vitro studies of garlic and *H. pylori*, several studies have used garlic to treat *H. pylori*–positive individuals, with the goal to eradicate the infection. To date, garlic supplementation—albeit in small, short-term studies—has not been effective (40, 41). In vitro, ginger inhibits COX activity of platelets. In healthy humans, effects of ginger supplementation (15 g of raw ginger root or 40 g of cooked stem ginger daily for 2 wk) compared with control had no effect on ex vivo platelet thromboxane B_2 production (42). Another study, designed to test the antigenotoxic potential of eugenol (150 mg/d for 7 d), showed no significant effects of eugenol on cytogenetic parameters (eg, ex vivo response of white blood cells to genotoxic agents) or overall GST activity except for a significant reduction of plasma GST-α concentration (43).

The capacity of spices to affect markers associated with cancer prevention mechanisms provides important data that can guide chemoprevention strategies in humans; however, so far, results of intervention trials have been disappointing. Furthermore, the effects of mixtures of spices in the context of the human diet have not been studied. Given that spices are seldom consumed as single flavorings but rather as part of complex dishes—some recipes for Indian dishes call for as many as 60 different spices—it seems reasonable to consider the potential synergistic effects of mixtures of spices (44).

Possible adverse effects of spices

Although the emphasis of this review has been on potential chemopreventive effects of spices, there are also data suggesting that some spices may increase cancer risk. Several case-control studies in India have observed that gastrointestinal cancer risk was higher with consumption of spicy foods and chili (45, 46). The work of Jensen-Jarolim et al (47) suggests that spices may increase intestinal epithelial permeability through loosening cell contacts (eg, paprika, cayenne pepper, chili pepper) or decrease permeability (eg, black pepper, nutmeg), possibly by cell swelling. Solanaceae spices (eg, chili peppers) increase permeability for macromolecules of 10–40 kDa. Although these study results were discussed in the context of pathogenesis of food allergy and intolerance, the potential effect on exposure to carcinogens might also be considered.

SUMMARY

In summary, there are several mechanisms through which spices and their constituents may elicit cancer-preventive actions. Data from in vitro and animal studies are promising; however, in general, these studies use high doses of pure compounds or spice extracts, whose metabolism in humans has not been elucidated. Only a handful of spices and their constituents have been tested, and nothing is known about the interactions and contributions of spice mixtures. Furthermore, the capacity of spices to influence disease risk within the context of culinary use has not been evaluated. There is a strong need to understand the effect of spices within the context of the total diet, where synergistic effects may be important.

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