

## Perspective

See related article by Citronberg et al., p. 271

## Ginger: Is it Ready for Prime Time?

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## Abstract

On the basis of substantial preclinical data showing the preventive efficacy of ginger and its constituents *in vitro* and in animal models, as well as a phase I pilot trial indicating that ginger extract is well tolerated in humans, Citronberg and colleagues conducted a pilot trial of ginger extract (2 g/day for 28 days) on biomarkers of cell proliferation [human telomerase reverse transcriptase (hTERT), MIB-1], differentiation (p21waf1/cip1), and apoptosis (Bax, Bcl-2) in colonic mucosa from individuals at high-risk for colorectal cancer. Results from the trial suggest that ginger may reduce proliferation in normal-appearing colorectal epithelium and increase apoptosis relative to proliferation, especially in the differentiation zone of colon crypts. The authors suggest that these results support a larger study to confirm the pilot data. Before proceeding with a larger trial, however, it seems prudent to confirm ginger as a chemopreventive for colorectal cancer in animals, particularly when tested in postinitiation protocols and to identify reliable molecular biomarkers of effect that could be evaluated in clinical trials. Pharmacokinetic studies to examine the distribution and localization of ginger compounds and metabolites in the differentiation and proliferative zones of colonic crypts in animals and humans would also be informative. Finally, because the effects of ginger on normal colonic mucosa seem minimal, consideration should be given to the conduct of future trials in humans with premalignant colorectal disease. *Cancer Prev Res*; 6(4); 257–62. ©2013 AACR.

The ginger root (*Zingiber officinale* Roscoe, Zingiberaceae) was initially cultured in Southeast Asia and is now grown in many parts of the world (1). The root or rhizome is typically consumed as a fresh paste, dried powder, or as a flavoring agent in beverages and other food preparations. Ginger root has been used in China for the treatment of headaches, nausea, and colds for more than 2,500 years, and in the Western world, it is used primarily as a remedy for digestive disorders including dyspepsia, colic, nausea, gastritis, vomiting, and diarrhea (2, 3). Because of its strong anti-inflammatory effects, ginger has gained considerable attention recently in the United States and Europe for the treatment of chronic inflammatory conditions, such as osteoarthritis and rheumatoid arthritis (1, 4).

Several population-based studies indicate that Southeast Asian countries have a much lower risk of gastrointestinal, colon, breast, prostate, and other cancers than their Western counterparts (5). This may be due, at least in part, to the high consumption of foods, such as soy, tea, garlic, turmeric, and ginger by Southeast Asian populations. There are no epidemiologic studies to suggest a protective effect of ginger, *per se*, on cancer development in humans; however, as will be discussed below, ginger contains many constituents that

have shown anticarcinogenic effects *in vitro* and in animal models. Small prevention trials focused on individuals considered to be at increased risk for cancer can be informative, as illustrated by the work reported by Citronberg and colleagues in this issue of the journal (6). They suggest that ginger supplementation might reduce the risk for colorectal cancer in high-risk individuals by its effects on colonic cell proliferation, apoptosis, and differentiation. They also suggest that their results are supportive of additional human trials to further investigate the use of ginger for the chemoprevention of colorectal cancer. This perspective provides a brief summary of our knowledge of the chemopreventive effects of ginger and some of its components and addresses the issue as to whether the existing database supports proceeding with additional human chemoprevention trials of ginger at this time.

Ginger is composed predominately of 2 groups of chemicals: volatile oils and pungent compounds (7). The volatile oil components represent about 1% to 3% of the plant and consist mainly of sesquiterpene compounds, predominately zingerberene, curcumene, farnesene, and zerumbone. These oil constituents contribute to the taste and aroma of ginger, and zerumbone (Fig. 1) may contribute to its anticarcinogenic effects. The pungent compounds include the gingerols, shogaols, and paradol (Fig. 1). Gingerols are the most abundant polyphenols in the root, and they vary in chain-length from n6 to n10 with the most abundant being 6-gingerol. Shogaols, the dehydrated form of gingerols, are the predominant polyphenolic constituents in dried ginger, with the most abundant being 6-shogaol. Paradol is similar to gingerol and is formed on hydrogenation of shogaol. The gingerols, shogaols, and

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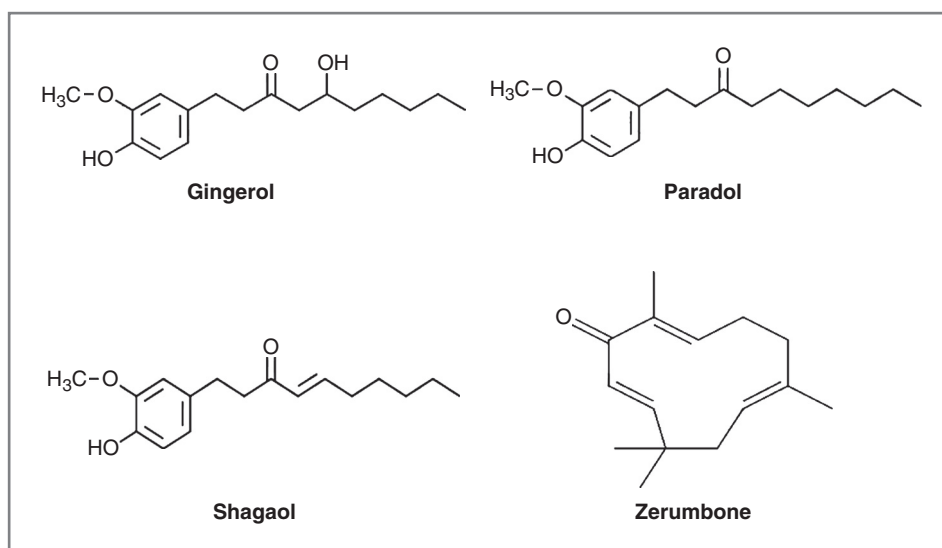


Figure 1. Components of ginger.

paradol are responsible for the "hot" sensation of ginger in the mouth and seem to be responsible for most of its anticarcinogenic effects.

Preclinical studies have shown protective effects of ginger and its constituents against skin (8–10), breast (11), oral cavity (12), liver (13), and colon (14) cancer in animals. Most studies were done with ginger root extract or with [6]-gingerol or [6]-paradol. For example, topical treatment of mouse skin with either ginger extract or its pungent constituents, [6]-gingerol, or [6]-paradol, results in inhibition of skin tumor promotion by the promoting agent, tetradecanoylphorbol-13-acetate (TPA; refs. 8–10). This inhibition has been associated with reductions in TPA-induced activation of epidermal ornithine decarboxylase, myeloperoxidase activity, TNF- $\alpha$  production, COX-2 expression, and NF- $\kappa$ B DNA-binding activity (8–10, 15). The antitumor-initiating and tumor-promoting activities of the ginger compound, zerumbone, in mouse skin were also evaluated, and the compound was found to inhibit both stages of skin tumorigenesis through the induction of antioxidative and phase II drug-metabolizing enzymes as well as attenuation of proinflammatory signaling pathways (16). A hot water extract of ginger root was found to inhibit spontaneous mammary tumorigenesis in mice when administered at a concentration of 0.125% in the drinking water; however, the mechanism(s) of this effect were not investigated (11). A recent study showed a protective effect of ginger powder added to the diet (final concentration unknown) on 4-nitroquinoline-1-oxide (4-NQO)-induced carcinogenesis in rat tongue (12). Relative to untreated controls, ginger treatment prevented the development and invasion of oral carcinomas, presumably by reducing cell proliferation and stimulating apoptosis. Ginger oleoresin, added to the diet at a concentration of 100 mg/kg body weight, reduced the incidence of ethionine-induced liver tumors in male rats from 100% to 17%, presumably by stimulating enzymes involved in scavenging free radicals and reducing lipid peroxidation (13).

Of direct relevance to the report in this issue by Citronberg and colleagues (6), ginger and its constituents have been evaluated in at least 3 studies for their ability to reduce the development of colon carcinogenesis in rodents. Yoshimi and colleagues (17) reported that the dietary administration of 0.02% gingerol during the initiation phase of intestinal carcinogenesis by azoxymethane inhibited the multiplicity of adenocarcinomas in rats after 20 weeks. This inhibiting effect was observed with regard to the entire intestine; however, when only the large intestine was considered, a protective effect was not observed for the development of colon tumors. Dias and colleagues (18) treated rats with 1,2-dimethylhydrazine (DMH) twice a week for 2 weeks after which they fed the rats a ginger extract at 0.5% and 1% of the diet for 10 weeks. Treatment with ginger in the postinitiation phase failed to suppress the formation of aberrant crypt foci (ACF) or the number of crypts per ACF in the DMH-treated group. Moreover, dietary ginger did not significantly change the proliferative or apoptotic indexes of colon crypt cells induced by DMH. Importantly, dietary consumption of the ginger at both dose levels did not induce any toxicity in the rats, and the 1% ginger meal significantly decreased serum cholesterol levels. In contrast, a third study found evidence for a protective effect of ginger on DMH-induced colon carcinogenesis (14). Rats were injected with DMH once weekly for 15 weeks and were fed ginger powder (50 mg/kg body weight) during both the initiation and postinitiation stages of carcinogenesis. Tumor incidence, multiplicity, and size were significantly decreased by ginger at the end of the 30-week study. The authors suggested that the protective effect of the ginger on DMH-induced tumorigenesis might have been due to its ability to enhance levels of circulating antioxidant and phase II enzymes and to reduce the level of lipid peroxidation in the treated animals. Biomarkers typically associated with the effects of chemoprevention agents on tumor promotion/progression were not evaluated in this study.

*In vitro* studies and *in vivo* studies in mouse skin have provided additional mechanistic information regarding the anticancer effects of ginger. Ginger extracts and individual ginger constituents have been evaluated for antiproliferative and proapoptotic effects in a variety of different cell lines including lung (19), leukemia (20), oral (21), skin (22, 23), endothelial (24), ovarian (25), gastric (26), pancreas, (27) and colon (28). Early studies showed that alcohol-soluble extracts of ginger were more cytotoxic for lymphoma ascites tumor cells and Chinese hamster ovary cells than aqueous extracts (29). Most early studies with individual ginger compounds were done with [6]-gingerol and [6]-paradol and indicated that these compounds suppress cell proliferation through induction of apoptosis by caspase-3-dependent mechanisms and by downregulation of the antiapoptotic protein Bcl-2 and increased expression of the proapoptotic protein Bax (21, 30). The effects of these 2 compounds on cell proliferation were also assessed by examining their inhibitory effects on the uptake of [<sup>3</sup>H]thymidine into cell DNA, and the inhibitory effect of [6]-paradol on DNA synthesis was more pronounced than that of [6]-gingerol (20). More recent studies of the effects of [6]-gingerol and other agents on molecular targets for cancer prevention have been summarized by Aggarwal and Shishodia (31). With respect to its effects on molecular events associated with cell proliferation and inflammation, [6]-gingerol was found to inhibit EGF-induced cell transformation and AP-1 activation in mouse epidermal cells and AP-1 activation in human skin keratinocytes (23). [6]-Gingerol also inhibited TPA-induced DNA binding and transcriptional activation of NF- $\kappa$ B through suppression of I $\kappa$ B $\alpha$  degradation and p65 nuclear translocation in mouse skin, as well as TPA-induced phosphorylation and catalytic activity of p38 mitogen-activated protein kinase, an enzyme that regulates COX-2 expression (15). These results suggest that [6]-gingerol inhibits TPA-induced COX-2 expression in mouse skin by blocking the p38 MAPK-NF- $\kappa$ B signaling pathway. [6]-Gingerol also produced a dose-dependent inhibition of nitric oxide production and a significant reduction in iNOS expression in lipopolysaccharide-stimulated mouse macrophages (32), and both [6]-gingerol and [6]-paradol inhibited TPA-induced TNF- $\alpha$  production and epidermal ornithine decarboxylase activity in mouse skin (10). Collectively, these data indicate that ginger polyphenols affect the expression and activities of multiple genes associated with cellular proliferation and inflammation. In addition, [6]-gingerol inhibits both vascular endothelial growth factor (VEGF)- and basic fibroblast growth factor-induced proliferation and capillary-like tube formation *in vitro* of human endothelial cells and ovarian cancer cells (24) and the activities of matrix metalloproteinase (MMP)-2 and -9 MMPs in MDA-MB-231 human breast cancer cells indicating that gingerol influences cellular and molecular events associated with angiogenesis, cell invasion, and metastasis (33).

With respect to colon cancer, *in vitro* studies have shown antiproliferative and proapoptotic effects of [6]-gingerol and ginger extracts specifically on colorectal cancer cells.

Jeong and colleagues (34) reported that [6]-gingerol suppressed anchorage-independent growth of human HCT 116 colorectal cancer cells by inhibiting leukotriene A<sub>4</sub> hydroxylase (LTA<sub>4</sub>H) activity. LTA<sub>4</sub>H is an enzyme that catalyzes the final rate-limiting step in the biosynthesis of leukotriene B<sub>4</sub> (LTB<sub>4</sub>), and LTB<sub>4</sub> stimulates the growth of colon cancer cells. More recently, an ethanol extract of ginger was shown to inhibit proliferation of human HCT 116 and HT 29 human colon cancer cell lines with an IC<sub>50</sub> for both lines of approximately 500  $\mu$ g/mL (28). This concentration of ginger extract far exceeds the amounts of [6]-gingerol (14.72  $\mu$ g/mL; 50  $\mu$ mol/L) required to inhibit MKP<sub>5</sub>, a mediator of prostate cancer cell growth (35) and of [6]-shogaol (2.21  $\mu$ g/mL; 7.5  $\mu$ mol/L) needed to induce apoptosis and inhibit growth of ovarian cancer cells (25). Importantly, Zick and colleagues (3) indicate that the concentrations of [6]-gingerol and [6]-shogaol required to elicit these effects on cultured prostate and ovarian cancer cells, respectively, far exceed the amounts of these 2 compounds detected in the serum of humans following oral dosing of 1.5 and 2.0 grams of ginger, putting the clinical validity of these *in vitro* studies in question. Nevertheless, the information derived from these studies provides important leads as to the selection of molecular biomarkers of proliferation, apoptosis, inflammation, angiogenesis, invasion, and metastases that could be used to evaluate the chemopreventive efficacy of ginger and its constituents against colorectal cancer in rodents and, potentially, in humans.

Before the report by Citronberg and colleagues (6) in this issue, 2 clinical trials were conducted by some of these same investigators with ginger extract. The initial study was a phase I trial to examine the pharmacokinetic profile of [6]-, [8]-, and [10]-gingerol and [6]-shogaol in 27 healthy human volunteers administered a single oral dose of either 100, 250, 500, 1,000, 1,500, or 2,000 mg ginger extract (3). Blood samples were taken at 15 minutes to 72 hours after oral dosing and analysis of these samples indicated that no free [6]-, [8]-, [10]-gingerol, or [6]-shogaol was detectable in plasma. All 4 analytes were rapidly absorbed and detected as glucuronide and sulfate conjugates, the glucuronide conjugates being the most prevalent. This suggests that the bioactive components of ginger might become rapidly inactivated in tissues through conjugation to glucuronic acid and sulfates. The major treatment-associated toxicities following single oral dosing of ginger extract consisted of minor gastrointestinal upsets that did not exceed National Cancer Institute Common Toxicity Criteria Grade 1. The second clinical trial of ginger extract was conducted to determine if a 2.0 g/day dose of ginger extract could decrease levels of the inflammatory eicosanoids, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), 13-hydroxy-octadecadienoic acid, and 5-, 12-, and 15-hydroxyeicosatetraenoic acid (5-, 12- and 15-HETE) in normal colonic mucosa of healthy volunteers (36). Thirty subjects were randomized to 2.0 g/day ginger extract or placebo for 28 days. Colon biopsies were taken by sigmoidoscopy at baseline and at day 28, and eicosanoid levels in the biopsies were measured by liquid chromatography/mass spectrometry. Results of this study indicated that there

was a significant decrease in mean percent change between baseline and day 28 for PGE<sub>2</sub> ( $P = 0.05$ ) and 5-HETE ( $P = 0.04$ ) and a trend toward significant decreases in 12-HETE ( $P = 0.09$ ) and 15-HETE ( $P = 0.06$ ) when the data were normalized to free arachidonic acid, but there were no significant differences in mean percent change for any of the eicosanoids when normalized to protein. Because the eicosanoid levels per amount of protein reflect the absolute concentrations of eicosanoids in tissue, these results suggest that ginger extract taken orally at a tolerable dose in humans has minimal effects on the metabolism of arachidonic acid in normal colonic epithelium. Perhaps, this is what might be expected following administration of the extract at a dose that presumably elicited minimal toxicity to the colon, although this was not confirmed by histopathologic evaluation of the biopsies.

In this issue, Citronberg and colleagues (6) report on the effects of oral administration of ginger extract on cell-cycle biomarkers in normal-appearing colonic mucosa obtained from individuals considered to be at high-risk for colon cancer. The 20 participants in this pilot study either had a first-degree relative with colorectal cancer under the age of 60 at diagnosis, or they had a previous adenomatous polyp or an early (Dukes A, B, or C) colon cancer resection. They were treated with 2.0 g of ginger extract or placebo daily, and biopsies of normal-appearing colonic mucosa were taken at baseline and within 24 hours after the final treatment with extract. Biomarkers examined by immunohistochemistry and quantitative image analysis in the tissues included p21<sup>waf1/cip1</sup> for cell differentiation, Bax and Bcl-2 for apoptosis, and MIB-1 and hTERT for cell proliferation. Results from the study indicated that Bax (which promotes apoptosis) expression increased 19% in the upper 40% (differentiation zone) of the crypt relative to the whole crypts, but this increase was not significant. Although p21 and Bcl-2 expression remained relatively unchanged, hTERT expression in the whole crypts decreased 41.2% ( $P = 0.05$ ), and the reduction was greater in the upper crypts than in the lower crypts. Similarly, changes in MIB-1 expression were more in the upper crypts than in the lower crypts, but they were not significant. The authors concluded that ginger may reduce proliferation in normal-appearing colorectal epithelium and increase apoptosis and differentiation relative to proliferation, especially in the differentiation zone of the crypts. They also suggest that these results support a larger trial(s) to further confirm these observations.

After reviewing the preclinical and clinical data on the chemopreventive effects of ginger, it seems prudent to make the following suggestions/recommendations with respect to future investigations:

1. The agent: Ginger has been evaluated in preclinical studies when administered in the diet as a powder, an ethanol extract, or as individual components (especially [6]-gingerol and [6]-paradol). In our studies with black raspberries, the powder form has repeatedly been more effective than the ethanol/water extract in preventing cancer in animals, however, there

are concerns regarding "standardization" of berry powders (37). These concerns also apply to ginger powder; therefore, it is probably not a viable candidate for routine chemoprevention. In contrast, the ethanol extract of ginger root is routinely standardized to 5% of total gingerols, which provides assurance that it contains some or most of the chemopreventive agents in ginger. In addition, the extract has significant biologic activity in preclinical studies, is relatively inexpensive (a 30-day supply at 2.0 g/day costs about \$50.00), and seems to be well tolerated in humans. Therefore, ginger extract has several qualities of an ideal chemopreventive agent. With respect to individual ginger compounds, [6]-gingerol exhibits multiple chemopreventive effects in preclinical studies and would seem ideal for further evaluation in humans. Unfortunately, the advertised cost of [6]-gingerol ranges from about \$280.00 to \$360.00 per 10 mg, which is prohibitive for both animal studies and for chemoprevention in humans. It seems that the commercial form of [6]-gingerol is isolated from ginger root; a more cost-effective method for producing the compound should be pursued.

2. Additional preclinical studies: Results from some phase III human chemoprevention trials in lung and prostate (38, 39) have emphasized the importance of obtaining definitive animal data before proceeding with large and expensive trials. In that regard, the above described data in support of ginger for the prevention of colorectal cancer in animals is equivocal and suggests that additional animal studies are warranted before embarking further into clinical trials. It seems that ginger has chemopreventive potential in the initiation phase of colon carcinogenesis, presumably due to its antioxidant effects and its ability to induce phase II enzymes involved in carcinogen metabolism; however, there is little evidence of its effectiveness in the promotion/progression stages of colon carcinogenesis. Postinitiation studies of ginger should be undertaken in appropriate animal models to confirm whether ginger produces antitumor effects through protective modulation of cellular and molecular events associated with colon carcinogenesis. It is apparent from the above described *in vitro* studies that ginger and several of its constituents positively influence cellular events and molecular targets associated with tumor progression, but it is not clear that the bioactive compounds in ginger reach sufficient levels in the colon of animals to influence these events. Only a few studies in rats have examined the pharmacokinetics of uptake, metabolism, and elimination of ginger constituents, principally [6]-gingerol, and the results suggest that when administered orally, [6]-gingerol is rapidly absorbed and conjugated in the intestinal epithelium and the liver to (S)-[6]-gingerol-4'-O- $\beta$ -glucuronide and

excreted through the bile and urine (40). Therefore, it is possible that the bioactive components of ginger may be rendered ineffective in rodent colon by their rapid conjugation to glucuronic acid.

Pharmacokinetic studies in animals using radiolabeled ginger compounds (e.g., [6]-gingerol) would be useful for determining the kinetics and extent of tissue distribution of these compounds and/or their metabolites in the different zones of colonic crypts. The results of these studies may suggest an explanation for the observation by Citronberg and colleagues (6) that ginger treatment of humans at high-risk for colon cancer led to a significant reduction in colon cell proliferation in the top (differentiation) zone of colon crypts but not in the bottom (proliferation) zone. Perhaps, the uptake of ginger bioactives into the proliferative zone of human colon crypts in the study by Citronberg and colleagues was either insufficient to influence the rates of cell proliferation and/or the bioactives were rapidly inactivated by conjugation to glucuronic acid and sulfate as suggested by the pharmacokinetic study of Zick and colleagues (3).

- Human trials: The results of human trials conducted so far suggest that ginger extract has only modest effects on biomarkers of cell proliferation, apoptosis, and differentiation, as well as on arachidonic acid metabolism, in "normal" colonic tissues when administered at a dose of 2 g/day. If found to be well tolerated, the higher doses of the extract should be evaluated. In addition, it seems possible that the evaluation of chemoprevention agents in normal-appearing colonic epithelium collected from either "normal" individuals or from individuals at high-risk for colon cancer may not reveal effects that these agents could exert on premalignant and malignant colon. The expression levels of target genes in normal colon may not be high enough to be altered significantly by chemoprevention agents, particularly at doses that elicit little or no toxicity for the colon. In that regard, in another chemoprevention trial involving subjects at high-risk for colorectal cancer, Fedirko and colleagues (41) treated 92 men and women with at least one pathology-confirmed colorectal adenoma

with 2.0 g/day of calcium or 800 IU/day of vitamin D<sub>3</sub> alone and in combination, versus placebo over 6 months. They examined the effects of these treatments on biomarkers of apoptosis and found that Bax expression along the full length of the crypts increased significantly (56%,  $P = 0.02$ ) in the vitamin D group and nonsignificantly (33%) in both the calcium ( $P = 0.31$ ) and calcium plus vitamin D ( $P = 0.36$ ) groups relative to the placebo group. Similar to the results of Citronberg and colleagues (6), the vitamin D effect was more pronounced in the top differentiation zone of the crypts than in the bottom proliferative zone. There were no significant treatment effects on Bcl-2 expression. These results suggest that, similar to ginger extract, the treatment effects of calcium and vitamin D on normal human colon are minimal and that studies of these agents directly on premalignant tissues (e.g., rectal polyps in FAP patients or, perhaps, ulcerative colitis) or on colorectal cancer tissues before surgery (42) may be more informative.

In summary, ginger has a long history of medicinal use in humans and, for many reasons, is an attractive agent for chemoprevention. Preclinical studies have shown its ability to reduce tumorigenesis in several organ sites and to protectively modulate multiple genes associated with cancer development. With respect to the colon, however, it seems prudent to more fully evaluate ginger for its effectiveness in inhibiting tumor progression and determining mechanisms of action in rodent models, including models of hereditary colon cancer. Pharmacokinetic studies to examine the tissue distribution on ginger components in the differentiation and proliferative zones of colonic crypts are also warranted. Finally, consideration should be given to the examination of the effects of ginger on premalignant human colon or perhaps on tissues from individuals with inflammatory bowel disease who are known to be at high risk for colon cancer.

#### Disclosure of Potential Conflict of Interest

No potential conflicts of interest were disclosed.

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