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## Pilot Clinical Study of the Effects of Ginger Root Extract on Eicosanoids in Colonic Mucosa of Subjects at Increased Risk for Colorectal Cancer

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### Abstract

Colorectal cancer (CRC) remains a significant cause of mortality. Inhibitors of cyclooxygenase (COX) and thus prostaglandin E<sub>2</sub>, are promising CRC preventives, but have significant toxicities. Ginger has been shown to inhibit COX, to decrease the incidence and multiplicity of adenomas, and decrease PGE<sub>2</sub> concentrations in subjects at normal risk for CRC. This study was conducted to determine the effects of 2.0 g/d of ginger given orally on the levels of PGE<sub>2</sub>, leukotriene B<sub>4</sub> (LTB<sub>4</sub>), 13-hydroxy-octadecadienoic acids, and 5-, 12-, & 15-hydroxy-eicosatetraenoic acid, in the colonic mucosa of subjects at increased risk for CRC. We randomized 20 subjects to 2.0 g/d ginger or placebo for 28 d. At baseline and Day 28, a flexible sigmoidoscopy was used to obtain colon biopsies. A liquid chromatography mass spectrometry method was used to determine eicosanoid levels in the biopsies, and levels were expressed per amount of protein or free arachidonic acid (AA). There was a significant decrease in AA between baseline and Day 28 ( $P = 0.05$ ) and significant increase in LTB<sub>4</sub> ( $P = 0.04$ ) when normalized to protein, in subjects treated with ginger versus placebo. No other changes in eicosanoids were observed. There was no difference between the groups in total adverse events (AE;  $P = 0.06$ ). Ginger lacks the ability to decrease eicosanoid levels in people at increased risk for CRC. Ginger did appear to be both tolerable and safe; and could have chemopreventive effects through other mechanisms. Further investigation should focus on other markers of CRC risk in those at increased CRC risk.

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## Keywords

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## INTRODUCTION

Despite recent decreases in mortality, colorectal cancer (CRC) remains the third most prevalent and second most deadly cancer in the United States [1]. Non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenase 1 & 2 (COX-1 & 2) enzymes and thus lower the levels of the inflammatory prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) are promising colorectal cancer (CRC) chemopreventive agents [2]. However, the gastrointestinal and cardiovascular side-effects of aspirin and other NSAIDs have raised concerns for their daily prescription to an otherwise healthy population [3,4]. Also, there is some thought that the inhibition of COX enzymes by these drugs could cause the shunting of arachidonic acid (AA), the substrate for COX, towards the production of other inflammatory eicosanoids [5]. In particular, various eicosanoids produced by the lipoxygenase (LOX) enzymes (5-, 12-, & 15-LOX) from AA, which are leukotriene B<sub>4</sub> (LTB<sub>4</sub>) and the hydroxy-eicosatetraenoic acids (HETEs), 5-, 12-, & 15-HETE and 13-hydroxy-octadecadienoic acid (13-HODE) produced from linoleic acid. Leukotriene B<sub>4</sub> and 5- & 12-HETE have all been implicated in the development of CRC [6-12], while both 15-HETE and 13-HODE appear to have anti-inflammatory and anti-tumorigenic activities [13-15]. Therefore, using natural nutritional components with low toxicity, which have the potential to affect COX and LOX, and their products is a potential area of investigation for the prevention of CRC.

One such natural nutritional compound is ginger root (*Zingiber officinale*), which has been shown to inhibit 5-LOX [16-19] and COX-1 & -2 [18,20-22]. Ginger root decreases inflammation in various murine models [16,23-26], and reduces serum concentrations of PGE<sub>2</sub> in rats [27]. Ginger root has also demonstrated preventative effects by decreasing tumor size, incidence and multiplicity in chemically induced animal models of colon carcinogenesis [28-30]. When ginger was administered in the post-initiation stage, it did not suppress aberrant crypt foci formation nor did ginger significantly change the proliferative or apoptotic indexes of the colonic crypt [31]. In our recent studies in participants at normal and increased risk for CRC we found that ginger significantly lowered COX-1 protein expression in increased risk participants, but not in normal risk participants [32]. In another study, ginger significantly reduced gut tissue concentrations of PGE<sub>2</sub> and 5-HETE and with a trend toward significant decreases in 12-HETE and 15-HETE in participants at normal risk for CRC [33].

The purpose of this study was to expand on our previous work in subjects at normal risk for CRC by examining the effect of 2.0 g of ginger taken daily for 28 days compared to placebo on eicosanoids in the colonic mucosa of subjects at increased risk for developing colorectal cancer. Secondary objectives were to evaluate the safety, tolerability, adherence and blinding of ginger supplementation.

## MATERIALS AND METHODS

### Study Participants

Fliers and word-of mouth were used to recruit 21 participants from the Ann Arbor, MI area between June 2009 and January 2010. Eligible participants had to be generally healthy individuals 18 years or older, who were at increased risk for CRC defined as having at least one of the following: (1) a first degree relative with CRC before the age of 60; (2) a previous adenomatous polyp; (3) or early stage resected (Dukes A, B, or C) colon cancer. Subjects were excluded if they were: lactose intolerant; had a diagnosis of peptic ulcer disease, gastrointestinal bleeding, or gastrin secreting tumors; had a known allergy to ginger; were taking supplements or medications which could obscure the ability to detect anti-inflammatory effects; and pregnant or lactating women. Also persons with hereditary non-polyposis colon cancer or familial adenomatous polyposis (HNPCC/FAP), inflammatory bowel disease, or coagulopathy disorders were excluded. Participants were told to stop eating any foods containing ginger within 14 days before drug administration and given a list of ginger-rich foods to avoid. All participants were reimbursed for their time.

The University of Michigan Institutional Review Board approved this study and all participants gave written, informed consent before beginning any study procedures. This study was conducted at the University of Michigan Clinical Research Unit (MCRU).

### Ginger Intervention

Details on quality control of the ginger extract have been previously published [33]. Briefly, a 2.0 g dose of powdered ginger root extract (*Z. officinale*) standardized to 15 mg (5%) of total gingerols and manufactured by Pure Encapsulations® (Sudbury, MA) was used in the study. This was the same ginger product used in our previous trials with identical amount (5%) of total gingerols. The 2.0 g dose of ginger was based on the maximum tolerated dose of ginger in a phase 1 study in healthy volunteers [34]. Lactose was used for the placebo capsules. Both the lactose and ginger powder were placed into identical opaque red capsules by the Investigational Drug Service (IDS) of the University of Michigan.

Toxicity of the intervention was evaluated at weekly intervals using The National Cancer Institute (NCI) Common Toxicity Scale V 4.02 [35].

### Randomization, Allocation, Adherence, and Blinding

Participants were randomized equally into the placebo or ginger group. The study biostatistician generated the randomization code, which was kept by the University of Michigan IDS. The next available randomization number was assigned by the IDS as eligible participants were identified. Participants and study personnel were unaware of the randomization list or treatment assignment. To determine if participants were blind to treatment allocation, participants were asked at their final visit which treatment they received (“ginger,” “placebo” or “don’t know”).

Adherence was assessed by weekly telephone calls, self-report, and pill counts at the end of the study. Adherence was defined as taking at least 70% of capsules as prescribed.

## Flexible Sigmoidoscopy and Tissue Collection

Two flexible sigmoidoscopies, one at baseline and the second within 24 h of the last ginger/placebo dose on Day 28 were performed. Participants were not asked to fast or to undergo any bowel cleansing preparation. Participants were placed in a left lateral decubitus position and a flexible sigmoidoscope was passed at least 15 cm above the anal sphincter and eight tissue samples were obtained. Each biopsy specimen was taken 2 cm or more from other biopsy sites in the distal sigmoid colonic mucosa by opening and pressing the biopsy forceps perpendicular to the mucosal surface with mild pressure.

## Tissue Handling and Disposition

Biopsies were frozen in liquid nitrogen and then stored at  $-70^{\circ}\text{C}$  after being placed into a sterile 1.5-mL Eppendorf tube. Biopsy samples were taken at precisely 50 s after the time the biopsy forceps were closed. Biopsies weighed approximately 5 mg and contained between 400 and 600  $\mu\text{g}$  protein. Eicosanoids assays were run in triplicate and required around 10–20  $\mu\text{g}$  of colon tissue, which is the equivalent of two biopsies.

## Analytical Methods

**Eicosanoids (PGE<sub>2</sub>, 5-HETE, 12-HETE, 15-HETE and 13-HODE)**—Eicosanoids were assayed according to previously reported methods [33,36,37] Briefly, reverse-phase LC electrospray ionization mass spectrometry (LC/MS/MS) analyses were used for quantitation of PGE<sub>2</sub>, LTB<sub>4</sub>, 5-HETE, 12-HETE, 15-HETE, and 13-HODE. LC/MS/MS analyses were performed using a Quattro Ultima tandem mass spectrometer (Micromass, Beverly, MA) equipped with an Agilent HP 1100 binary pump HPLC inlet. Eicosanoids were separated using a Luna 3  $\mu$  Phenyl-Hexyl 2 mm  $\times$  150 mm LC column (Phenomenex, Torrance, CA). The mobile phase consisted of 10 mM ammonium acetate (pH 8.5) and methanol. For the analysis of PGE<sub>2</sub>, HETEs, and 13-HODE, the separation was achieved using a linear methanol gradient from 40% to 60% over 18 min followed by a methanol flush. The flow rate was 250  $\mu\text{L}/\text{min}$  with a column temperature of  $50^{\circ}\text{C}$ . The sample injection volume was 25  $\mu\text{L}$ . Samples were kept at  $4^{\circ}\text{C}$  during the analysis. All eicosanoids were detected using electrospray negative ionization and multiple-reaction monitoring of the transition ions for the metabolites and their internal standards [38].

The mass spectrometer (Thermo Finnigan TSQ Quantum, San Jose, CA) was operated in the electrospray negative ion mode with a cone voltage of 2300 V, a cone gas flow rate of 117l/h, and a desolvation gas flow rate of 998l/h. The temperature of the desolvation region was  $350^{\circ}\text{C}$ , and the temperature of the source region was  $120^{\circ}\text{C}$ . Fragmentation for all compounds was performed using argon as the collision gas at a collision cell pressure of  $2.10 \times 10^{-3}$  Torr. The collision energy ranged from 16 to 31 V depending on the analyte. The results were either expressed as nanogram (ng) of eicosanoid per milligram (mg) of protein or as ng of eicosanoid per microgram ( $\mu\text{g}$ ) of free AA. All of the biopsy samples from a given individual were assayed in the same batch to eliminate any batch effects over time.

## Statistical Methods and Sample Size

Statistical analyses were conducted using SAS 9.2 statistical software (SAS Institute Inc., Cary, NC). A P-value  $\leq 0.05$  (two-sided) was considered statistically significant. Baseline characteristics stratified by treatment group were analyzed and reported as mean standard deviations (SD) for continuous variables, and as counts and percentages for categorical variables. Balance between treatment groups on baseline characteristics was tested using independent sample *t*-tests for continuous variables and Pearson's Chi-square and Fisher exact tests, as appropriate, for categorical variables.

We calculated the mean percent change within treatment group, for PGE<sub>2</sub>, LTB<sub>4</sub>, 5-HETE, 12-HETE, 15-HETE, and 13-HODE from baseline to Day 28. Results are reported as mean  $\pm$  SD. Pearson's Chi-square or Fisher's exact test were used to calculate between group differences for adverse events.

Assessment of blinding and adherence were determined using an independent sample *t*-test to determine the difference in the proportion of participants in each group who correctly guessed their correct group assignment or who took 70% or greater of their study medication. Mean and SD for percent adherent per group was tested using independent sample *t*-test.

We determined using a two sample *t*-test that a sample size of 10 per treatment group would have better than 80% power and a 5% level of significance to detect a reduction of at least 25% mean difference in PGE<sub>2</sub> mucosal concentration in the ginger group compared to the placebo group at the end of a 28d intervention. This is based on previously reported data on PGE<sub>2</sub> levels in participants at increased risk of CRC human colon tissue who had baseline PGE<sub>2</sub> mucosal concentrations of  $14.4 \pm 1.7$  pg/ $\mu$ g protein, which decreased after 28 d of 81 mg of aspirin to a mean concentration of  $4.7 \pm 0.70$  pg/ $\mu$ g protein which was roughly a 70% reduction compared to the placebo group [39].

## RESULTS

### Subjects and Toxicity

We screened 47 persons of whom 21 met all eligibility criteria and were randomized: 11 to placebo and 10–2.0 g ginger, for 28 d. However, one participant randomized to the placebo group was removed from study after it was determined that he was not at increased risk for CRC. Figure 1 documents the numbers of participants, reasons for exclusions and reasons for discontinuing the intervention.

Table 1 reports demographic and clinical characteristics by group. No significant differences for any demographic or clinical characteristic between treatment groups were found. The mean age of the study subjects was  $51.0 \pm 12.9$  (range 29–73 yr) with less than half of the participants being male ( $N = 7$ , 35.0%). The majority of the participants self-reported as being Caucasian ( $N = 15$ , 75.0%), with two (25%) indicating that they were African American ( $N = 2$ ), American Indian ( $N = 2$ ), or mixed race ( $N = 1$ ), while none of the participants reported being of Hispanic ethnicity. The majority of participants ( $N = 10$ , 50.0%) were at increased risk for CRC due to having had a prior adenoma ( $N = 12$ , 60.0%),

and seven subjects had a first degree relative with a diagnosis of CRC before the age of 60. Only one participant had a history of early stage colon cancer (5%), and three participants had multiple reasons (both a prior adenoma and a first degree relative) for being at increased colon cancer risk.

Possible, probably or likely treatment-related toxicities are reported by participants in Table 2. All adverse events were non-serious and reported as grade 1 per the NCI Common Toxicity Criteria (v. 4.02) [35]. No significant difference was observed between the groups for total adverse events ( $N = 13$ ,  $P = 0.06$ ) or specific categories of adverse events such as gastrointestinal (GI) toxicities ( $N = 10$ ,  $P = 0.18$ ).

### **Eicosanoids (PGE<sub>2</sub>, LTB<sub>4</sub>, 5-HETE, 12-HETE, 15-HETE, and 13-HODE)**

In Table 3, all continuous outcomes and mean percent change from baseline to Day 28 of PGE<sub>2</sub>, LTB<sub>4</sub>, 5-, 12-, 15-HETE, 13-HODE, and AA are shown normalized to both protein and AA, with the exception of AA. The baseline values of PGE<sub>2</sub>, LTB<sub>4</sub>, 5-HETE, 12-HETE, 15-HETE, and 13-HODE in colon biopsies across both groups were  $11.8 \pm 12.8$ ,  $2.60 \pm 1.7$ ,  $6.3 \pm 6.3$ ,  $2.7 \pm 1.8$ ,  $10.1 \pm 13.6$ , and  $47.2 \pm 77.5$  pg/ $\mu$ g protein, respectively (mean  $\pm$  SD,  $n = 20$ ). Baseline values normalized to AA of PGE<sub>2</sub>, LTB<sub>4</sub>, 5-HETE, 12-HETE, 15-HETE, and 13-HODE were  $1.4 \pm 1.2$ ,  $0.5 \pm 0.7$ ,  $1.9 \pm 5.0$ ,  $0.5 \pm 0.6$ ,  $1.9 \pm 3.2$ , and  $4.9 \pm 8.1$  ng/ $\mu$ g, respectively.

There was no significant difference in mean percent change between the placebo and ginger group for any of the eicosanoids when normalized to AA after 28 d. In contrast, when normalized to protein there was a significant increase ( $P = 0.04$ ) in LTB<sub>4</sub> in the ginger group ( $-4.7 \pm 54.9\%$  placebo versus  $54.0 \pm 63.2\%$  ginger) and a significant ( $P = 0.05$ ) decrease in AA in the ginger group ( $229.4 \pm 413.7\%$  placebo versus  $-44.2 \pm 41.5\%$  ginger). There were no other significant differences in the other eicosanoids.

### **Blinding and Adherence**

Participants were unable to determine whether they had received ginger or placebo ( $P = 0.53$ ). The majority of participants ( $N = 9$ , 45.0%) indicated they were taking placebo, with seven participants reporting ginger (35.0%) and four (20.0%) being unable to decide to which treatment they were randomized.

Participants on average took  $79.1 \pm 7.4\%$  of their capsules and all participants were adherent per our definition of taking at least 70% of their capsules with a mean  $\pm$  SD of  $78.4 \pm 8.6\%$  in the placebo group and  $79.8 \pm 6.6\%$  in the ginger group. There was no significant difference in adherence between treatment groups ( $P = 0.70$ ).

## **DISCUSSION**

We found that ingesting 2.0 g per d of ginger root extract for 28 d significantly decreased AA and significantly increased concentrations of LTB<sub>4</sub>, when normalized to protein, in normal appearing gut mucosa in participants who were at increased risk of developing colon cancer. Ginger had no significant effect on any other eicosanoid including PGE<sub>2</sub> in gut tissue whether normalized to protein or AA. Although not statistically significant, the

concentrations of all eicosanoids were increased, and in some cases to a large extent, in the ginger treatment group compared to the placebo group at the end of a 28d intervention using either method of normalization. Of import, however, mean percent increases in eicosanoid concentrations were accompanied by a high level of variability implying that the response to ginger was highly heterogeneous with some participants experiencing no change, others decreases in and others large increases in eicosanoid concentrations.

These findings are in contrast to previous studies in humans as well as those conducted in a rat model and in vitro. Whole ginger root and various ginger constituents have been shown to inhibit leukotriene synthesis by blocking 5-LOX activity [21,40], reduce COX-1 and COX-2 activity and subsequently reduce concentrations of PGE<sub>2</sub> in a variety of cell lines [20-22,41-47], and significantly reduce serum levels of PGE<sub>2</sub> in female Sprague–Dawley rats given 50 mg/kg ginger extract daily [27]. Our previous work in participants at normal risk for CRC showed that a 2.0 g dose of ginger root extract given for 28 d significantly reduced PGE<sub>2</sub> concentrations in colonic mucosa [33]. We also demonstrated that COX-1 protein expression was significantly reduced in participants at increased risk for CRC (those reported on, in this study), although it remained unchanged in participants at normal risk [32]. In contrast, a study by Black and colleagues saw no significant difference in plasma PGE<sub>2</sub> levels in healthy volunteers after 28 d of taking 2.0 g of either raw or heat treated ginger root [48]. Different to previous studies, but in agreement with our results, a study in 21 people with knee and hip osteoarthritis found that 28 d of ingesting a 340 mg of a standardized ginger extract (EV.EXT 35) significantly increased levels of several prostaglandins including PGE<sub>2</sub> in the stomach mucosa [49].

Differences between these various studies could be due to different doses and formulations of the ginger products, the absorption and metabolism of ginger in in vivo environments; or differential effects of ginger on different tissue types or in situations of underlying inflammation. A clear challenge with natural health products, such as ginger, is the heterogeneity of ginger preparations. A few in vitro studies have shown significant differences between various ginger constituents in impacting COX enzyme activity and PGE<sub>2</sub> production [22,42,46]. However, systematic differences in structure and function of various ginger constituents have not been examined in animal models or humans, thus making it unclear if different ginger formulations would behave differently in in vivo situations.

Underlying the importance of examining the effect of ginger in humans and on tissues of interest is the possible differential effects of ginger on different tissue cell types or in situations of underlying inflammation. While ginger and its components appear to decrease the production of inflammatory products such as PGE<sub>2</sub> and LTB<sub>4</sub>, many of these studies were conducted in isolated cell lines and quite a few in murine macrophages (RAW 264.7) using lipopolysaccharide (LPS)-elicited production of PGE<sub>2</sub>. In vitro studies such as these are useful for exploring possible mechanisms, but they do not model the complex biological interactions that occur in animals or humans. For instance the study by Drozdov and colleagues [49] found that PGE<sub>2</sub> and related eicosanoids were elevated in gastric tissue after ginger consumption and they also found an increased concentration of PGE<sub>2</sub> in the gastric mucosa.

Another interpretation of our findings, if eicosanoids are good biomarkers of CRC risk, is that ginger may not be an effective CRC prevention agent. Alternately, although a controversial idea, is that inhibition of inflammatory eicosanoids may not equate with prevention of CRC. There is a robust and growing body of evidence that NSAIDs may not act via their conventional anti-COX effects for colon cancer prevention [50]. Consequently, it may be more fruitful for future investigations to focus on ginger's effect on underlying biological pathways rather than basing ginger's evaluation on biochemistry such as eicosanoid levels. Numerous in vitro studies have shown significant impacts on various cell cycle markers [51,52]. Moreover, research in people at increased risk of CRC have demonstrated significant effects of ginger on proliferation, differentiation, and apoptosis markers [53].

This study had several limitations, which include a small sample size, a short intervention period, and a fairly large amount of variability in eicosanoid levels. This was intended to be a pilot study for a larger human trial. Thus, it is possible that extended ginger consumption and more study participants might provide additional power to detect the effects of dietary ginger root intake on various prostaglandin pathways. Further, the small sample size did not allow us to conduct additional subgroup analyses by risk type, for example, family history, previous adenoma, previous CRC nor by sociodemographic variables such as age, race, and gender. This study would need to be further replicated in larger trials, which would have adequate power to examine several independent groups defined by baseline colonic mucosal eicosanoid concentrations to account for the presence of low levels of inflammation. Also, future studies may need to focus on outcomes with less variability than tissue eicosanoids such as proliferation, differentiation, and apoptosis markers, which have already been demonstrated to be significantly affected in humans by ginger [53].

In summary, 28 d of supplementation with ginger root extract in participants who were at increased risk for CRC caused a significant decrease in normal colonic mucosa of AA and significantly increased concentrations of LTB<sub>4</sub>, when normalized to protein. Ginger had no significant effect on any other eicosanoid including PGE<sub>2</sub> in colon tissue whether normalized to protein or AA. Ginger did increase eicosanoids other than PGE<sub>2</sub>, as compared to placebo, when normalized to either AA or protein, but these increases were not statistically significant. Future, larger studies with ginger supplementation should perhaps focus on other biomarker outcomes.

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## Abbreviations

<b>CRC</b>	colorectal cancer
<b>COX</b>	cyclooxygenase
<b>PGE<sub>2</sub></b>	prostaglandin E <sub>2</sub>
<b>LTB<sub>4</sub></b>	leukotriene B <sub>4</sub>
<b>13-HODE</b>	13-hydroxy-octadecadienoic acids
<b>5-, 12-, &amp; 15-HETE</b>	5-, 12-, & 15-hydroxyeicosatetraenoic acid
<b>AA</b>	arachidonic acid
<b>AE</b>	adverse events
<b>NSAIDs</b>	non-steroidal anti-inflammatory drugs
<b>COX-1 &amp; 2</b>	cyclooxygenase 1 & 2
<b>LOX</b>	lipoxygenase
<b>5-, 12-, &amp; 15-LOX</b>	enzymes
<b>HETEs</b>	hydroxyeicosatetraenoic acids
<b>MCRU</b>	University of Michigan Clinical Research Unit
<b>IDS</b>	Investigational Drug Service
<b>NCI</b>	National Cancer Institute
<b>LC/MS/MS</b>	reverse-phase LC electrospray ionization mass spectrometry
<b>ng</b>	nanogram
<b>mg</b>	milligram
<b>µg</b>	microgram
<b>SD</b>	standard deviations

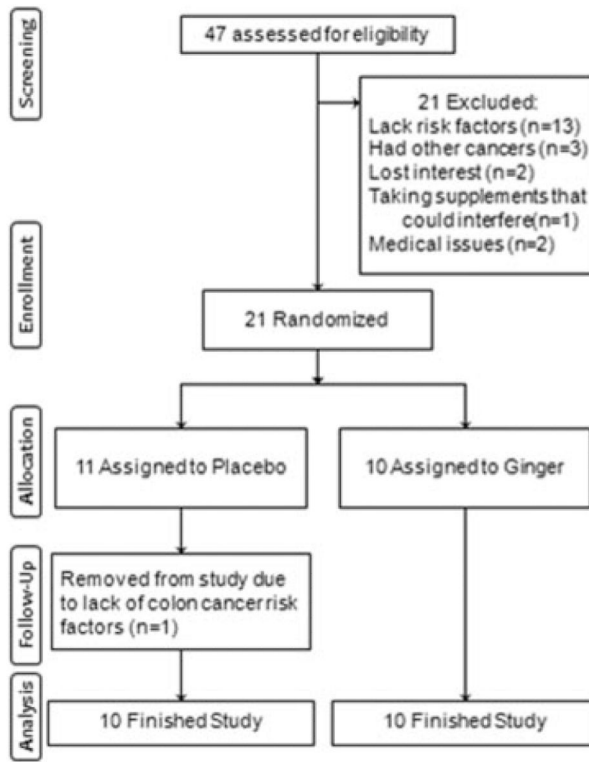
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**Figure 1.** Flow diagram of a trial of ginger supplementation over 4 wk on eicosanoids in normal-appearing colorectal mucosa of individuals at increased risk of for colorectal cancer

**Table 1**

## Baseline Characteristics of the Randomization Groups

Characteristics	Ginger (N = 10)	Placebo (N = 10)	P-value
Sex, no. (%)			
Men	4 (40)	3 (30)	0.64 <sup>a</sup>
Women	6 (60)	7 (70)	
Race, no. (%)			
White	8 (80)	7 (70)	0.38 <sup>a</sup>
Age, mean (SD), yr	51.1 (11.7)	50.8 (14.6)	0.95 <sup>b</sup>
Reason for being high risk for CRC <sup>c</sup> , no. (%)			
First degree relative <sup>d</sup>	4 (40.0)	6 (60.0)	0.47 <sup>b</sup>
Previous adenoma	5 (50.0)	4 (40.0)	
Previous CRC	1 (10.0)	0 (0.0)	

<sup>a</sup>P-value is based on an independent samples *t*-test.

<sup>b</sup>P-value is based on a Chi-Squared.

<sup>c</sup>CRC, colorectal cancer.

<sup>d</sup>First degree relative diagnosed with colorectal cancer before the age of 60 yr.

**Table 2**

## Adverse Events Reported by Person

Adverse Events	Ginger (n = 10)	Placebo (n = 10)	P-value <sup>a</sup>
All participants with any AE, No. (%)	9 (90.0)	4 (40.0)	0.06
CGI <sup>b</sup>	7 (70.0)	3 (30.0)	0.18
Other <sup>c</sup>	3 (30.0)	1 (10.0)	0.58

<sup>a</sup>P-value: Chi-Square or Fisher's exact test as appropriate.

<sup>b</sup>GI symptoms includes: bloating, urgency, gas, nausea, heartburn, sores in mouth & anorexia.

<sup>c</sup>Other includes: allergic reaction, nose bleed, skin rash, struck with water tube after biopsy procedure.

**Table 3**

Eicosanoids Levels in Normal Mucosa in Participants at Increased Risk for Colorectal Cancer [Mean (SD)\*]

Eicosanoid	Placebo (n = 10)			Ginger (n = 10)			P-value <sup>a</sup>
	Baseline	After 28 d	Mean % change <sup>b</sup>	Baseline	After 28 d	Mean % change <sup>b</sup>	
Standardized to protein (pg/μg)							
PGE <sub>2</sub>	12.9 (15.2)	12.8 (16.8)	37.0 (113.4)	10.6 (10.5)	23.6 (21.2)	333.5 (773.6)	0.26
LTB <sub>4</sub>	2.9 (1.7)	2.6 (2.1)	-4.7 (54.9)	2.4 (1.9)	3.5 (2.3)	54.0 (63.2)	0.04
HETE5	8.9 (8.0)	9.0 (8.0)	39.1 (108.9)	3.7 (2.0)	15.2 (14.0)	412.1 (755.6)	0.16
HETE12	3.2 (2.2)	5.1 (5.5)	59.4 (149.1)	2.2 (1.3)	4.5 (4.4)	101.7 (196.1)	0.60
HETE15	14.7 (17.7)	11.1 (9.8)	82.1 (189.5)	5.5 (5.6)	20.6 (18.8)	602.5 (1047.8)	0.16
HODE13	41.4 (50.8)	30.9 (22.0)	27.7 (105.2)	53.0 (100.1)	35.0 (32.6)	55.7 (122.4)	0.59
AA (ng/pg) <sup>c</sup>	1.0 (1.3)	1.4 (1.4)	229.4 (413.7)	1.6 (1.1)	0.7 (0.4)	-44.2 (41.5)	0.05
Standardized to arachidonic acid (ng/μg)							
PGE <sub>2</sub>	1.7 (1.4)	3.70 (8.4)	147.6 (368.7)	1.0 (1.0)	3.0 (2.9)	1149.2 (3194.5)	0.17
LTB <sub>4</sub>	0.7 (1.0)	0.34 (0.3)	84.3 (205.9)	0.2 (0.2)	0.5 (0.4)	173.8 (248.9)	0.27
HETE5	3.4 (6.9)	1.72 (2.5)	362.7 (718.9)	0.4 (0.3)	2.4 (3.7)	1079.6 (2297.0)	0.15
HETE12	0.7 (0.7)	0.57 (0.5)	247.1 (598.9)	0.2 (0.1)	0.6 (0.7)	279.2 (487.4)	0.38
HETE15	3.3 (4.1)	2.00 (3.2)	290.6 (545.8)	0.5 (0.5)	3.2 (5.2)	1406.3 (2993.3)	0.13
HODE13	6.8 (10.9)	4.98 (6.3)	140.5 (453.7)	3.1 (3.4)	4.4 (4.5)	114.1 (164.02)	0.23

\* SD, ±standard deviation.

<sup>a</sup> independent *t*-test of the difference between the mean percent change from baseline to Day 28.

<sup>b</sup> Mean percent change between baseline and Week 4 is calculated as [(eicosanoid at time 2/eicosanoid at time 1)/eicosanoid at time 1] per participant and then an average is obtained. Mean percent change may not appear reflective of change in baseline and 28-d follow-up mean values. This is due to the large amount of variability in the baseline measures.

<sup>c</sup> AA, arachidonic acid; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; 5-HETE, 12-HETE, 15-HETE, 5-, 12- & 15-hydroxyeicosatetraenoic acid; 13-HODE, 13-hydroxy-octadecadienoic acids.