A review on ginger (*Zingiber officinale*): Pre-clinical and clinical trials

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Received 7 February 2002; revised September 2002

Ginger (*Zingiber officinale*) is used in folk medicine for relief from many ailments, especially nausea, motion sickness, and other gastrointestinal disorders. This paper reviews various aspects of ginger, like chemical constituents, different pharmacological activities, which have been proved in pre-clinical and clinical trials along with its therapeutic uses and side effects.

**Keywords:** *Zingiber officinale*, Ginger, Gingerols, Motion sickness

Ginger consists of the fresh or dried rhizomes of *Zingiber officinale* Rosc. The English botanist William Roscoe (1753-1831) gave the plant the name *Zingiber officinale* in an 1807 publication. The ginger family is a tropical group especially abundant in Indo-Malaysia, consisting of more 1200 species in 53 genera. The genus *Zingiber* includes about 85 species of aromatic herbs from East Asia and tropical Australia.

**Description**

Ginger is native to the coastal regions of India and the name *Zingiber* is derived from a Sanskrit term used to describe a horn-shaped object. A perennial with a thick tuberous rootstock, *Z. officinale* has an annual shoot with simple, alternate, lanceolate leaves, and greenish-purple flowers. The rhizome is aromatic and is the source of the dried powder spice. Ginger is naturalized in Jamaica, China, Africa, and the West Indies, and is cultivated in these countries.

**History and traditional uses**

Ginger has been used for millennia in both China and India and reached the West at least two thousand years ago, and recorded as a subject of a Roman tax in the second century after being imported via the Red Sea to Alexandria. Tariff duties appear in the records of Marseilles in 1228 and in Paris by 1296. Ginger was known in England before the Norman
Conquest, as it is commonly found in the 11th century Anglo-Saxon leech books. Ginger is detailed in a 13th century work, "Physicians of Myddvai," a collection of recipes and prescriptions written by a physician, Rhiwallon, and his three sons, by mandate of Rhys Gryg, prince of South Wales (who died in 1233). By the 13th and 14th centuries it was familiar to English palates, and next to pepper, was the most popular spice. Ginger, as a product of the Far East, was indelibly imprinted on the taste buds of Westerners before potatoes, tomatoes, and corn were even known to Europeans. Ginger has been cultivated in India since well before written history, and the Chinese documented its use as early as 400 BC. Ginger is valued all over the world for its flavour and as a spice in food dishes. Traditionally, ginger has been used in folk medicine for indigestion, flatulence, diarrhoea, malaria and fever. In China, ginger is used to detoxify meat, applied externally to relieve inflamed joints, and taken for gastrointestinal distress.

Chemistry
The most notable chemical constituents in ginger are the so-called "pungent principles", the gingerols, which give ginger its characteristic aroma. Also present are volatile oils, other oleoresin compounds, and starches, proteins, and fats. The oleoresin contains the pungent principles as well as some non-pungent compounds. The pungent constituents comprise about 33% of the oleoresin and are called the gingerols, which are a series of homologous phenols with 6-gingerol (5-Hydroxy-1-(4'-hydroxy-3'-methoxyphenyl)-3-decanone) being most common. Also pungent, but comprising a much smaller fraction of the oleoresin, are the shogaols. These anhydro-gingerols are formed during the drying of ginger. Other minor pungent compounds are paradols, gingediols, gingediacetates, gingerdiones, and gingenones. Oleoresin is about 25% volatile oil. The steam-distilled oil contains terpenoids, which usually include sesquiterpene hydrocarbons and monoterpenic hydrocarbons. Other principal components include zingiberene, ar-curcumene, sesquipellandrene, and bisabone. When ginger is stored, the amount of ar-curcumene increases and zingiberene and sesquipellandrene decrease. Ginger also contains starch, lecithins and phosphatidic acid, saturated fatty acids (lauric, palmitic, and stearic), unsaturated acids (linoleic and oleic), and proteins.

Therapeutic applications
Studies indicate that the rhizome of ginger possesses the following activities: anti-emetic; promotes secretion of saliva and gastric juices; cholagogue; anti-inflammatory; carminative; spasmolytic; molluscicidal; antischistosomal; peripheral circulatory stimulant; and increases tone of and peristalsis in intestines. Ginger is valued in traditional medicine for other gastrointestinal disorders, though studies need to be performed to confirm these actions.

Toxicity in animal models
There is no reported LD₅₀, because it has been impossible to feed lab rodents a
sufficient amount of crude ginger to induce death. Doses of 3.0 g/kg and 3.5 g/kg of an ethanolic extract of ginger rhizome produced death by involuntary contractions of skeletal muscle in 10-30% of laboratory mice within 72 hours of administration. The LD$_{50}$ of the main active constituents is 250-680 mg/kg for 6-gingerol and 6-shogaol, which is 3,500 to 9,000 times the normal adult human dose.

**PRE-CLINICAL STUDIES (Animal model/in vivo study)**

**Digestive, hepatic, and gastrointestinal functions**

**Gastric functions**

Ginger has been shown in clinical trials to be effective in minimizing the effects of motion sickness, with some indications that it may be more effective than dimenhydrinate (Dramamine). In contrast to dimenhydrinate, which is central nervous system-active, the effectiveness of ginger has been explained according to its ability to neutralize gastrointestinal toxins and acids, thereby slowing feedback from the stomach to nausea centers in the brain. The study carried out identified active anti-emetic constituents of a methanolic extract of ginger in copper sulfate pentahydrate-induced nausea in leopard and randid frogs as [6]-, [8]-, and [10]-gingerols and as [6]-, [8]-, and [10]-shogaols; the latter prolonging emetic latency more than any other (146.8% prolongation from 20 mg/kg p.o.).

**Cardiovascular and circulatory functions**

**Cardiotonic; cardioprotection**

Studies investigating the role of gingerol in heart function have shown that gingerols increased cardiac activity. [8]-Gingerol (gingerol), produced a concentration-dependent positive inotropic effect on guinea pig isolated left atria at concentrations of $1 \times 10^{-6}$ to $3 \times 10^{-5}$ M. Gingerol also exhibited positive inotropic and chronotropic effects on guinea pig right atria. The cardiotonic properties of ginger were evaluated on the isolated atria of a sacrificed guinea pig. It was discovered that ginger had a positive inotropic effect on the atria. Gingerol may provide a valuable chemical tool for studies aimed at clarifying the regulatory mechanisms of SR Ca$^{2+}$-pumping systems and the causal relationship between the Ca$^{2+}$-pumping activity of SR and muscle contractility.

**Thrombosis, hemostasis, and embolism**

Gingerol exhibits a concentration-dependent (0.5-20 μM) inhibition of platelet aggregation in rabbit platelets against collagen and arachidonic acid in vitro, but not against platelet-activating factor- or thrombin-induced aggregations. At the same concentrations, gingerol dose-dependently inhibited the release of prostaglandin D2 and thromboxane B2 formation elicited by arachidonic acid. In platelet-rich human plasma, primary aggregation was not inhibited by gingerol (5μM), but aggregation secondary to adrenaline and adenosine 5'-diphosphate.
was prevented, and the release of adenosine triphosphate (ATP) induced by the latter agents was blocked. The authors concluded that the platelet aggregation-inhibitory activity of gingerol is the result of arachidonate metabolism-inhibition and secondary inhibition of thromboxane formation\textsuperscript{16}.

**Immune functions; inflammation and disease**

**Cancer**

**Chemotherapy adjunct treatments**

Since the cancer chemotherapy agent cisplatin inhibits the gastric emptying rate and causes vomiting and nausea, ginger juice, an acetone extract of ginger, and a 50% ethanolic extract were used to test for anti-emetic activity against cisplatin-induced gastric emptying rates in rats. The delay in gastric emptying induced by cisplatin (10 mg/kg i.p.) was significantly reversed by 30 min. pre-administration of the acetone extract (200 and 500 mg/kg p.o.), at a rate similar to that of ondansetron (10 mg/kg p.o.), a 5-HT\textsubscript{3} receptor antagonist, compared to the control. The cisplatin-induced delay in gastric emptying was more significantly ameliorated by pre-administration of ginger juice (4 mL/kg p.o., \(p<0.001\)) than ondansetron (3 mg/kg p.o., \(p<0.01\)). The 50% ethanol extract was comparatively less effective at reversing the delay in gastric emptying induced by cisplatin than either the acetone extract or the juice (significant only at 500 mg/kg p.o.). Based on studies proposing the involvement of free radical-induced release of serotonin and an antiserotonergic effect of ginger acetone extract, the study summarized that either a free radical scavenging or an antiserotonergic mechanism may account for the reversal activities of ginger seen in their own study\textsuperscript{17}.

**Chemopreventive activity**

The carcinogenesis-inhibiting (chemopreventive) activity of a methanol extract of ginger was studied in a skin tumorigenesis model in mice. Topical application of the extract on the skin of mice subsequently exposed to the tumour inducer TPA (12-\textit{O}-tetradecanoylphorbol-13-acetate) resulted in significant inhibition of tumour development and multiplication. TPA-induced tumorigenesis was significantly inhibited (\(p<0.0005\)) by the ginger extract (2 mg/mouse; 56% inhibition). The same dose significantly inhibited TPA-induced cyclooxygenase (\(p<0.0005\)) and lipoxygenase activity (38-72% inhibition)\textsuperscript{18}.

**Inflammatory response**

Jana et al demonstrated that ginger (100 mg/kg) was as effective as acetylsalicylic acid (100 mg/kg) in reducing carrageenin induced oedema in rats. However this dose of ginger also reduced inflammation, it was not as effective as phenylbutazone\textsuperscript{19}. Similar results for the anti-inflammatory and analgesic activities of ginger were reported by Mascolo et al\textsuperscript{5}. It is thought that these anti-inflammatory actions are a result of inhibition of prostaglandin release, and hence ginger may act in a similar fashion to other non-steroidal anti-inflammatory drugs, which interfere
with prostaglandin release or biosynthesis.

Infectious diseases

Parasitic infections

The effect of ginger constituents [6]-shogaol and [6]-gingerol were examined on the pathogenic parasite Anisakis, the larvae of which are found in raw tuna, cuttlefish, halibut, mackerel, cod and other fish. The authors suggested that the popularity of Japanese cuisine in the West in which raw fish is a main dish would lead to a corresponding increased incidence of infection by the parasite. Therefore, garnishes such as ginger, which are traditionally eaten with raw fish in Japanese cuisine, need to be examined for potential anti-Anisakis activity. Following their finding that an extract of ginger could kill the larvae of Anisakis, fractions of a methanolic extract of ginger were tested to determine the most active constituents involved. Since the pungent fraction was most effective (100% lethality at 1% concentration), they tested the pungent principles [6]-shogaol and [6]-gingerol. With 100% lethality to Anisakis larvae, [6]-shogaol (62.5 µg/mL) showed 4 times the potency of [6]-gingerol. While the amount of [6]-gingerol in the methanolic extract of ginger was not sufficient to be lethal to the larvae, close to that amount (50 µg/mL) with the addition of a small amount of [6]-shogaol (2.5 µg/mL) appeared to act synergistically; 23.8% of the larvae were killed and spontaneous movements were halted in 100%20. The residues from a 50% ethanol/water extract of the rhizome were used to treat dogs naturally infected with filariasis from Dirofilaria immitis. The microfilarial count was reduced by 98% after the last treatment phase and rose slowly there after. At 55 days post-treatment (100 mg/kg s.c., 1x/day for 4 daysx3 with 7-day gaps), the microfilarial count was still reduced by 83%21.

CLINICAL STUDIES

Digestive, hepatic, and gastrointestinal disorders

Gastric disorders

Ginger as an antinauseant and antiemetic

In a randomized double blind study, Riebenfeld and Borzone examined the comparative efficacy and tolerability of a standardized ginger root powder extract (Zintona® standardized to pungent phenolic compounds) and dimenhydrinate in identical marked capsules. Effectiveness of the ginger extract was rated very good (n=21) or good (n=7) in most cases. A similar result was shown in the dimenhydrinate group (n=15 and n=12, respectively). Total motion sickness mean scores revealed that dimenhydrinate was slightly more effective compared to the ginger group, although the difference was not statistically significant22.

A double blind comparative study of ginger root powder extract (Zintona®) and dimenhydrinate was conducted in 10 girls and 18 boys aged 4-8, all sensitive to motion sickness. There was an underlying significant difference between the two groups in terms of general sensitivity to
nausea and vomiting; the ginger group having had a greater tendency in the past to experience motion sickness, whether on a bus, train, airplane, or merry-go-round. In this, the first test of ginger against motion sickness in children, Careddu pointed out that total relief of symptoms by any motion sickness agent is unheard of, and that owing to the study design he "may well have missed partial successes". In short, he concluded that the study offered some indication that ginger is effective in ameliorating symptoms of motion sickness in children.

Phillips and team had pointed out that the incidence of side effects from anti-emetic medications is significant, and reported the results of a placebo-controlled, double blind, randomized crossover trial of powdered ginger root in 16 volunteers aged 18 years plus, all in good health. The ginger powder was administered in 500 mg capsules and the placebo was indistinguishable in appearance, smell, and taste. While no adverse effects were reported of any kind, one gram of ginger ingested at the same time as paracetamol had no effect on the gastric absorption rate compared to placebo. In a blinded fashion, placebo, ginger, or metoclopramide (10 mg) was administered in the form of two capsules per subject in each of 3 respective groups prior to anesthesia (atracurium following propofol and fentanyl). Although no assessment was made of nausea severity, the researchers found ginger significantly superior to placebo \( p = 0.006 \) in reducing nausea, whereas the anti-nausea effect of metoclopramide compared to ginger was insignificant. The superior benefit of ginger was apparent in the number of patients who required anti-emetics: placebo, 38%; metoclopramide, 32%; and ginger, 15%. Adverse effects were of very low incidence and showed no difference in occurrence between the study groups. Ginger was compared to metoclopramide and a placebo for anti-emetic activity in 60 women who had undergone major gynecological surgery. The study was randomized and double blinded. The incidence of nausea in the two groups given either ginger or metoclopramide was similar, although there were significantly fewer recorded instances of nausea in the groups that received ginger compared to the placebo group. In another controlled double blind study, Holtman et al found that ginger root had no influence on artificially induced nystagmus in test subjects, which is consistent with its reported lack of action on the central nervous system.

In a double blind study, a group of 80 naval cadets were recruited, each of who was given either 1 gram of powdered ginger or a placebo while at sea. Symptoms of nausea were recorded once an hour during 4 hours following treatment administration. Symptoms in the ginger group were 38% less than in the placebo group. A study was conducted with 36 patients with histories of severe motion sickness. Each received either a placebo, 100 mg of dimenhydrinate, or 940 mg of powdered ginger. A half-hour later they were blindfolded and spun in a mechanical chair until the individual asked to stop, or vomited. On an average, the ginger group...
remained in the chair for 5.5 minutes, versus 3.5 minutes for those who received dimenhydrinate, and 1.5 minutes for the placebo group. A double-blind randomized clinical trial was conducted to investigate the effect of ginger on the nausea and vomiting following gynaecological laparoscopic surgery. Both 0.5 and 1.0 g ginger were effective in reducing nausea, with only the higher dose being effective at reducing vomiting. In contrast, one study found that 2 g ginger was ineffective in preventing the post-operative nausea and vomiting associated with diagnostic gynaecological laparoscopy. Since it is well known that different anesthetics have varying potential to produce post-operative nausea and vomiting it is possible that these varying responses are a result of the varying mechanisms by which different anaesthetics produce nausea and vomiting.

Suekawa and group reported that 6-gingerol and 6-shogaol suppressed gastric contraction but increased gastrointestinal motility and spontaneous peristaltic activity in laboratory animals. Ginger has been suggested as suitable for relieving the gastrointestinal effects of cancer chemotherapy. Sharma and his colleagues found that only acetone and ethanolic, but not aqueous, extract of ginger were effective against cisplatin induced emesis but not emesis due to apomorphine. However in the former case ginger was less effective than 5-hydroxytryptamine-3 (5-HT₃) antagonists.

As apomorphine acts primarily by direct stimulation of the central chemoreceptive trigger zone while cisplatin acts directly in the gastrointestinal tract it is thought that ginger may act by increasing gastrointestinal motility reducing the feedback from the gastrointestinal tract to the central chemoreceptors. Further support for this notion comes from studies investigating the effectiveness of ginger on nausea associated with motion. When ginger was compared to scopolamine (0.6 mg), neither powdered (500 mg and 1g) or fresh ginger (1g) proved useful in preventing motion sickness. Other studies have also failed to show an effect on either motion or seasickness. It would then seem likely that although ginger is effective when the symptoms of nausea and vomiting are gastrointestinal in origin, it is of little benefit when the symptoms are either vestibular in origin, as in motion sickness, or when they are central in origin, as in opioid induced emesis.

Another use for ginger's antinauseant properties has been in the treatment of morning sickness. Double-blind randomized cross-over trial found that 1g/day ginger was effective in reducing the symptoms of morning sickness and did not appear to have any side effects or adverse effects on pregnancy outcome. Never the less, of the alternative therapies cited ginger did appear to have the most promise as a safe, effective treatment. Jewell and Young found similar results in their Cochrane report on "Treatments for nausea and vomiting in early pregnancy". These authors also concluded that...
although there may be some benefit from ginger, the evidence thus far is weak\textsuperscript{37}. While ginger does appear to be an effective anti-nauseant in these instances there is some doubt as to its safety. Backon has suggested that ginger may affect binding of testosterone to its receptor and, when this occurs \textit{in utero}, may alter steroid dependent differentiation. As yet no supporting evidence for this has been published\textsuperscript{38}. Several sources including the American Herbal Products Association advise against the use of therapeutic doses of ginger during pregnancy unless advised to do so by a health care professional\textsuperscript{39}. It should also be noted that in general non-medical/scientific information sources were found to be contradictory and information, and therapeutic recommendations, unsupported by original research findings.

It would seem then that while ginger is effective for postoperative, chemotherapy and other gastrointestinal induced nausea there is still further research required to determine whether ginger is safe to use in pregnancy.

\textbf{Inflammatory response}

In Indian Ayurvedic medicine ginger is used as an anti-inflammatory compound and it has been suggested that ginger may be useful as a treatment for arthritis and a number of commercial preparations are available for this use. For example Bio-
Organics Arthri-Eze Forte (Bullivants, Aust.) and Extralife Artri-Care (Felton Grimwade & Bickford Pty Ltd, Aust.) are marketed as arthritis treatments and contain 500 mg dried, powered ginger rhizome. Srivastava and Mustafa found that more than 75\% of patients receiving 3-7 g powered ginger daily for 56 days had a significant reduction in pain and swelling associated with either rheumatoid or osteoarthritis. No adverse effects were reported from these chronic uses of relatively high doses of ginger. These results are also supported by research investigating the anti-inflammatory actions of ginger\textsuperscript{30}.

\textbf{Dosage}

Approximately one gram of powdered dried root per day has been used and recommended as an anti-emetic. This seems to be an effective and safe dose\textsuperscript{41}. Other studies have used extracts or the fresh root, although the powdered root is considered more potent\textsuperscript{2,6,42}.

\textbf{Safety profile}

\textbf{Pregnancy and lactation}

In Chinese medicine, ginger is recommended at low doses (about one gram/day) for morning sickness. However, in Germany it is contraindicated in pregnancy because of the hypothesis that ginger may inhibit testosterone binding. This is an untested hypothesis, and there is no evidence from any study to support it. Furthermore, there are no reports of miscarriage or birth defects from ginger, but caution should be exercised. A recent clinical study of women hospitalized for severe morning sickness (\textit{Hyperemesis gravidarum}) found ginger to be useful in 70\% of the women, and no side effects were reported\textsuperscript{34}. The use of ginger during
pregnancy is probably safe, but if symptoms develop a physician should be consulted. The safety of ginger use during lactation is unknown.

**Side effects**

In a double blind study of a standardized ginger extract (Zintona, 500 mg every 4 hours for two days) in adults known to have sensitivity to motion sickness, side effects were reported by 13.3% of participants in the ginger group. These were somnolence in 3 and headache in one, both of which could have occurred from motion sickness rather than the ginger extract. No side effects were reported in a double blind study of motion sickness sensitive children (ages 4-8) taking 250 mg of a standardized ginger root extract every 4 hours or as needed over two days. Overdosage could potentially appear in central nervous system problems or cardiac arrhythmias.

**Special precautions**

Although studies thus far have shown ginger to be relatively safe, it is a strong thromboxane synthetase inhibitor and prostacyclin agonist; therefore, post-operative patients taking ginger as an anti-emetic should be monitored closely.

**Toxicology**

**Mutagenicity**

Surh and team had reviewed the mutagenic studies of ginger and ginger constituents. They noted that in one study an ethanolic extract of the rhizome showed mutagenic activity (in *Salmonella typhimurium* TA102 and TA98) without metabolic activation; another found no mutagenic activity from ginger extract and a third found that genotoxicity elicited by several carcinogens was suppressed by ginger extract in mammalian and bacterial cells. Yamamoto *et al* (1982), using a modified Ames test with *S. typhimurium* TA100 and TA98, found no mutagenicity from a water and methanol extract of *Zingiber*, but did from an extract of *Zingiber siccatum rhizoma*. The former name refers to the fresh rhizome while that of the latter is given to the dried rhizome. The difference may owe to the presence of contaminants or to the balance of mutagenic and anti-mutagenic constituents of the two rhizome samples; shogaol and gingerol have shown mutagenic activity in the Ames test, whereas zingerone has been shown to dose-dependently suppress their mutagenic activity.

**Conclusion**

The efficacy of ginger has been established by results of various preclinical and clinical trials in different conditions carried out in different centres. Proper double blind clinical trials with standardized extract containing gingerols and other active ingredients present in extract need to be undertaken to confirm its efficacy in various conditions. These studies would give a special place for ginger product as a digestive, anti-emetic, anti-arthritic/anti-inflammatory, anti-platelet aggregation and in parasitic infection in future.
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