

Can nausea and vomiting be treated with ginger extract?

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Abstract. – Ginger (*Zingiber officinale*) is a spice traditionally used to treat indigestion, nausea and vomiting. Ginger extracts accelerate gastric emptying and stimulate gastric antral contractions. These effects are mainly due to the presence of gingerols and shogaols and their activity on cholinergic M receptors and serotonergic 5-HT and 5-HT receptors. Various researches on this subject have led to controversial results, due to the chemical instability of ginger extracts and particularly of gingerols, which are readily-oxidizable substances. A systematic review of double-blind, placebo-controlled, randomized studies highlighted the potential efficacy of ginger on the prevention and treatment of nausea and vomiting of various origins, even though additional controlled studies are needed. This review focuses on pregnancy-induced nausea and vomiting and on chemotherapy induced nausea, and hypothesizes a therapeutic role for ginger extracts in case of side effects, as an alternative to traditional prokinetic drugs such as domperidone, levosulpride or metoclopramide.

Key Words:

Ginger, Gingerols, Prokinetic drugs, Nausea, Vomiting, Gastric motility, Zingiber officinale.

Introduction

Ginger (*Zingiber officinale*) is a plant that has been cultivated and used for centuries for health purposes: its medical use is well described in Chinese treaties from 400 BC. Ginger is known everywhere as a spice and traditionally used as a medicinal plant to treat indigestion, flatulence, fever, nausea and vomiting. The plant rhizome is included in different pharmacopeias. Recent clinical studies confirmed many of these activities,

but the results are controversial because of the well-known chemical instability of ginger most active ingredients, gingerols, which are readily-oxidizable substances.

Ginger consists of the dried, whole cut rhizome of *Zingiber officinale Roscoe*, with the cork removed either completely or from the wide flat surfaces only. Whole or cut, it contains not less than 15 ml/kg of essential oil, calculated with reference to the anhydrous drug¹.

The essential oil of ginger (0.25-3.3% V/m)²⁻⁵ contains monoterpenes – mainly geranial (citral a) and neral (citral b) – and sesquiterpenes (30.7%) – mainly Beta-sesquiphellandrene, Beta-bisabolene, ar-curcumen and alpha-zingiberene⁴⁻⁶. Moreover, pungent principles (4.7-5% w/w)⁷ consisting of gingerols, shogaols and related phenolic ketone derivatives can be found⁸⁻¹¹. Other constituents include diarylheptenones¹², diterpenes^{13,14}, 6-gingsulphonic-acid¹⁵ and monoacyldigalactosyl glycerols¹⁵.

Mechanism of Action of Ginger Extracts

The herbal drug ginger (*Zingiber officinale Roscoe*) may be effective for treating nausea, vomiting and gastric hypomotility. Cholinergic M³ receptors and serotonergic 5-HT³ and 5-HT⁴ receptors are involved in these conditions. The major chemical constituents of ginger are 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol. Pertz et al¹⁶ studied the interaction of 6-gingerol, 8-gingerol, 10-gingerol (racemates) and 6-shogaol with guinea pig M³ receptors, guinea pig 5-HT³ receptors and rat 5-HT⁴ receptors. In whole segments of guinea pig ileum (bioassay for contractile M³ receptors), 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol slightly but significantly depressed the maximal carbachol response at an

antagonist concentration of 10 μ M. In the guinea pig myenteric plexus preparation (bioassay for contractile 5-HT³ receptors), the 5-HT maximal response was depressed by 10-gingerol from 93 \pm 3% to 65 \pm 6% at an antagonist concentration of 3 μ M and to 48 \pm 3% at an antagonist concentration of 5 μ M, following desensitization of 5-HT⁴ receptors and blockade of 5-HT¹ and 5-HT² receptors. 6-Shogaol (3 μ M) induced depression to 61 \pm 3%. In rat esophageal tunica muscularis mucosae (bioassay for relaxant 5-HT⁴ receptors), 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol (2-6.3 μ M) showed no agonist effects. The maximal 5-HT response remained unaffected in the presence of these compounds. It can therefore be concluded that the efficacy of ginger in reducing nausea and vomiting may be based on a weak inhibitory effect of gingerols and shogaols on M³ and 5-HT³ receptors. 5-HT⁴ receptors, which play a role in gastroduodenal motility, do not appear to be involved in the activity of these compounds.

Another study¹⁷ suggests that 6-, 8-, 10-gingerol and 6-shogaol exert their anti-emetic effect at least partly by acting on the 5-HT³ receptor ion-channel complex, probably by binding to a modulatory site distinct from the serotonin binding site. This may lead to indirect effects in the signal cascade behind the 5-HT³ receptor channel complex, through receptors such as substance P and muscarinic receptors. However, this hypothesis needs further investigation since ginger is effective against motion sickness which is treated by some vanilloids and by anticholinergics such as scopolamine.

Ginger preparations have a long history of human use for their anti-inflammatory properties. However, only recently some of the compounds responsible for this activity and their mechanisms of action have been identified. 6-Shogaol exhibited the most potent antioxidant and anti-inflammatory properties: these effects can be attributed to the presence of alpha,beta-unsaturated ketone moiety¹⁸. The carbon chain length also plays a significant role in making 10-gingerol the most potent among all the gingerols.

Van Breemen and Tao¹⁹ provided information regarding the identification of gingerol-related compounds that have anti-inflammatory activity through the specific inhibition of COX-2. According to these data, although the enzyme inhibitory activities observed are weak, at least some gingerol-related compounds, including gingerols and shogaols, selectively inhibit the in-

ducible form of cyclooxygenase COX-2, but not the constitutive form COX-1. Since inhibition of COX-1 is associated with gastrointestinal side effects, selective inhibition of COX-2 should help minimize these side effects.

Gastric Motility

Great attention has always been paid to the anti-nausea effect of ginger extracts, while very few studies have been conducted about the effects of ginger on gastric emptying and gastrointestinal motility before and after meals. Micklefield et al²⁰ investigated the effects of a ginger extract (100 mg, corresponding to 2 g of rhizome twice a day) on gastroduodenal motility in a double-blind, randomized, placebo-controlled trial on a group of 12 volunteers, by using the manometric technique. In this study, a statistically significant increase in interdigestive motility was observed in the intervention group in comparison with the placebo group.

Other studies demonstrated a prokinetic effect of ginger extracts, in agreement with the indications of popular medicine. Wu et al²¹ showed that ginger accelerates gastric emptying and stimulates antral contractions in healthy volunteers. Twenty-four healthy volunteers were studied in a randomized double-blind trial²¹. After ingestion of 1200 mg of ginger extract or placebo, followed after 1 h by 500 ml of low-nutrient soup, the antral area, the fundus area and diameter, and the frequency of antral contractions were measured using an ultrasound technique at frequent intervals over 90 min. The antral area decreased more rapidly ($p < 0.001$) and the gastric half-emptying time was shorter after ginger than after placebo ingestion; whereas the frequency of antral contractions was greater in the ginger group vs the placebo group²¹. Fundus dimensions did not differ between the two groups, and there was no significant difference in any gastrointestinal symptoms²¹.

A similar experiment has been performed in patients with functional dyspepsia. The study²² has been conducted including 11 patients with functional dyspepsia, Gastric emptying was faster after ginger than after placebo. There was a trend towards more antral contractions, but fundus dimensions and gastrointestinal symptoms did not differ between the two groups, nor did serum concentrations of GLP-1, motilin and ghrelin. It is important to underline that different types of functional dyspepsia were not specifically considered in this study and that the number of studied patients was very small (11 patients).

Based on these experiences it can be concluded that the effects of ginger extracts on gastric motility appear interesting and promising, but have still to be confirmed by controlled clinical studies conducted on a larger number of patients in order to ensure an objective statistical assessment and final conclusions.

Nausea and Vomiting

A systematic review of double-blind, placebo-controlled, randomized studies on the prevention of nausea and vomiting of various origins highlighted the potential efficacy of ginger, albeit with the limits of the chemical stability of the preparations²³.

In 2000, Ernst and Pittler²³ performed a systematic review of randomized controlled trials for or against the efficacy of ginger in the treatment of nausea and vomiting. Six studies met all the inclusion criteria and were reviewed. Three studies on postoperative nausea and vomiting were identified and two of these suggested that ginger was superior to placebo and equally effective as metoclopramide²³. However, the pooled absolute risk reduction for the incidence of postoperative nausea indicated a non-significant difference between 1 g of ginger and placebo taken before operation (absolute risk reduction: 0.052). One study was found for each of the following conditions: seasickness, morning sickness and chemotherapy-induced nausea²³. These studies collectively favored ginger over placebo.

Pregnancy-Induced Nausea and Vomiting

Ginger has been used throughout the world for centuries as a therapeutic agent for pregnancy-induced nausea and vomiting (PINV).

In 2013, four randomised controlled trials (RCTs)²⁴ on the use of ginger for PINV were sourced from CINAHL, the Cochrane library, MEDLINE and TRIP. All the trials showed that orally administered ginger was significantly more effective than placebo in reducing the frequency of vomiting and the intensity of nausea. Adverse events were generally mild and infrequent.

Therefore, the best available evidence suggests that ginger is a safe and effective treatment for PINV. However, there is still uncertainty regarding the maximum safe dosage of ginger, the appropriate duration of treatment, the consequences of over-dosage and potential drug-herb interactions, all of which are important areas for future research.

A 2010 Cochrane review²⁵ assessed the effectiveness and safety of interventions for nausea and vomiting in pregnancy before 20 weeks of gestation. The interventions included acupuncture, acupressure, acustimulation, acupuncture, ginger, vitamin B6, and antiemetic medications. The review evaluated nine RCTs involving ginger. Ginger was compared with placebo in four studies, with pyridoxine (vitamin B₆) in four studies and with dimenhydrinate in one study. The Cochrane review found that pyridoxine and one antihistamine compound (hydroxyzine) reduced nausea more than placebo; however, the authors cautioned that the evidence was not very strong. Four trials with ginger versus placebo demonstrated a greater reduction of nausea with ginger treatment, and three studies showed reduced vomiting after ginger use. However, only two out of four studies reported statistically significant differences. Cochrane reviewers could not perform a global meta-analysis because of the heterogeneous outcomes used in the studies, although they were able to perform a meta-analysis of four RCTs that compared ginger (975 to 1500 mg per day) with pyridoxine (30 to 75 mg per day). Two trials found no difference in nausea and vomiting by day 3. In addition the other two trials, surveying the percentage of women reporting no relief, did not find any statistically significant difference between ginger and pyridoxine. The study comparing ginger with dimenhydrinate revealed that the two products had similar effectiveness.

A systematic literature search on herb remedies during pregnancy, covering the period from January 1990 to September 2010, was performed using various electronic databases²⁶. Out of 511 identified papers, 14 RCTs were eligible. Ginger was the most investigated remedy and was consistently reported to ameliorate nausea and vomiting during pregnancy better than placebo; its efficacy was noted to be equal to that of vitamin B6 and dimenhydrinate²⁶. A recently published metanalysis on the effects of ginger for nausea and vomiting in early pregnancy (NVEP) identified 135 potentially relevant records²⁷. Only 6 studies met the final criteria. Out of 508 subjects, 256 were randomly assigned to receive ginger, while 252 received placebo. The use of ginger (~1 g daily) for at least 4 days was associated with a 5-fold likelihood of improvement in NVEP and the authors concluded that ginger is an effective non-pharmacological treatment for NVEP²⁷.

In addition to this, the American College of Obstetricians and Gynecologists (ACOG) states that: "treatment of nausea and vomiting of pregnancy with ginger has shown beneficial effects and can be considered as a non-pharmacologic option." However, ACOG acknowledges that the recommendation is based on limited or inconsistent scientific evidence. Moreover, the U.K. National Health Service, through the National Institute for Health and Clinical Excellence, has included ginger in its list of acceptable therapies for the treatment of nausea and vomiting during early pregnancy.

Chemotherapy-Induced Nausea

Nausea and vomiting are among the most prevalent and disturbing side effects of chemotherapy and various attempts have been made to evaluate the role of ginger in the treatment and prevention of these symptoms. Recently, a well conducted NCI-supported multi-center, randomized, double blind and placebo controlled study²⁸ in cancer patients submitted to chemotherapy has been published. In this trial, 744 cancer patients were randomly assigned to four arms (placebo, 0.5 g ginger, 1 g ginger, 1.5 g ginger). Patients, co-treated with 5-HT₃ receptor antagonists on day 1 of all cycles, received treatments with placebo or ginger preparations for 6 days, starting 3 days before the first day of chemotherapy. The results of the study clearly showed that all doses of ginger significantly reduced acute nausea severity compared to placebo on day 1 of chemotherapy. The largest reduction in nausea intensity occurred with 0.5 g and 1.0 g of ginger.

Another study²⁹ evaluated the effects of ginger against both acute and delayed forms of chemotherapy-induced nausea and vomiting (CINV) in a population with advanced breast cancer as the main malignancy. In this pilot, randomized, open-label clinical trial, 100 women with advanced breast cancer, who were initially assigned to standard chemotherapy protocol with docetaxel, epirubicin and cyclophosphamide (the TEC regimen), were randomized to receive ginger (1.5 g/d in 3 divided doses every 8 hours) plus standard antiemetic regimen (granisetron plus dexamethasone) or standard antiemetic regimen alone (control group). The duration of treatment with ginger was limited to 4 days from the initiation of chemotherapy. A significantly lower prevalence

of nausea was observed in the ginger group during 6 to 24 hours post-chemotherapy. Despite this effect, no other significant additional benefits were observed with ginger (1.5 g/d) in terms of prevalence or severity of nausea, vomiting or retching, in any of the assessed periods.

Furthermore, studies conducted in cultured cells as well as in experimental animals revealed that ginger contains several nonvolatile pungent phenolics (gingerols, shogaols, paradols and zingerone,) which possess anticarcinogenic properties³⁰.

Conclusions

Ginger (*Zingiber officinale*) may represent a reasonable and safe alternative to treat PINV and it may be useful to treat CINV. The prokinetic effects shown on gastric motility may suggest a potential role of ginger extracts in the treatment of various digestive diseases and particularly in functional dyspepsia, as well as in patients with neurologic or endocrinologic side effects to traditional prokinetic drugs such as domperidone, levosulpiride or metoclopramide. In particular, treatment with ginger extracts could avoid the risk of sudden cardiac death observed in the elderly treated with domperidone at doses of more than 30 mg per day³¹⁻³⁴. Additional controlled studies are needed to confirm these interesting hypotheses. In addition, ginger does present other intriguing properties that may be worth investigation³⁵.

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