Ginger in the Prevention of Nausea and Vomiting: A Review

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Nausea and vomiting are physiological processes experienced by every human being at some stage of their life. They are complex protective mechanisms and the symptoms are influenced by the emetogenic response and stimuli. However, when these symptoms recur frequently, they can significantly reduce the quality of life and can also be detrimental to health. The existing antiemetic agents are ineffective against certain stimuli, are expensive, and possess side effects. Herbal medicines have been shown to be effective antiemetics, and among the various plants studied, the rhizome of Zingiber officinale, commonly known as ginger, has been used as a broad-spectrum antiemetic in the various traditional systems of medicine for over 2000 years. Various preclinical and clinical studies have shown ginger to possess antiemetic effects against different emetogenic stimuli. However, conflicting reports especially in the prevention of chemotherapy-induced nausea and vomiting and motion sickness prevent us from drawing any firm conclusion. The current review for the first time summarizes the results. An attempt is also made to address the lacunae in these published studies and emphasize aspects that need further investigations for it to be of use in clinics in the future.

Keywords Zingiber officinale, ginger, nausea, vomiting

INTRODUCTION

The 2 common distressing symptoms of nausea, which in Greek means seasickness and vomiting (emesis), herald the onset of derangement in health and adverse effect of most drugs (Berger and Clark-Snow, 1997; Baines, 1998; Pasricha, 2006; Pleuvrya, 2006). These indications are not diseases, but symptoms of conditions like stomach flu, food poisoning, overeating, blocked intestine, migraines, motion sickness or seasickness, morning sickness during pregnancy, gastric irritation, postoperative factors, cancer chemotherapy and radiotherapy (Berger and Clark-Snow, 1997; Baines, 1998; Pasricha, 2006; Pleuvrya, 2006). However, these symptoms at times can also be due to the more serious diseases such as appendicitis, heart attacks, kidney or liver disorders, central nervous system disorders, brain injury, brain tumors, and some forms of cancer and merits critical and detail investigations (Berger and Clark-Snow, 1997; Baines, 1998; Pasricha, 2006; Pleuvrya, 2006).

In a normal situation, vomiting is a protective mechanism and removes the harmful ingested substances. Once initiated, vomiting occurs in 2 stages, retching (also called dry heaving) and expulsion. Retching, can also occur without vomiting or can precede or follow vomiting (Berger and Clark-Snow, 1997; Baines, 1998; Pasricha, 2006; Pleuvrya, 2006). The process of vomiting is a highly coordinated physiological process as the contracting muscles responsible for this sequence of events are controlled by either a vomiting center or a central pattern generator (probably in the area postrema) and the nearby nucleus tractus solitaries (Berger and Clark-Snow, 1997; Baines, 1998; Pasricha, 2006; Pleuvrya, 2006). Nausea is a conditioned response to avoid ingestion of offending substances and can occur without vomiting or may precede vomiting (Berger and Clark-Snow, 1997; Baines, 1998; Pasricha, 2006; Pleuvrya, 2006).

Although considered to be beneficial when minimal, severe or protracted nausea and vomiting can lead to serious complications, which can be life-threatening. It can result in the loss of water and electrolytes, hypokalemic hypochloremic alkalosis, dehydration, loss of gastric hydrogen ions, altered rennin angiotensin system, mucosal damage, Mallory Weiss tears, esophageal rupture, decreased hematocit, GIT rupture, and...
<table>
<thead>
<tr>
<th>Class of antiemetic</th>
<th>Compounds</th>
<th>Uses</th>
<th>Adverse effects</th>
</tr>
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<tbody>
<tr>
<td>5-HT\textsubscript{3} receptor antagonists</td>
<td>Ondansetron (0.15 mg/kg, i.v.), CINV 8 mg oral/10 mg, i.v.), Tropisetron, Granisetron (10 μg/kg, i.v.), Dolasetron (0.6–3 mg/kg), Palonosetron (0.25 mg/kg, i.v.), Ramsoetron (300 μg/kg, i.v.)</td>
<td>Cytotoxic drug-induced vomiting, postoperative vomiting, hyperemesis of pregnancy</td>
<td>Diarrhea, headache, light-headedness, asthenia, abdominal discomfort, rash, and allergic reaction</td>
</tr>
<tr>
<td>5-HT\textsubscript{4} receptor agonists</td>
<td>Cisapride (10–20 mg TDS), Mosapride (5 mg, TDS), Tegaserod, Prucalopride</td>
<td>Gastroesophageal reflux disease (GERD), nonulcer dyspepsia, impaired gastric emptying, chronic constipation, inflammatory bowel syndrome (IBS)</td>
<td>Loose stools, abdominal cramps, dizziness, occasional raise in serum transaminases, ventricular arrhythmias</td>
</tr>
<tr>
<td>Dopamine receptor antagonists</td>
<td>NeurolepticsProchlorperazine (5–10 mg oral/i.v., 25 mg rectal suppository), Promethazine, Thiethylperazine (10 mg oral/i.m./rectal suppository), Chlorpromazine, Phenytozone, Haloperidol, Droperidol Metoclopramide (10 mg TID, CINV 0.3–1.0 mg/kg i.v./i.m.)</td>
<td>Drug-induced and postoperative vomiting, diseases (gastroenteritis, uremia, liver disease, migraine), malignancy associated and cancer chemotherapy (mild emetogenic) induced vomiting, morning sickness</td>
<td>Extrapyramidal side effects, dystonia usually occurring acutely after iv administration, sedation, anticholinergic side effects, galactorrhoea</td>
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<tr>
<td>H1 antihistaminics</td>
<td>Dimenhydrinate, Cyclizine, Cinnarizine, Diphenhydramine, Promethazine, Hydroxyzine, Meclizine, Doxylamine</td>
<td>Motion sickness, morning sickness, postoperative vomiting, adjuvant to cancer chemotherapy induced vomiting, abdominal cancer</td>
<td>Sedation, dizziness, tinnitus, blurred vision, euphoria, uncoordination, constipation, dry mouth, urinary retention, palpitations, hypotension</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone (8–20 mg, i.v.), Betamethasone, Methylprednisolone</td>
<td>Vomiting due to moderately emetogenic cancer chemotherapy drugs, adjuvant antiemetic with cisplatin, delayed emesis</td>
<td>Suppression of HPA axis, cushing’s habitus, fragile skin, purple striae, easy bruising, telangectasias, hirsutism, hyperglycemia, peptic ulcer, osteoporosis, muscular weakness</td>
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<tr>
<td>Muscarinic receptor antagonists</td>
<td>Scopolamine (Hyoscine) (0.2–0.4 mg oral, i.m.) Dicyclomine (10–20 mg oral)</td>
<td>Motion sickness, postoperative vomiting</td>
<td>Dry mouth, Xerostomia, reddened skin, increased body temperature, mydriasis; photophobia, loss of accommodation, blurred vision, tachycardia, urinary retention, increased intraocular pressure, confusion, disorientation, respiratory depression</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Diazepam, Lorazepam, Alprazolam, Midazolam</td>
<td>Adjuvant to Metoclopramide/Ondansetron in cytotoxic drug-induced vomiting</td>
<td>Vertigo, disorientation, amnesia, impairment of psychomotor skills, weakness, blurring of vision, dry mouth, urinary incontinence, irritability, nightmares</td>
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<tr>
<td>Cannabinoids</td>
<td>Dronabinol (10 mg oral), Nabilone, Marinol, Phentothiazines, Betgrophones, Cannabis</td>
<td>With moderately emetogenic cytotoxic drugs</td>
<td>Tachycardia, hypotension, euphoria, somnolence, dizziness, anxiety, nervousness, panic, paranoid reaction, thinking abnormalities. After abrupt withdrawal abstinence syndrome manifest by irritability, insomnia, restlessness</td>
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<td>NK1 antagonists</td>
<td>Aperpitant</td>
<td>Cytotoxic drug-induced delayed vomiting</td>
<td>Asthenia, fatigue, anorexia, constipation, diarrhea, hiccups</td>
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<tr>
<td>Casopitant</td>
<td>Neutropenia, dehydration</td>
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<tr>
<td>Fosaprepitant</td>
<td>Hypotension, puritis, headache, flushing, erythema</td>
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<td>Maropitant</td>
<td>Drooling, drowsiness, diarrhea, appetite loss</td>
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<tr>
<td>Vestipitant</td>
<td>Headache, fatigue, dry mouth</td>
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### Table 2
Combination of antiemetics that has synergistic action (Pasricha, 2006)

<table>
<thead>
<tr>
<th>Primary agent</th>
<th>Supplemental agent</th>
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<tbody>
<tr>
<td>5-HT3 receptor antagonist</td>
<td>Corticosteroid, neuroleptics/aprepitant</td>
</tr>
<tr>
<td>Metaclopramide, domperidone</td>
<td>Corticosteroid ± scopolamine</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Corticosteroid</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Corticosteroid</td>
</tr>
</tbody>
</table>

aspiration pneumonia. Nausea and vomiting can also cause patients to experience increased anxiety and dissatisfaction with the hospital experience and can contribute to future anticipatory nausea (Berger and Clark-Snow, 1997; Baines, 1998; Pasricha, 2006; Pleuvrya, 2006).

Nausea and emesis can be prevented by the use of chemicals and these drugs known as antiemetics, which are effective in most conditions (Pasricha, 2006). The most effective antiemetics are the 5-HT3 receptor antagonists, dopamine antagonists, NK1 receptor antagonist, antihistamines or H1 histamine receptor antagonists, cannabinoids, anticholinergics, and steroids (Pasricha, 2006). (Tables 1, 2, 3). However, their repeated use is observed to possess side effects, and this limits their daily use (Pasricha, 2006). In view of these observations, a need is felt for an antiemetic agent that is effective and does not possess any side effects.

### PLANTS AS ANTIEMETIC AGENTS

Complementary therapies are widely used throughout the world, and as per a recent report, almost 80% of the global population relies on alternative therapies for their health care (Arora, 2010). Observations suggest that *Cannabis sativa*, commonly known as marijuana, used in the traditional practices for centuries have contributed to the development of antiemetic drugs like the cannabinoids dronabinol, nabilone, marinol, and medicinal cannabis (Pasricha, 2006). However, these drugs also possess side effects like tachycardia, hypotension, euphoria, somnolence, dizziness, anxiety, nervousness, panic, paranoid reaction, and thinking abnormalities. Additionally, abrupt withdrawal causes abstinence syndrome necessitating a need for medical care (Pasricha, 2006).

The rhizome of *Zingiber officinale* (family Zingiberaceae) (Figure 1), commonly known as ginger, is an important herb in the various traditional systems of medicines (Ernst and Pittler, 2000; Vasala, 2004). It is supposed to have originated in South-East Asia (today’s northeast India) and is also grown in China, Nigeria, Sierra Leone, Indonesia, Bangladesh, Australia, Fiji, Jamaica, Nepal, Haiti, Mexico, and Hawaii (Govindarajan, 1982a, b; Ernst and Pittler, 2000; Vasala, 2004; Ali et al., 2008). In Sanskrit, ginger is known as Sringavera, and it is speculated that this term may have given way to Zingiberi in Greek and then to the Latin term Zingiber (Vasala, 2004).

Since ancient times, the rhizome of ginger has been used in Greek, Roman, Asian, Indian, Mediterranean, and Arabic systems of alternative medicines (Ali et al., 2008). Because of its aroma and flavor, the Romans and the Greeks valued ginger more for its medicinal properties than as a culinary agent. The Greek physician Galen used ginger as a purificant of body and to treat conditions caused by imbalances in body (Langner et al., 1998). The Africans and West Indians also use ginger for medicinal purposes (Ernst and Pittler, 2000; Vasala, 2004; Ali et al., 2008).

### Chemistry of Ginger

Phytochemical studies have shown that ginger rhizome contains a wide variety of biologically active compounds. The characteristic organoleptic properties of ginger are due to steam volatile oil and the non-volatile pungent compounds, and their concentration vary with growing conditions, temperature, harvesting, and process of the ginger rhizome (Govindarajan, 1982a, b). The pleasant aroma of ginger is caused by more than 70 constituents present in the steam volatile oil like the mono and sesquiterpenes; camphene, β-phellandrene,

### Table 3
Combination of antiemetics that decreases the side effects (Brunton et al., 2006)

<table>
<thead>
<tr>
<th>Primary agent</th>
<th>Supplemental agent</th>
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<tbody>
<tr>
<td>Metaclopramide, domperidone</td>
<td>Corticosteroid, antihistamine, benzodiazepine</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Antihistamine</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Chlorpromazine/fluphenazine</td>
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Figure 2  Some important phytochemicals present in ginger rhizome.
circumene, cineole, geranyl acetate, terphineol, terpenes, bornesol, geraniol, limonene, \( \beta \)-elemene, zingiberol, linalool, \( \alpha \)-zingiberene, \( \beta \)-sesquiphellandrene, \( \beta \)-bisabolene, zingiberenol, and \( \alpha \)-farnesene (Govindarajan, 1982a, b; Vasala, 2004).

The non-volatile pungent phytochemicals of ginger consists of gingerols, shogaols, paradols, and zingerone (Fig. 2) (Vasala, 2004). These compounds are responsible for the warm pungent sensation in the mouth and are also reported to account for many of its pharmacological effects (Govindarajan, 1982a, b). Fresh ginger contains gingerols, a series of chemical homologs differentiated by the length of their unbranched alkyl chains; \([3–6] \), \([7–10] \), \([12] \), and \([16] \)-gingerols; and having a side-chain with 7–10, 12, 14, or 16 carbon atoms, respectively as the major active components. Of all the gingerols, the compound 6-gingerol is the most abundant and well-investigated ginger phytochemical (Govindarajan, 1982a, b; Ali et al., 2008).

Gingerols are thermally labile because of the presence of a \( \beta \)-hydroxy keto group and readily undergoes dehydration to form the corresponding shogaols. The extent of this conversion is likely to have a significant impact on the medicinal benefits of ginger, as the 2 classes of compounds vary in their bioavailability, pharmacokinetics, and pharmacological properties (Govindarajan, 1982a, b; Ali et al., 2008). Shogaols may be further converted to paradols by hydrogenation and is similar to gingerol (Govindarajan, 1982a, b).

The major pharmacological activity of ginger appears to be due to gingerol and shogaol and the relative proportions of gingerols, shogaols, and paradols (Govindarajan, 1982a, b; Ali et al., 2008). The other constituents include capsaicin, gingediol, galanolactone, gingesulfonic acid, galactosylglycerols, gingerglycolipids, diarylheptanoids, neral, and phytosterols (Govindarajan 1982a, b; Ali et al., 2008).

Traditional and Pharmacological Effects of Ginger

Ginger has a long history of use in South-East Asia, both in dried and fresh form. In India, ginger has been used as medicine from Vedic period and is called “maha aushadhi,” meaning the great medicine (Ernst and Pittler, 2000; Vasala, 2004). It is an integral part of several medicinal formulations in Ayurveda, the traditional system of Indian medicine. In various traditional systems of medicine, ginger is reported to be a carminative, diaphoretic, antispasmodic, peripheral circulatory stimulant, astringent, appetite stimulant, and antiinflammatory agent. It is also useful in treating common cold, headaches, arthritis, rheumatological conditions, and muscular discomfort (Ernst and Pittler, 2000; Vasala, 2004; Ali et al., 2008).

Studies have shown that ginger possesses antimicrobial, anti-

schistosomal, antiinflammatory, antipyretic, antioxidant, hypoglycemic hepatoprotective, diuretic, and hypocholesterolemic effects (Chrubasik et al., 2005; Ali et al., 2008). Ginger benefits the gastrointestinal tract, by increasing the bile secretion and preventing gastric ulcers (Chrubasik et al., 2005; Ali et al., 2008). Scientific studies have also shown that ginger prevents nausea and/or emesis resulting from pregnancy, motion sickness, postoperation chemotherapy and radiation, thereby validating the traditional observations and emphasizing its broad-spectrum antiemetic effects (Chrubasik et al., 2005; Ali et al., 2008). In the United States, ginger is recommended to relieve and prevent nausea (Ernst and Pittler, 2000; Vasala, 2004). In the following sections, the scientific studies analyzing the effect of ginger in various emeses are addressed.

Ginger in Preventing Motion Sickness

Motion sickness is a common condition caused while traveling in cars, boats, airplanes, and trains; by riding amusement rides that spin; and for some, when using a swing at a playground. It affects nearly 30% of the general population of whom nearly 5% find it very distressing. The astronauts who undertake space expeditions can also suffer from a form of motion sickness, called “space adaptation syndrome” in the zero-gravity environment. Motion sickness is supposed to be caused by the conflicting signals from vestibular, vision, and proprioception systems (Oosterveld, 1995).

The normal symptoms associated with motion sickness are change in pallor and cold sweat, which is usually followed by epigastric discomfort, nausea, and emesis. Prolonged motion sickness cause drowsiness, apathy, and even a feeling of impending doom. At times, cortical centers may also be involved, which may trigger anticipatory nausea before traveling (Oosterveld, 1995). Conventionally, antimuscarinics and antihistamines are used to reduce antimotion sickness (Lien et al., 2003). However, their use is associated with incomplete symptom control and side effects such as dry mouth, lethargy, and drowsiness (Lien et al., 2003; Pasricha, 2006).

With regard to ginger’s effect on motion sickness, studies have been contradictory. In one of the earliest studies, Mowrey (1982) investigated the effect of ginger in humans. The volunteers were blindfolded and placed in a tilted rotating chair to induce motion sickness. The motion sickness effect was evaluated by measuring their perceived degree of gastrointestinal distress for every 15 seconds for up to 6 minutes by means of psychophysical methods. The study showed that ginger was more effective than dimenhydrinate in reducing experimentally induced motion sickness (Mowrey, 1982).

Studies by other investigators have shown that ginger was also effective in reducing the circularvection-induced nausea, tachygastria, prolonged the latency before nausea onset, shortened the recovery time after vection cessation, and also reduced the vasopressin release (Lien et al., 2003). The antimotion sickness effect of ginger is possibly due to its influence on the gaster and also due to the vestibular and oculomotor disparity (Holtmann et al., 1989). Animal studies also suggest that ginger juice produces antimotion sickness action possibly by its action on the central and peripheral cholinergic, histaminergic, and serotonergic pathways (Qian and Liu, 1992).

However, contradictory observations have also been reported on the efficacy of ginger in preventing motion sickness. Stewart
et al. (1991) evaluated the efficacy of pretreatment with ginger on preventing motion sickness by subjecting volunteers to timed head movements in a rotating chair until they reached an endpoint of motion sickness short of vomiting (malaise III or M-III). It was observed that neither ginger powder (whole root, 500 or 1000 mg) nor fresh ginger (1000 mg) was effective in altering the gastric function and was also devoid of antimotion sickness (Stewart et al., 1991).

Scientific studies have also shown that ginger was effective in reducing seasickness. In a double-blind randomized placebo trial Grosalshntvedab et al. (1988) evaluated the antisickness effects of ginger in naval cadets unaccustomed to sailing in heavy seas by measuring the symptoms every hour for 4 consecutive hours after ingestion of 1 gram of ginger or placebo. When compared with the placebo, ginger was observed to be effective in reducing the tendency to vomiting, nausea, vertigo cold, and sweating (Grosalshntvedab et al., 1988). Similar observations were also seen in another study (Grøntvedab et al., 1988) with naval cadets suggesting ginger to be effective in preventing seasickness.

**Ginger Prevents Pregnancy Induced Nausea and Vomiting**

Nausea and vomiting in early pregnancy (NVP) remain a significant public health problem. It has significant physiological, emotional, social, and economic consequences to women, their families, and society. NVP affect 50%–80% of pregnant women and can range from morning sickness to moderate NVP to hyperemesis gravidarum (HG) (O’Brien and Naber, 1992; Gadsby et al., 1993; Ensiyeh and Sakineh, 2009). All 3 forms are commonly present in the first trimester with increased frequency especially between 10 and 15 weeks of gestation, and generally subside at about 20 weeks (O’Brien and Naber, 1992; Gadsby et al., 1993). However, exceptions have been reported where the symptoms extend beyond the fourth month of pregnancy (O’Brien and Naber, 1992; Gadsby et al., 1993).

The physical and emotional impact of NVP often results in feelings of angst and concern about the outcome of the symptoms on the fetus (O’Brien and Naber, 1992). The biochemical reason for nausea and vomiting during pregnancy is unknown, but factors like human chorionic gonadotropin hormone, estrogen, placental serum markers, adrenocorticotropic hormone, cortisol, growth hormone, prolactin, pregnancy-associated alterations to the vestibular system, taste and olfaction, and behavioral and/or psychological aspects are attributed to NVP (O’Brien and Naber, 1992; Gadsby et al., 1993).

Morning sickness is the term given for symptoms of nausea that may or may not be accompanied by vomiting, occurring mostly in the morning and reduces during the day without altering the daily activities (O’Brien and Naber, 1992). On the contrary, NVP occurs throughout the day and frequently affects activities of daily living (O’Brien and Naber, 1992). HG is the most severe of all NVP and occurs in about 1% of pregnancies with regional, social, and temporal differences existing (Jordan et al., 1995; Goodwin, 1998). HG is associated with severe nausea and vomiting that persists throughout the day and leads to loss of greater than 5% of prepregnancy weight, with associated electrolyte imbalance and ketonuria (Gadsby et al., 1993).

 Clinically, HG is classified as grade 1, with feelings of sickness without metabolic imbalance, and grade 2, with pronounced feelings of sickness and metabolic imbalance (O’Brien and Naber, 1992; Gadsby et al., 1993). The condition can be life-threatening for the women and has to be diagnosed and treated at once, as if left unmanaged, can cause immense suffering (Gadsby et al., 1993). NVP has a negative impact on family relationships and also affects women’s working abilities (Järnfelt-Samsoe et al., 1983).

Ginger has been used since antiquity as an antiemetic herb for NVP in Chinese and Ayurvedic medicine, and the scientific studies have substantiated these observations. Multiple studies have shown that ginger was effective as an antiemetic in NVP and that it did not alter or affect the pregnancy outcome (Ernst and Pittler, 2000; Chrubasik et al., 2005; Ali et al., 2008).

In one of the earliest study, Fischer-Rasmussen et al. (1991) performed a double-blind randomized crossover trial where ginger (250 mg) was administered to pregnant women with HP for 4 days and interrupted by a 2-day wash out before administering the alternative medication in the second 4-day period. The severity and relief of symptoms before and after each period were evaluated by 2 scoring systems, and the authors observed that 70.4% of the subjects preferred ginger when compared with the placebo (Fischer-Rasmussen et al., 1991).

Vutyavanich et al. (2001) have also observed that ginger was effective in preventing NVP when ginger (250 mg) was taken 3 times daily after meals and once before bedtime for 4 consecutive days when compared with the placebo-treated group. Furthermore, the average number of vomiting episodes over the 4 days of treatment was lesser when compared to the same patient before initiation of the ginger. Ginger treatment did not cause spontaneous abortions, affect the term delivery, or cause any congenital anomalies (Vutyavanich et al., 2001).

The extract of ginger (EV.EXT35; equivalent to 1.5 g of dried ginger) given 4 times per day for 4 days help in reducing the symptoms of morning sickness. They observed that the nausea experience and retching were reduced, while there was no significant effect on vomiting. The follow-up of the pregnancies showed ginger did not affect the birth weight, gestational age, Apgar scores, and frequencies of congenital abnormalities (Willetts et al., 2003). Oral administration of ginger (0.5 g twice a day) for 1 week was observed to be as effective as dimenhydrinate (50 mg twice a day) in the treatment of nausea and vomiting during pregnancy and did not possess any severe side effects (Pongrojpaw et al., 2007).

In another randomized controlled equivalence trial with 8- to 16-week-pregnant women with NVP, administering standardized and quality controlled ginger (350 mg × 3 times a day = 1.05 g) daily for 3 weeks caused a reduction in the nausea, retching, and vomiting. The effect was comparable to that of vitamin B6 (25 mg × 3 times a day = 75 mg) used as a known...
control (Smith et al., 2004). Recent studies have also shown that administering ginger (1g/day) was more effective than vitamin B6 (40 mg/day) for 4 days in decreasing both NVM (below 17 weeks of gestation) (Ensiyeh and Sakineh, 2009).

Consuming ginger did not increase the risk of pregnancy complications, pregnancy outcome, and congenital abnormalities. There was also no difference in the mean birth weight, birth length, and head circumference for babies of mothers having taken ginger (Smith et al., 2004). Ginger does not appear to increase the rates of major malformations above the baseline rate of 1%–3% and has a mild effect in the treatment of NVP (Portnoi et al., 2003). All these observations suggest ginger to be effective in preventing NVP.

**Ginger in Preventing Post-operative Nausea and Vomiting**

Despite advances in surgical techniques and introduction of less-emetogenic anesthetic methods and drugs, postoperative nausea and vomiting (PONV), which occurs within 24 hours after surgery is one of the most common and distressing symptoms, following anesthesia and surgery (Watcha and White, 1992; Kovac, 2000). PONV normally affects 20%–30% of patients of whom severe intractable condition occurs in approximately 0.18% of all the patients (Watcha and White, 1992). In severe cases, serious medical complications such as increased intracranial pressure, pulmonary aspiration, tension on suture lines, wound bleeding and dehiscence, dehydration, and electrolyte imbalance may occur, and with it, also increases the patient discomfort and hospitalization stay and costs (Ho and Chiu, 2005).

The etiology of PONV is thought to be multifactorial, involving individual, anesthetic, and surgical risk factors (Watcha and White, 1992; Kovac, 2000). Among the surgical risks, studies have shown that certain surgeries like that involving otolaryngological, dental, breast augmentation, orthopedic shoulder, laparoscopy, strabismus, and varicose vein stripping are reported to have a higher incidence of PONV than other procedures (Sinclair et al., 1999; Ho and Chiu, 2005). Furthermore, operations that are lengthy and involve increased exposure time to potentially emetogenic anesthetic drugs are also associated with a higher risk of PONV (Ho and Chiu, 2005).

With regard to ginger in a double blind randomized controlled trial, Pongrojpaw and Chiamchanya (2003) tested the efficacy of ginger as an antiemetic in women undergoing gynecological laparoscopy in an outpatient setup. One group was administered ginger (1 gram) 1 hour before the laparoscopy, while the other group was administered with placebo. The visual analog nausea scores and vomiting times were evaluated at 2, 4, and 24 hours after operation in both groups and documented. The authors observed that administering ginger reduced the visual analog nausea scores at 2 and 4 hours, while at 24 hours there was no difference. The incidence and frequency of vomiting was also decreased by ginger administration but was statistically insignificant (Pongrojpaw and Chiamchanya, 2003).

Similar studies but with higher dose of ginger (1.5 g) were also performed in women undergoing laparoscopic operations for noncancerous gynecologic conditions (Apariman et al., 2006). Administering ginger 1 hour before the operation decreased the visual analog scores for nausea and vomiting at 6 hours postoperation time point. However, at the earlier time point of 2 hours post surgery, the presence of vomiting was not different between the placebo and ginger groups (Apariman et al., 2006). Studies have also shown that the prophylactic combination of antiemetic treatment with dexamethasone and ginger (0.5g) was not clinically or statistically superior to dexamethasone alone in preventing PONV in patients undergoing thyroidectomy, suggesting the combination does not possess an additive effect (Tavlan et al., 2006).

**Ginger in Preventing Chemotherapy-Induced Nausea and Vomiting**

Among the various types of emesis, chemotherapy-induced nausea and vomiting (CINV) is the most distressing and at times warrants unnecessary hospitalization and needless financial expenditure. It is also the most feared adverse effect of cytotoxic drugs and may prompt the patient to discontinue therapy. It can lead to the development of complications like fluid-electrolyte imbalances, weight loss, dehydration, anorexia, weakness, fractures, esophageal tears, prerenal azotemia, wound dehiscence, decline in behavioral and mental status (Anonymous, 1999).

CINV is a common adverse event and nearly 70%–80% of patients undergoing chemotherapy experience this effect. This also has a negative influence on the treatment regimen and causes nonadherence to chemotherapy or dose reductions, which will ultimately have an adverse impact on their treatment and survival (Naylor and Rudd, 1996). CINV is classified into 4 categories: 1) acute, occurring in the first 24 hours following chemotherapy; 2) delayed occurring after the first 24 hours and up to 120 hours after chemotherapy, 3) anticipatory, a learned or conditioned response in patients who have had severe nausea and vomiting during chemotherapy; and 4) breakthrough nausea and vomiting that occurs despite preventive therapy (Naylor and Rudd, 1996; Anonymous, 1999).

The major factors that determine the incidence and severity of nausea and vomiting in patients receiving chemotherapy include the dose and type of chemotherapy given, treatment schedule, the use of combinations of chemotherapeutic agents, and the individual patient characteristics (Anonymous, 1999; Antonarakis and Hain, 2004). Chemotherapeutic agents like carbustine, cisplatin, cyclophosphamide (≥1500 mg²), dacarbazine, mechlorethamine, and streptozocin are highly ametogenic and cause high frequency of nausea and vomiting (Bartlett and Koczwara, 2002). Additionally, increased risk of CINV is observed in patients below the age of 50, had history of light alcohol use; in patients who have had vomiting during previous chemotherapy, history of motion sickness, anxiety; and in women who have had pregnancy-induced nausea/vomiting.
Additionally, in patients who are dehydrated, debilitated, those who have an electrolyte imbalance, or those who have recently undergone surgery or radiation therapy are at greater risk of experiencing serious complications from CINV.

**Animal Studies**

Preclinical studies have shown that ginger possess antiemetic effects and prevents gastric emptying against the highly emetogenic cisplatin. In this study, Sharma et al. (1997) evaluated the antiemetic effects of various ginger extracts (acetone, 50% ethanolic and aqueous) against emesis induced by 3 mg/kg cisplatin in the healthy mongrel dogs. The standard 5-HT3 receptor antagonist ondansetron was used as a known control. The authors observed that the acetone and 50% ethanolic extract at the doses of 25, 50, 100, and 200 mg/kg p.o. exhibited significant protection, while aqueous extract at these doses was ineffective against emesis. The acetone extract was more effective than ethanolic extract but was less effective than granisetron (Sharma et al., 1997).

The acetone and 50% ethanolic extract of ginger in the doses of 100, 200, and 500 mg/kg (p.o.) and fresh ginger juice (2 and 4 mL/kg) were also investigated against cisplatin effect on gastric emptying in rats. It was observed that all the 3 ginger preparations reversed the cisplatin-induced delay in gastric emptying and that the ginger juice and acetone extract were more effective than the 50% ethanolic extract (Sharma and Gupta, 1998). The reversal produced by the ginger juice was better than the 5-HT3 receptor antagonist ondansetron, while that of the acetone extract of ginger was similar to it (Sharma and Gupta, 1998).

Together, these studies suggest that ginger possess antiemetic effects and also reduces the gastrointestinal side effects of cisplatin (Sharma et al., 1997; Sharma and Gupta, 1998).

Gingerol, the active principle of raw ginger, was also investigated for its antiemetic effects against the cisplatin, (7.5 mg/kg, intraperitoneal)-induced emesis in minks (Qian et al., 2010). Pretreatment with gingerol caused a concentration dependent (50 mg/kg, 100 mg/kg, or 200 mg/kg, i.g.) reduction in the number of retching and vomiting incidents during the 6-hour observation period. The effect of 200 mg/kg of gingerol and ondansetron, used as positive control, was almost similar (Qian et al., 2010). Immunohistochemical studies showed that gingerol caused a dose-dependent suppression in the levels of substance P and NK1 receptors in area postrema and ileum and suggest its action to be similar to aprepitant (Qian et al., 2010).

**HUMAN STUDIES**

The antiemetic studies with ginger in humans have been mixed and contradictory. In a double-blinded crossover study Manusirivithaya et al. (2004) have observed that the addition of ginger to standard antiemetic regimen of gynecologic oncology patients receiving cisplatin offered no advantage in reducing nausea or vomiting in acute phase of cisplatin-induced emesis, while in the delayed phase, it was effective and that the beneficial effect was comparable to that of the clinically used dopamine receptor antagonist metoclopramide (Manusirivithaya et al., 2004).

Additionally, experiments have confirmed that ginger was also effective in reducing nausea and vomiting induced by low-dose cyclophosphamide in combination with other anticancer drugs causing emesis (Sontakke et al., 2003). The results of this study indicated that the antiemetic efficacy of ginger was found to be equal to that of metoclopramide but inferior to that of ondansetron (Sontakke et al., 2003). Additionally, combining high protein meals with ginger was also observed to reduce the chemotherapy-induced delayed nausea and the use of standard antiemetic medications in cancer patients (Levine et al., 2006).

Contradicting these observations, recent studies by Zick et al. (2009) suggest that ginger is of no benefit in reducing the prevalence or severity of acute or delayed CINV when combined with 5-HT3 receptor antagonists and/or aprepitant. Furthermore, the authors also observed that the participants who took both ginger and aprepitant had more severe acute nausea than participants who took only aprepitant, suggesting a possible antagonism (Zick et al., 2009).

**Ginger in Preventing Radiotherapy-Induced Nausea and Vomiting**

Radiation-induced nausea and emesis (RINV) is an important secondary effect of treatment and depends on the site of irradiation, the field size, and the dose per fraction (Maranzano, 2001; Tonini et al., 2003). The pathophysiology of RINV is incompletely understood but is thought to be similar to that caused by chemotherapy (Tonini et al., 2003). Unlike chemotherapy, radiotherapy is localized, and RINV depends on both the treatment features like the radiation dose, fractions, total dose, irradiation site, and the clinical characteristics of the patients (Maranzano, 2001). RINV is very high when the total body, proper abdominal and gastrointestinal regions are irradiated; moderate when the upper abdomen, pelvic and cranial parts are involved; low when the lower thorax and craniospinal regions are subjected; and minimal when breast and extremities are irradiated (Maranzano, 2001; Tonini et al., 2003).

Radiation-induced taste aversion, mediated by harmful effects of radiations on neurobiological and gastrointestinal tract, is a standard assay to observe for the effect of radiation in rodents that do not express nausea and vomiting (Rabin and Hunt, 1986). The conditioned taste aversion (CTA) learning and emesis are also considered to be behavioral endpoints (Sharma et al., 2005). Radiation causes aversion to the taste of saccharin in rodents, and this is controlled by the same pathway(s) that control nausea and vomiting in man and also shares many similarities with emesis (Riley and Tuck, 1985). Because of these reasons, the CTA has been proposed as a standard procedure and a reliable paradigm for evaluating behavioral alterations induced by
radiation or other environmental agents/toxins (Riley and Tuck, 1985).

Studies by Sharma et al. (2005) have shown that the administration of the hydroalcoholic extract of ginger by intraperitoneal route 1 hour before exposure to 2 Gy of γ irradiation was effective in blocking the saccharin avoidance response for 5 posttreatment observational days. A concentration and time-dependent protective effect was observed and a dose of 200 mg/kg b wt was the most effective in males (Sharma et al., 2005), while 250 mg/kg was effective in female rats, suggesting the existence of sex dichotomy in the effect (Haksar et al., 2006). The authors hypothesize that the observed protective effects of ginger may be due to the antioxidant properties of ginger (Sharma et al., 2005; Haksar et al., 2006).

Mechanism of Action

Ginger (rhizomes of Zingiber officinale) has been shown to exert potent antiemetic properties, but its mode of action has not yet been elucidated. Among its active constituents, [6]-, [8]-, and [10]-gingerol as well as [6]-shogaol were shown in different in vivo studies to be at least partly responsible for the drug’s antiemetic properties. In an attempt to gain more insight into the mode of action of these compounds, 3 different in vitro models were used to investigate their effects on 5-HT (3) receptors (serotonin receptor subtype). It was observed that [6]-, [8]-, [10]-gingerol, and [6]-shogaol exert their antiemetic effect at least in part by acting on the 5-HT(3) receptor ion-channel complex, probably by binding to a modulatory site distinct from the serotonin binding site. This may include indirect effects via receptors in the signal cascade behind the 5-HT (3) receptor channel complex such as substance P receptors and muscarinic receptors (Abdel-Aziz et al., 2006). Hence, its action can be summarized as the activity of a 5HT3 antagonist, NKI antagonist, antihistaminic and prokinetic effects without their side effects.

CONCLUSIONS

Preclinical studies have shown that ginger is effective as an antiemetic agent against different emetogenic stimuli. However, the clinical data is insufficient to draw firm conclusion especially against the CINV. The pharmacological activity of ginger appears to be due to gingerol, paradols, and shogaol. The final ratio of these compounds in ginger are determined by a number of factors, including the geographic origin, the maturity of the rhizomes at the time of harvest, and the method by which the extracts are prepared. The gingerols are thermally labile and readily undergoes dehydration to form the corresponding shogaols. The extent of this conversion is likely to have a significant impact on the medicinal benefits of ginger, as the 2 compounds vary in their bioavailability, pharmacokinetics, and pharmacological properties.

The opposing results observed with human studies on antiemetic effects against CINV and motion sickness may be due to the variations in the bioactive compounds, as these studies were performed in different countries. In milieu of these observations, it is imperative that a quality control be established for the presence of active phytochemicals in the required levels. Additionally, preclinical studies should also be performed to understand the efficacy of important ginger phytochemicals like gingerols, shogaols, paradols, zingerone, dehydrozingerone, terpinolene, β-pinene, α-phellandrene, β-sesquiphellandrene, α-pinene, β-lemene, etc., as antiemetics.

Because of its abundance, low cost, and safety in consumption, ginger remains a species with tremendous potential and countless possibilities for further investigation. Ginger has the potential to develop as a nontoxic broad-spectrum antiemetic agent when gaps existing in knowledge are bridged. The outcomes of such studies may be useful for the applications of ginger in humans in various emeses and may open up a new therapeutic avenue.

In addition to its antiemetic effects, ginger is observed to possess carminative, diaphoretic, antispasmodic, chemopreventive, radioprotective, anti-inflammatory effects and useful in treating cold, headaches, arthritis, rheumatological conditions, and muscular discomfort. All these beneficial effects will also be of help in improving the general health of the individual. The evidence suggests there is a role for ginger in the management of nausea and vomiting in a number of settings, particularly in the light of the broad safety profile of these therapies.

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REFERENCES


