

Tahlequah Medical Group - Gastroenterology

William G. Simpson M.D., FACP, AGAF

Jennifer Carter APRN-CNP

January 22, 2019

Editor-in-Chief

Chronicles of Complementary, Alternative and Integrative Medicine

GRF Publishers

Level 13

114 William Street

Melbourne VIC 3000 Australia

Dear Colleague,

Please find attached a manuscript for consideration for publication in the Chronicles of Complementary, Alternative and Integrative Medicine as a Mini-Review. We have been interested in upper GI motility disorders for some time, and the prospect of a safe herbal therapeutic alternative is outline in the review entitled "Ginger as a Possible Alternative Treatment for Gastroparesis." It is our hope that this Mini-Review will serve as a point from which to formally investigate the role of ginger in this disease.

This manuscript is submitted in response to your invitation to contribute. As such, if reviewed favorably, we kindly request the discounted publication fee outlined in your correspondence.

Thank you for your consideration. We welcome your upcoming review.

Sincerely,

William G. Simpson, M.D., FACP, AGAF

Director of Endoscopy

**Ginger as a Possible Alternative Treatment for**

**Gastroparesis**

Laila Khan, D.O. 1 and William G. Simpson, M.D 2\*

1 Department of Family Medicine, Northeastern Health System, Tahlequah, OK

2\* Department of Internal Medicine, Northeastern Health System, Tahlequah, OK

2\* Department of Rural Health - Gastroenterology, Oklahoma State University College of Osteopathic Medicine

Correspondening author:

William G. Simpson, M.D.

205 Harris Circle

Suite 205

Tahlequah, OK 74464

Phone: 918-506-6880

Fax: 918-506-6881

[wsimpson@nhs-ok.org](mailto:wsimpson@nhs-ok.org)

Conflicts: None to disclose

Grant Support: None

Authors both drafted and edited the manuscript.

**Keywords**

Ginger, gastroparesis, nausea, vomiting

**Abstract**

Gastroparesis is frequently a difficult gastrointestinal disease to adequately treat with currently available conventional medications producing a variable response at the cost of a potentially significant side effect burden. The medicinal herb ginger has been found effective in the management of nausea and vomiting related to pregnancy and chemotherapy, post-operative nausea and vomiting, and functional dyspepsia. These data, supported by animal model data and human studies demonstrating an augmentation of gastric motility, indicate that ginger may be a potential alternative or adjunct treatment for gastroparesis.

**Introduction**

Ginger has been used for thousands of years for both dietary and medicinal purposes. The first recorded medical application was from the fourth century B.C. in China, at which time the proposed uses included stomach upset, diarrhea, nausea, cholera, bleeding, rheumatic disease, and toothache [1]. For centuries derived from the perennial herb *Zingiber officinale* from southern Asia, it is now grown throughout the tropics. The root or rhizome is the part consumed in varying preparations: dried, fresh, pickled, crystallized, candied, ground, and powdered. Medicinal formulations are available in capsules, tablets, tinctures, and extracts. It can be broken down into volatile oils (zingiberol) and nonvolatile phenol compounds (gingerols, shogaols, paradols, and zingerone), with the gingerols and shogaols demonstrating the most medicinal effect. These compounds appear to have both anticholinergic and antiserotonergic effects which may contribute to a pharmacologic effect [2].

Research into the medicinal use of ginger has increased significantly, with investigators exploring the benefits in a variety of clinical situations. The largest number of studies have looked at nausea and vomiting, functional dyspepsia, and gastric motility, but there have also been studies that have shown a benefit of ginger in conditions such as ulcerative colitis [3,4], peptic ulcer disease [5], gastrointestinal cancer [6], drug induced liver toxicity [7], and non-alcoholic fatty liver disease [8].

Disordered gastric motility clinically manifests as a gastroparesis [9]. Among gastroparesis patients seen at large referral centers the predominant underlying etiologies include diabetes mellitus (29%), postsurgical (13%), typically following procedures to the stomach and/or distal esophagus, and idiopathic (36%) in which no primary etiology is apparent [10]. Patients with this upper gastrointestinal motility disorder display symptoms related to both impaired gastric peristalsis and delayed emptying, but also the loss of accommodation (reflex relaxation of the gastric fundus to accommodate a volume of ingested food). Symptoms range from bloating and pressure after meals, early satiety, persistent abdominal fullness, epigastric pain, and nausea and vomiting which may be intractable. Available treatment options including behavioral modification (eating behavior and dietrary changes), pharmacotherapy, the implantation of a gastric electrical stimulator or even surgery [9]. Unfortunately many patients experience significant debility despite best medical efforts. Available reports suggest a possible role for ginger in the management of gastrointestinal motility disorders, notably gastroparesis.

**Nausea and vomiting**

A variety of studies have investigated the use of ginger to treat nausea and vomiting, particularly that associated with pregnancy, chemotherapy, and the post-operative state. Animal models have suggested that the mechanism of action is related to gingerol and shogaol inhibition of cholinergic M3 receptors and serotonergic 5-HT3 receptors in the gastrointestinal tract [11].

For pregnancy-associated nausea and vomiting, ginger has shown benefit in two separate randomized controlled trials. The first trial showed decreased self-reported nausea and episodes of vomiting versus placebo [12] and the second showed treatment equivalence with pyridoxine hydrochloride (a commonly recommended therapy for pregnancy-associated nausea) [13].

Nausea and vomiting is a very common side effect of cancer chemotherapy with up to 60% of patients reporting nausea despite prescription antiemetics [14]. Four separate randomized controlled trials, with a total of over 700 patients studied, have shown benefit of ginger for patients undergoing chemotherapy in both adults and children [15-18]. The largest of the studies included greater than 500 adult patients from 23 private oncology groups in New York in their final analysis. Three dosages of ginger (0.5 g, 1.0 g, and 1.5 g orally) were compared to placebo. A significant reduction in the self-reported severity of nausea was demonstrated with all doses of ginger, with the greatest benefit in the 0.5 g and 1.0 g groups [16].

Ginger has also shown benefit in regards to nausea and vomiting in surgical patients. A meta-analysis of 10 randomized controlled trials totaling 918 patients concluded that overall post-operative nausea and vomiting (PONV) was decreased with use of ginger [19]. The need for postoperative antiemetics was greatly reduced. A study of 120 laparoscopic gynecologic surgery patients showed equivalence between ginger and metoclopramide versus placebo in terms of PONV and antiemetic requirements [20]. A randomized controlled study of laparoscopic cholecystectomy patients showed superiority of pre-operative ginger (500mg administered 1 hour prior to surgery) versus intravenous Zofran for PONV [21].

**Functional Dyspepsia**

Functional dyspepsia is defined as chronic or recurrent epigastric or upper abdominal pain without identified underlying organic gastrointestinal pathology. Although overlapping, there appear to be two syndromes of dyspepsia: postprandial distress syndrome and epigastric pain syndrome [22]. Associated symptoms may include bloating, early satiety, fullness, belching, and nausea with or without vomiting, and may be associated with eating. Proposed causes for these symptoms include impaired proximal stomach relaxation in response to meals, increased visceral sensitivity to distension, gastric motility disorders, and alterations in central nervous system function. Given these varying mechanisms, treatment for this condition can be difficult. Trials with H2-blockers and proton-pump inhibitors have only shown slight benefit relative to placebo [23]. That said, separating functional dyspepsia and gastroesophageal reflux or a gastroparesis may be a challenge [22].

One multi-center randomized controlled trial in Italy randomized 126 adults with functional dyspepsia to receive either a combination of ginger and artichoke leaf or placebo twice daily (before lunch and dinner) over 4 weeks [23]. Patients in the treatment group showed significant self-reported symptom reduction after 14 days of treatment, and this benefit was continued for the duration of the study. Specific benefit was noted for nausea, epigastric fullness, epigastric pain, and bloating. The reported treatment benefit for ginger and artichoke extract (measured as a percentage difference between the treatment group and placebo group) was higher than reported in studies of artichoke extract alone, antisecretory medications (such as proton-pump inhibitors and H2-blockers), and prokinetic medications [23]. These patients had a high prevalence of motility disorders and motility-related symptoms, including early satiety, bloating, and fullness [23].

**Gastric motility**

Disorders of gastric motility such as gastroparesis are relatively common. The medications most often prescribed for these conditions, erythromycin (a motilin agonist), domperidone (a dopamine D2 receptor antagonist) and metoclopramide (a dopamine D2 receptor agonist), display variable clinical response and may be associated with significant side effects, making many patients unable to tolerate them [9]. An alternative treatment for this patient population, especially one with minimal side effects and improved tolerance, would be of significant clinical benefit. Studies of ginger have provided evidence that it may be a good alternative for patients that are either unable to tolerate or unwilling to risk the side effects of prescription prokinetic medicines.

Animal models have demonstrated a positive effect of ginger extract on gastric motility. Electromyography demonstrated increased contractions of the reticulum and rumen of sheep after administration of ginger extract [24]. A separate study looked at the effects of ginger extract on rabbit, rat, and guinea-pig small bowel motility. The largest stimulatory effect was noted in rabbit and rat small bowel, with a lesser but still significant effect in guinea-pigs [25]. Interestingly, the mechanism of action was found to be somewhat different between the animal models, with rabbits and rats demonstrating muscarinic receptor involvement and guinea-pigs showing a separate and unknown mechanism. Ex vivo animal preparations used as bioassays were exposed to gingerols and shogoal, active ingredients from ginger, with results suggesting mild antagonistic effects on the M3 and 5-HT3 receptors (possibly involved in alleviating nausea) but no effect on 5-HT4 receptors involved in gastroduodenal motility [26].

Hu et al. [27] evaluated the physiological effect of ginger versus placebo on gastric motility in patients with functional dyspepsia. After fasting for 8 hours, patients were given either capsules of ginger (1.2 g) or placebo, followed 1 hour later by 500mL of soup. Ultrasound was used to measure antral area, fundal area/diameter, and antral contraction frequency; gastric half-emptying time was calculated using the change in antral area seen on ultrasound. The patients in the ginger group demonstrated faster gastric emptying, with median half-emptying time of 12.3 minutes versus 16.1 minutes in the placebo group, as well as demonstrating an increase in antral contractions. Ginger administration did not result in significant changes in GLP-1, motilin or ghrelin [27]. A larger study in 24 healthy volunteers, performed in the same method, showed a similar effect on gastric motility. In this study, the median gastric half-emptying time in the test group was 13.1 minutes versus 26.7 minutes in the placebo group [28]. Emptying of liquids clinically is considered a passive process, and no authors have yet evaluated changes in solid phase gastric emptying.

A double-blind, randomized controlled trial of 12 healthy men showed stimulation of gastroduodenal motility based on stationary manometry [29]. A total of 200 mg of ginger extract was administered, and the fasting and post-prandial motility was then assessed. Motility was found to be increased by ginger extract in both the fasting state and after the test meal in the test group.

The stimulatory effect of ginger on gastric motility was applied in a clinical setting in a separate study on adult patients admitted to an intensive care unit with respiratory distress [30]. This study randomized 32 ventilator-dependent patients with nasogastric feedings to either receive 120 mg of ginger extract or 1 g of coconut oil as placebo. Patients were evaluated for 21 days for end-points including the amount of feeding tolerated within 48 hours, total amount of feeding tolerated, nosocomial pneumonia (attributed primarily to aspiration), number of ICU-free days, number of ventilator-free days, and overall mortality. Patients in the test group were found to tolerate an increased amount of feeding during the first 48 hours and developed fewer nosocomial pneumonias. The remaining end-points were not significantly altered. The authors suggested a utility for ginger extract in stimulating gastric motility in patients not know to have gastroparesis who were at risk for decreased gastric motility and associated aspiration pneumonia.

**Summary**

Ginger, an ancient medicinal herb, clearly appears to have a role in contemporary medicine. A clear benefit in the management of nausea and vomiting, both during pregnancy and associated with the administration of cancer chemotherapy, has been demonstrated. Interesting data in humans and animal models suggest a possible role in the management of patients with functional dyspepsia or gastroparesis. The availability of a readily available, inexpensive product with little reported toxicity would be welcome as clinicians try to manage these complicated and challenging patients. It is our hope that this review will result in a more in depth investigation of the use of ginger in the management of patients with a gastroparesis.

**References**

1. Pizzorno J, Murray M. *Zingiber officinale* (Ginger). In: Textbook of Natural Medicine. St. Louis, MO: Elsevier/Saunders; 2012: p 1147-1153.
2. Lete I, Allué J. The Effectiveness of Ginger in the Prevention of Nausea and Vomiting During Pregnancy and Chemotherapy. Integr Med Insights. 2016;11:11-7.
3. Zhang F, Ma N, Gao Y, Sun, L, and Zhang J. Therapeutic Effects of 6‐Gingerol, 8‐Gingerol, and 10‐Gingerol on Dextran Sulfate Sodium‐Induced Acute Ulcerative Colitis in Rats. Phytother Res. 2017; 31: 1427–1432.
4. Kim MS, Kim JY. Ginger Attenuates Inflammation in a Mouse Model of Dextran Sulfate Sodium-Induced colitis. Food Sci Biotechnol. 2018; 27:1493-1501.
5. Zaghlool SS, Shehata BA, Abo-Seif AA, Abd El-Latif HA. Protective Effects of Ginger and Marshmallow Extracts on Indomethacin-Induced Peptic Ulcer in Rats. J Nat Sci Biol Med. 2015;6(2):421-8.
6. Prasad S, Tyagi AK. Ginger and its Constituents: Role in Prevention and Treatment of Gastrointestinal Cancer. Gastroenterol Res Pract. 2015;2015:142979.
7. Badawi M. Histological Study of the Protective Role of Ginger on Piroxicam-Induced Liver Toxicity in Mice. J Chin Med Assoc. 2018 Aug 9. Pii S1726-4901(18), doi: 10.1016/j.jcma.2018.06.006.
8. Rahimlou M, Yari Z, Hekmatdoost A, Alavian SM, Keshavarz SA. Ginger Supplementation in Nonalcoholic Fatty Liver Disease: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. Hepat Mon. 2016; 16: e34897.
9. Camilleri M, Parkman H, Shafi M, Abell T, Gerson L. Clinical Guideline: Management of Gastroparesis. Am J Gastroenterol. 2013; 108:18-38.
10. Hyett B, Martinez F, Gill B, Mehra S, Lembo A, Kelly C, et al. Delayed Radionucleotide Gastric Emptying Studies Predict Morbidity in Diabetics with Symptoms of Gastroparesis. Gastroenterology. 2009; 137: 445-452.
11. Giacosa A, Morazzoni P, Bombardelli E, Riva A, Bianchi Porro G, Rondanelli, M. Can Nausea and Vomiting be Treated with Ginger Extract? Eur Rev Med Pharmacol Sci. 19; 2015. 1291-6.
12. Vutyavanich T, Kraisarin T, Ruangsri R. (2001). Ginger for Nausea and Vomiting in Pregnancy: Randomized, Double-Masked, Placebo-Controlled Trial. Obstet Gynecol. 97; 2001: 577-82.
13. Smith C, Crowther C, Willson K, Hotham N, McMillian V. A Randomized Controlled Trial of Ginger to Treat Nausea and Vomiting in Pregnancy. Obstet Gynecol. 2004; 103:639-645.
14. Marx W, Ried K, McCarthy A, Vitetta L, Sali A, McKavanagh D, et al. Ginger–Mechanism Of Action In Chemotherapy‐Induced Nausea And Vomiting: A Review. Crit Rev Food Sci Nutr. 2017; 57:141-146.
15. Konmun J, Danwilai K, Ngamphaiboon N, Sripanidkulchai B, Sookprasert A, Subongkot S. (2017). A phase II Randomized Double-Blind Placebo-Controlled Study of 6-Gingerol as an Anti-Emetic in Solid Tumor Patients Receiving Moderately to Highly Emetogenic Chemotherapy. Med Oncol. 2017; 34:69. 10.1007/s12032-017-0931-4.
16. Ryan JL, Heckler CE, Roscoe JA, Dakhil SR, Kirshner J, Flynn PJ, et al. Ginger (Zingiber officinale) Reduces Acute Chemotherapy-Induced Nausea: a URCC CCOP Study of 576 Patients. Support Care Cancer. 2011; 20(7):1479-1489.
17. Pillai AK, Sharma KK, Gupta YK, Bakhshi S. Anti‐Emetic Effect of Ginger Powder Versus Placebo as an Add‐On Therapy in Children and Young Adults Receiving High Emetogenic Chemotherapy. Pediatr Blood Cancer. 2011; 56:234-238.
18. Marx W, McCarthy AL, Ried K, McKavanagh D, Vitetta L, Sali A, et al. The Effect of a Standardized Ginger Extract on Chemotherapy-Induced Nausea-Related Quality of Life in Patients Undergoing Moderately or Highly Emetogenic Chemotherapy: A Double Blind, Randomized, Placebo Controlled Trial. Nutrients. 2017; 9(8):867.
19. Tóth B, Lantos T, Hegyi P, Viola R, Vasas A, Benko R, et al. Ginger (Zingiber officinale): An Alternative for the Prevention of Postoperative Nausea and Vomiting. A Meta Analysis. Phytomedicine. 2018; 50:8-18.
20. Phillips S, Ruggier R, Hutchinson SE. Zingiber officinale (Ginger)–An Antiemetic for Day Case Surgery. Anaesthesia. 1993; 48(8): 715-717.
21. Soltani E, Jangjoo A, Afzal Aghaei M, Dalili A. Effects of Preoperative Administration of Ginger (Zingiber officinale Roscoe) on Postoperative Nausea and Vomiting after Laparoscopic Cholecystectomy. J Tradit Complement Med. 2017; 8(3):387-390.
22. Talley NJ. (2017). Functional Dyspepsia: Advances in Diagnosis and Therapy. Gut Liver. 2017; 11(3): 349-357.
23. Giacosa A, Guido D, Grassi M, Riva A, Morazzoni P, Bombardelli E, et al. The Effect of Ginger (Zingiber officinalis) and Artichoke (Cynara cardunculus) Extract Supplementation on Functional Dyspepsia: A Randomised, Double-Blind, and Placebo-Controlled Clinical Trial. Evid Based Complement Alternat Med. 2015; 2015:1-9.
24. Mamaghani A, Maham M, Dalir-Naghadeh B. Effects of Ginger Extract on Smooth Muscle Activity of Sheep Reticulum and Rumen. Vet Res Forum. 2013; 4(2):91-97.
25. Ghayur MN, Gilani AH. Species Differences in the Prokinetic Effects of Ginger. Int J Food Sci Nutr. 2006; 57:65-73.
26. Pertz HH, Lehmann J, Roth-Ehrang R, Elz S. Effects of Ginger Constituents on the Gastrointestinal Tract: Role of Cholinergic M3 and Serotonergic 5-HT3 and 5-HT4 Receptors. Planta Med. 2011; 77:973-978.
27. Hu ML, Rayner K, Wu KL, Chuah SK, Tai WC, Chou YP, et al. Effect of Ginger on Gastric Motility and Symptoms of Functional Dyspepsia. World J Gastroenterol. 2011; 17(1):105-110.
28. Wu KL, Rayner CK, Chuah SK, Changchien CS, Lu SN, Chiu YC, et al. Effects of Ginger on Gastric Emptying and Motility in Healthy Humans. Eur J Gastroenterol Hepatol. 2008; 20(5):436-440.
29. Micklefield GH, Redeker Y, Meister V, Jung O, Greving I, May B. Effects of Ginger on Gastroduodenal Motility. Int J Clin Pharmacol Ther. 1999; 37:341-346.
30. Shariatpanahi ZV, Taleban FA, Mokhtari M, Shahbazi S. Ginger Extract Reduces Delayed Gastric Emptying and Nosocomial Pneumonia in Adult Respiratory Distress Syndrome Patients Hospitalized in an Intensive Care Unit. J Crit Care. 2010; 25(4):647-650.