

# Ginger as an Antiemetic Modality for Chemotherapy-Induced Nausea and Vomiting: A Systematic Review and Meta-Analysis

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**C**hemotherapy-induced nausea and vomiting (CINV) is a well-known and distressing side effect of chemotherapy. The control of CINV is significantly improved with effective antiemetics such as 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonists (RAs), neurokinin-1 (NK-1) RAs, and dexamethasone. The use of currently recommended antiemetic regimens has enabled the achievement of high rates of complete response, which is defined as no emesis and no need for rescue medication (Gralla et al., 2003; Hesketh et al., 2003; Poli-Bigelli et al., 2003). However, considerable numbers of patients report experiencing nausea from chemotherapy. An estimated 36%–62% of patients report experiencing nausea during the delayed phase, defined as 24 hours postchemotherapy, even with concurrent use of a guideline-recommended antiemetic regimen (i.e., aprepitant, palonosetron, and dexamethasone for highly emetogenic chemotherapy; palonosetron and dexamethasone for moderately emetogenic chemotherapy) (Aapro et al., 2010; Celio et al., 2011; Navari, Gray, & Kerr, 2011). Less effective control of CINV during the delayed phase and the symptom of nausea with currently available antiemetics have led researchers to search for nonpharmacologic approaches for improving the control of CINV.

Ginger (*Zingiber officinale*) is a traditional antiemetic, the effects of which have been investigated since ancient times. Studies have found antiemetic properties of ginger as the inhibitory effects of its components (i.e., gingerols and shogaols) at 5-HT<sub>3</sub> receptors (Abdel-Aziz, Windeck, Ploch, & Verspohl, 2006; Pertz, Lehmann, Roth-Ehrang, & Elz, 2011) and cholinergic M<sub>3</sub> receptors (Pertz et al., 2011). An antiemetic effect of ginger in the control of postoperative nausea and vomiting has been supported by a meta-analysis (Chaiyakunapruk, Kitikannakorn, Nathisuwan, Leeprakobboon, & Leela-settagool, 2006). A Cochrane review suggested the possible benefit of ginger in the control of pregnancy-related nausea and vomiting (Matthews, Dowswell, Haas, Doyle, & O'Mathúna, 2010). However, studies

**Purpose/Objectives:** To evaluate the effect of ginger as an antiemetic modality for the control of chemotherapy-induced nausea and vomiting (CINV).

**Data Sources:** Databases searched included MEDLINE® (PubMed), Embase, CINAHL®, Cochrane Central Register of Controlled Trials, Korean Studies Information Service System, Research Information Sharing Service by the Korean Education and Research Information Service, and Dissertation Central.

**Data Synthesis:** A systematic review was conducted of five randomized, controlled trials involving 872 patients with cancer. Ginger was compared with placebo or metoclopramide. The participant characteristics, chemotherapy regimen and antiemetic control, ginger preparation and protocol, measurements, results of the studies, adherence to the treatment protocol, and side effects were reviewed systematically. The incidence and severity of acute and delayed CINV were subject to meta-analysis. The incidence of acute nausea ( $p = 0.67$ ), incidence of acute vomiting ( $p = 0.37$ ), and severity of acute nausea ( $p = 0.12$ ) did not differ significantly between the ginger and control groups.

**Conclusions:** Current evidence does not support the use of ginger for the control of CINV. Ginger did not contribute to control of the incidence of acute nausea and vomiting or of the severity of acute nausea.

**Implications for Nursing:** Ginger has long been regarded as a traditional antiemetic modality, but its effectiveness remains to be established. The findings of this study could be incorporated into clinical guidelines, such as the Oncology Nursing Society's Putting Evidence Into Practice resources. Current evidence supports the need for more methodologically rigorous studies in this area.

**Knowledge Translation:** Although ginger is known as a traditional antiemetic, current evidence does not support the effect of ginger in CINV control. The findings of this study inform healthcare providers that its effectiveness remains to be established from methodologically rigorous future trials.

regarding the effect of ginger in CINV control have yielded both positive and negative results, making its efficacy uncertain (Dabbour, 2007; Levine et al., 2008; Manusirivithaya et al., 2004; Pace, 1986; Pecoraro,

Patel, Guthrie, & Ndubisi, 1998; Pillai, Sharma, Gupta, & Bakhshi, 2011; Ryan et al., 2009, 2012; Sontakke, Thawani, & Naik, 2003; Zick et al., 2009). A systematic review would be helpful in providing a comprehensive overview and evaluation of the current evidence regarding the effectiveness of ginger as an antiemetic modality for CINV control, and this review aimed for that overview and evaluation.

## Methods

MEDLINE® (PubMed), Embase, CINAHL®, Cochrane Central Register of Controlled Trials, Korean Studies Information Service System, Research Information Sharing Service by the Korean Education and Research Information Service, and Dissertation Central were searched using the following keywords: *chemotherapy, nausea, vomiting, chemotherapy induced nausea and vomiting, ginger, ginger extract, and Zingiber officinale*. Additional searches were conducted using reference lists from the identified studies and Web searches (see Figure 1).

Eleven randomized, controlled trials were identified: seven published journal articles, two abstracts from conference proceedings, and two dissertations (Dabbour, 2007; Levine et al., 2008; Lu, Yang, Meng, & Chen,

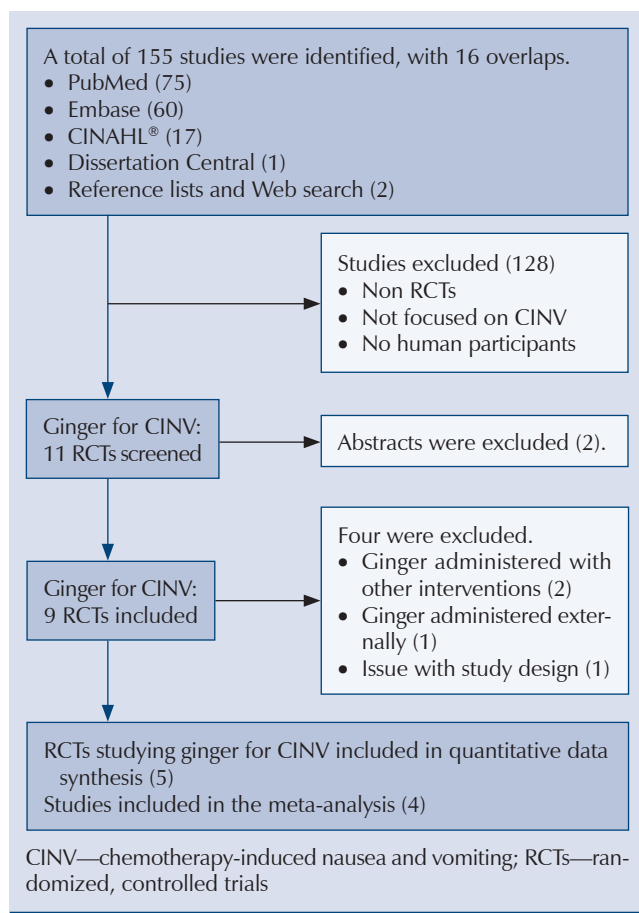
2010; Manusirivithaya et al., 2004; Pace, 1986; Pecoraro et al., 1998; Pillai et al., 2011; Ryan et al., 2009, 2012; Sontakke et al., 2003; Zick et al., 2009). Two studies that combined ginger with another intervention such as protein or peppermint were excluded because the other interventions would make it difficult to evaluate the individual effect of ginger (Dabbour, 2007; Levine et al., 2008). A study by Pecoraro et al. (1998) suggested a positive effect of ginger in acute CINV control, but the abstract did not provide sufficient details about the study, such as the patient characteristics, ginger treatment protocol, chemotherapy regimen, antiemetic control, and measurement and statistical analysis of the data; therefore, the study was excluded from the present systematic review. Pillai et al. (2011) investigated the effects of ginger in acute and delayed CINV among children and young adults. The positive findings of the study were excluded from this systematic review because the data were collected multiple times from the same participants in a nonuniform fashion (i.e., the unit of analysis was each collected data point rather than each study participant). Ryan et al. (2012) reported their trial in two forms (an abstract and an article); the article version of the trial was used in this review because it provided more details about the study. The study by Lu et al. (2010) was excluded from this systematic review because it was difficult to compare the external ginger application (using point plaster therapy) implemented therein with the orally administered ginger used in the other studies. Therefore, five studies were included in the systematic review. However, only four studies could be included in the meta-analysis because the study of Ryan et al. (2012) did not provide sufficient data for that type of analysis.

## Assessment of Methodologic Quality

The methodologic qualities of the five studies included in this review were evaluated using the **Jadad scale**, an instrument to assess the quality of reports of randomized clinical trials (Jadad et al., 1996). The Jadad scale yields scores in the range of 0 to 5, with higher scores suggesting methodologic rigorousness in terms of randomization, blinding, and accountability of participants. Three studies yielded a score of five (Pace, 1986; Ryan et al., 2012; Zick et al., 2009) and the other two had a score of four (Manusirivithaya et al., 2004; Sontakke et al., 2003).

## Analyses

A systematic review was conducted and Cochrane Review Manager, version 5, was used to conduct a meta-analysis of the data. Binary outcome variables were reported as the risk ratio (RR) using the Mantel-Haenszel method with the fixed effects model. Continuous outcome variables were evaluated in terms of mean difference (MD) using the inverse variable weighted method



**Figure 1. Study Diagram**

**Table 1. Literature Review of the Use of Ginger for Chemotherapy-Induced Nausea and Vomiting (CINV) Control**

Study	Sample and Design	Chemotherapy	Antiemetic Control	Treatment	Measurement	Result and Comments
Manusirivithaya et al., 2004	43 female patients with ovarian or cervical cancer Double-blinded, randomized, controlled trial (cross-over design)	Cisplatin-based regimen	Metoclopramide, dexamethasone, and lorazepam in the acute phase, and no antiemetic coverage during the delayed phase for the ginger arm; metoclopramide for the control arm during the delayed phase	Ginger versus placebo during the acute phase, and ginger versus metoclopramide 40 mg PO during the delayed phase; 1 g ginger for days 1–5 (two cycles) starting 30 minutes prior to chemotherapy	Severity of nausea (visual analog scale [VAS]) Number of emetic episodes Measured once for five days	Adding ginger to metoclopramide 50 mg + dexamethasone + lorazepam did not improve acute nausea severity and acute vomiting incidence control, and ginger was not different from metoclopramide 40 mg in delayed nausea severity and delayed vomiting incidence control. Suboptimal use of antiemetic Ginger was compared to metoclopramide during the delayed phase without antiemetic coverage.
Pace, 1986	17 women and 24 men with leukemia Double-blinded, randomized, controlled trial	Cytarabine-based regimen	Prochlorperazine	Ginger versus placebo; 3.5 g ginger on day 1, 1.5 g ginger on day 2 (single cycle), starting 30 minutes prior to chemotherapy	Severity of nausea and vomiting (semantic rating scale, VAS) Duration of nausea and vomiting Frequency of vomiting (semantic rating scale) Measured once for day 1 and day 2	Significantly less severe nausea ( $p = 0.04$ ) and less duration of nausea ( $p = 0.02$ ) in the acute phase with ginger No statistical difference in the severity, frequency, and duration of vomiting Suboptimal use of antiemetic
Ryan et al., 2012	521 women and 55 men with breast (72%), alimentary (10%), gynecologic (7%), lung (7%), and other cancers (4%) Double-blinded, randomized, controlled trial	Article lacks information about chemotherapy agents and regimen	5-hydroxytryptamine-3 receptor antagonists plus dexamethasone	Ginger versus placebo; 0.5 g, 1 g, or 1.5 g ginger for six days (two to three cycles), starting three days prior to the start of chemotherapy and three days after chemotherapy	Severity of nausea (semantic rating scale) measured four times per day Number of vomiting episodes	Significant difference in percent decrease in acute nausea severity in ginger arms (measured average nausea $p = 0.013$ , measured worst nausea $p = 0.003$ ), particularly for the 0.5 g per day and 1 g per day arms (measured average nausea, $p = 0.046$ for 0.5 g ginger and $p > 0.05$ for 1 g ginger; measured worst nausea, $p = 0.017$ for 0.5 g ginger and $p = 0.036$ for 1 g ginger) Not effective in acute and delayed vomiting control or delayed-phase nausea Ginger treatment started three days before the start of chemotherapy. Lacked information about the incidence of CINV
Sontakke et al., 2003	39 women and 11 men with undisclosed diagnoses Double-blinded, randomized, controlled trial (cross-over design)	Cyclophosphamide-based regimen	No antiemetic coverage for the ginger treatment group	Ginger versus metoclopramide (20 mg IV + 10 mg PO) or ondansetron (4 mg IV + 4 mg PO); 2 g ginger for day 1 (three cycles), starting 20 minutes prior to chemotherapy	Severity of nausea and episode of vomiting (complete control, partial control, and no control) Measured once in the acute phase only	Ginger was comparable to metoclopramide 20 mg IV + 10 mg PO in controlling acute nausea and vomiting incidence; ondansetron 4 mg IV + 4 mg PO was superior to ginger ( $p < 0.01$ ). No antiemetic coverage Ginger compared to conventional antiemetics Measured severity of the symptoms but analysis focused on the incidence of symptoms  (Continued on the next page)

Table 1. Literature Review of the Use of Ginger for Chemotherapy-Induced Nausea and Vomiting (CINV) Control (Continued)

Study	Sample and Design	Chemotherapy	Antiemetic Control	Treatment	Measurement	Result and Comments
Zick et al., 2009	122 women and 40 men with undiagnosed diagnoses Double-blinded, randomized, controlled trial	Highly, moderately, and low emetogenic chemotherapy; detailed list of chemotherapy agents; however, lacking information about chemotherapy regimen	5-hydroxytryptamine-3 receptor antagonists with or without aprepitant	Ginger versus placebo; 1 g or 2 g ginger for three days (single cycle), starting after chemotherapy (within one hour of completion of chemotherapy)	Morrow Assessment of Nausea and Emesis for acute-phase CINV Modified Morrow Assessment of Nausea and Emesis for delayed-phase CINV Measured twice for day 1 and for days 2–3	Ginger arm did not differ from placebo arm in the incidence of acute and delayed CINV. Patients with 2 g per day of ginger reported significantly more severe delayed nausea than placebo and 1 g per day of ginger ( $p = 0.03$ ). Patients with aprepitant with 1 g per day of ginger and 2 g per day of ginger experienced more severe delayed nausea than placebo ( $p = 0.001$ ). Ginger treatment started after the start of chemotherapy Suggests possible interaction between ginger and aprepitant Suggests dose-limiting effect of ginger

with a fixed effects model. Confidence intervals of 95% (95% CIs) were calculated. Higgins'  $I^2$  values higher than 50% were considered as having substantial heterogeneity and, therefore, the random effects model was applied to analyze the data (Higgins & Green, 2011).

## Results

### Participant Characteristics

In total, 872 patients with cancer were included in this review. The mean age of these patients ranged from 46.1–58.3 years, and about 85% of them were women (see Table 1). The reported cancer diagnoses of the participants were breast (12%), gynecologic (6%), hematologic (5%), alimentary (2%), lung (1%), and other (0.5%). Two studies did not specify their participants' diagnosis profiles (Sontakke et al., 2003; Zick et al., 2009). Previous experience of CINV was the main inclusion criterion (Ryan et al., 2012; Sontakke et al., 2003; Zick et al., 2009), and patients whose medical condition—rather than the chemotherapy—might have caused nausea and vomiting (Manusirivithaya et al., 2004; Pace, 1986; Ryan et al., 2012; Sontakke et al., 2003; Zick et al., 2009) or patients with a bleeding tendency or disorder were excluded from study participation (Ryan et al., 2012; Zick et al., 2009).

### Study Design

The five studies included in this systematic review all were double-blinded, randomized, controlled trials (Manusirivithaya et al., 2004; Pace, 1986; Ryan et al., 2012; Sontakke et al., 2003; Zick et al., 2009). A crossover design was applied in two studies (Manusirivithaya et al., 2004; Sontakke et al., 2003). Three studies (Pace, 1986; Ryan et al., 2012; Zick et al., 2009) compared ginger to placebo as an intervention for the control group. Manusirivithaya et al. (2004) compared ginger to placebo during the acute phase, but to metoclopramide during the delayed phase. The main comparison of Sontakke et al. (2003)'s study was ginger versus conventional antiemetics such as metoclopramide or ondansetron. Ryan et al. (2012) and Zick et al. (2009) compared different doses of ginger with respect to CINV control.

### Chemotherapy

Most of the participants were on combination chemotherapy regimens, such as those based on cisplatin (Manusirivithaya et al., 2004), cyclophosphamide (Sontakke et al., 2003), and cytarabine (Pace, 1986), which were mostly moderate to highly emetogenic (Manusirivithaya et al., 2004; Pace, 1986; Sontakke et al., 2003; Zick et al., 2009). Ryan et al. (2012) lacked information regarding the chemotherapy agents and regimens, although the prescribed antiemetics were indicative that the chemotherapy regimens would have been considered moderate to highly emetogenic. Participants received single-day chemotherapy (Zick et al., 2009), and single- and multiple-day chemotherapy (Manusirivithaya et al., 2004). Three studies did not specify the duration of chemotherapy (Pace, 1986; Ryan et al., 2012; Sontakke et al., 2003).

### Antiemetic Control

Antiemetic controls for the ginger trials were less than optimal when compared to current guidelines for antiemetic use. Aprepitant



was used only by Zick et al. (2009), in which 30% of the participants received aprepitant with 5-HT<sub>3</sub> RA for the control of CINV from moderate to highly emetogenic chemotherapies. The use of dexamethasone or other antiemetics was not reported. All participants in the study by Ryan et al. (2012) received 5-HT<sub>3</sub> RAs and dexamethasone. In two of the studies, less-optimal antiemetics such as prochlorperazine (Pace, 1986), metoclopramide, dexamethasone, and lorazepam (Manusirivithaya et al., 2004) were administered only for the acute phase. Sontakke et al. (2003) did not provide antiemetic coverage because ginger was compared to conventional antiemetics in that study.

### Ginger as an Antiemetic Treatment

The form of the ginger treatment was encapsulated ginger, which contained powdered ginger root (0.25 g or 0.5 g) (Manusirivithaya et al., 2004; Pace, 1986; Sontakke et al., 2003), dry ginger extract of gingerols and shogaol (each 0.25 g capsule of ginger contained 5.38 mg of 6-gingerol, 1.8 mg of 8-gingerol, 4.19 mg of 10-gingerol, and 0.92 mg of 6-shogaol) (Zick et al., 2009), or purified liquid extract of ginger root (0.25 g) containing gingerols, zingerone, and shogaol (Ryan et al., 2012). The daily doses of ginger varied from 0.5–3.5 g, and the treatment duration ranged from one to six days. The ginger treatment protocols involved administering ginger 20 minutes to three days before the start of chemotherapy (Manusirivithaya et al., 2004; Pace, 1986; Ryan et al., 2012; Sontakke et al., 2003), or within one hour after the start of chemotherapy (Zick et al., 2009). Participants received ginger capsules either during the acute phase only (Sontakke et al., 2003) or during the acute and delayed phases (Manusirivithaya et al., 2004; Pace, 1986; Ryan et al., 2012; Zick et al., 2009). The participants in Zick et al. (2009) were able to correctly guess their assignment by the way the capsule worked and the taste of the capsule. Other trials did not evaluate the effectiveness of the blinding.

### Measurements

The experience of CINV was evaluated subjectively by the participants, with the exception of the acute phase assessment of nausea and vomiting in the study of Manusirivithaya et al. (2004), in which the symptoms were assessed by the investigators. Rating scales such as visual analog scales (Manusirivithaya et al., 2004; Pace, 1986) and semantic rating scales (Pace, 1986; Ryan et al., 2012; Sontakke et al., 2003; Zick et al., 2009) were the predominant tools used to evaluate nausea and vomiting. Each episode of vomiting was counted and further categorized based on the participants' responses (Manusirivithaya et al., 2004; Sontakke et al., 2003). The Morrow Assessment of Nausea and Emesis was the only validated CINV measurement tool used by Zick et al. (2009). Four studies investigated acute as well as

delayed CINV (Manusirivithaya et al., 2004; Pace, 1986; Ryan et al., 2012; Zick et al., 2009), but Sontakke et al. (2003) measured only acute CINV.

## Findings

The findings of three of the studies supported the effect of ginger in the control of acute nausea (Pace, 1986; Ryan et al., 2012; Sontakke et al., 2003) and acute vomiting (Sontakke, 2003). Participants in Pace's study (1986) reported that nausea was significantly less severe ( $p = 0.04$ ) and of shorter duration ( $p = 0.02$ ) in the acute phase, as well as less severe ( $p = 0.03$ ) in the delayed phase, when ginger was compared to either placebo or the antiemetic prochlorperazine. No statistically significant differences existed in the severity, frequency, or duration of vomiting. Sontakke et al. (2003) reported that ginger was comparable to metoclopramide in controlling the incidence of acute nausea and vomiting, although ondansetron was found to be superior to ginger and metoclopramide ( $p < 0.01$ ). Ryan et al. (2012) did not provide data regarding the incidence of CINV, but their findings did support a significant decrease in acute nausea severity in the ginger arms, measured as average nausea ( $p = 0.013$ ) and worst nausea ( $p = 0.003$ ), particularly for the average nausea in the group with 0.5 g per day of ginger ( $p = 0.046$ ) and worst nausea with 0.5 and 1 g per day of ginger ( $p = 0.017$  and  $p = 0.036$ , respectively). The findings of Ryan et al. (2012) did not support the effect of ginger in acute and delayed vomiting control or in delayed nausea control.

Two studies did not support an antiemetic effect of ginger in acute- and delayed-phase CINV (Manusirivithaya et al., 2004; Zick et al., 2009). Manusirivithaya et al. (2004) found that adding ginger to a metoclopramide plus dexamethasone plus lorazepam regimen did not improve antiemetic control during the acute phase, and that the nausea severity and vomiting incidence during the delayed phase did not differ between ginger and metoclopramide. Zick et al. (2009) reported no differences in the incidence of acute and delayed CINV with ginger use. In addition, delayed nausea was more severe in patients who received 2 g per day of ginger than in those receiving 1 g per day of ginger or placebo ( $p = 0.03$ ). In the subgroup analysis of participants who received aprepitant with ginger, both 1 g and 2 g per day of ginger resulted in more severe delayed nausea than placebo ( $p = 0.001$ ).

### Adherence to the Treatment Protocol

Adherence to the treatment protocol was found to be moderate to high. Study completion rates ranged from 71%–100% (Manusirivithaya et al., 2004; Pace, 1986; Ryan et al., 2012; Sontakke et al., 2003; Zick et al., 2009),

and more than 80% of the participants adhered to the ginger treatment protocol in the three studies for which the adherence rate was reported (Pace, 1986; Ryan et al., 2012; Zick et al., 2009).

## Side Effects of Ginger

Zick et al. (2009) reported no significant difference in adverse events between each dose of ginger and placebo. Sontakke et al. (2003) found no side effects that were attributable to ginger. Three other ginger trials found that it had various side effects. More diarrhea and dizziness were reported from patients who received ginger in the study by Manusirivithaya et al. (2004); however, the difference did not reach statistical significance. Pace (1986) found that drowsiness, sleepiness, dry mouth, thirst, heartburn, or restlessness were experienced by one more participant in the ginger group than in the placebo group. Ryan et al. (2012) reported ginger-related adverse events such as grade 2 heartburn, bruising or flushing, and rash.

## Meta-Analysis

A meta-analysis was conducted for the evaluation of ginger for the control of acute nausea and vomiting incidence for Manusirivithaya et al. (2004), Sontakke et al. (2003), and Zick et al. (2009). Ginger treatment groups of any doses and duration were compared to control groups of placebo or metoclopramide. Providing ginger did not significantly affect the incidence of acute nausea ( $p = 0.67$ ) or acute vomiting ( $p = 0.37$ ). The incidence of delayed nausea could not be analyzed because it was reported for only one of the studies (Zick et al., 2009). A meta-analysis of the incidence of delayed vomiting was complicated by the issue of heterogeneity ( $I^2 = 64\%$ ) and was, therefore, analyzed using the random effect model ( $RR = 1.22$ , 95% CI = [0.44–3.43],  $p = 0.7$ ); no statistically significant difference was found (Manusirivithaya et al., 2004; Zick et al., 2009).

Another set of meta-analyses was conducted to evaluate the effectiveness of ginger in controlling the severity of acute nausea. Providing ginger with aprepitant did not significantly affect the severity of acute nausea ( $p = 0.12$ ) (Manusirivithaya et al., 2004; Pace, 1986; Zick et al., 2009). In subanalyses using parts of the data from the study of Zick et al. (2009), the random effect model was applied to deal with heterogeneity; no significant difference was found between ginger and control. The analysis of acute nausea severity produced  $I^2 = 62\%$  for the 1 g dose of ginger without aprepitant (MD =  $-0.31$ , 95% CI [ $-1.4$ ,  $0.78$ ],  $p = 0.58$ ) and  $I^2 = 59\%$  for the 2 g dose of ginger without aprepitant (MD =  $-0.34$ , 95% CI [ $-1.37$ ,  $0.69$ ],  $p = 0.52$ ). The analysis of delayed-nausea severity produced  $I^2 = 59\%$  for the 1 g dose of ginger without aprepitant (MD =  $-0.35$ , 95% CI [ $-1.09$ ,  $0.39$ ],  $p = 0.35$ ),  $I^2 = 75\%$  for the 1 g dose of ginger with aprepitant (MD =  $-0.2$ , 95% CI

[ $-1.26$ ,  $0.85$ ],  $p = 0.7$ ),  $I^2 = 65\%$  for the 2 g dose of ginger without aprepitant (MD =  $-0.31$ , 95% CI [ $-1.13$ ,  $0.51$ ],  $p = 0.46$ ), and  $I^2 = 91\%$  for the 2 g dose of ginger with aprepitant (MD =  $0.1$ , 95% CI [ $-1.54$ ,  $1.74$ ],  $p = 0.91$ ).

The results of this meta-analysis of the effectiveness of ginger in the control of CINV do not support an antiemetic effect of ginger. Providing ginger did not significantly affect the incidence of acute nausea or vomiting and did not help to control the severity of acute nausea. The limited number of available ginger trials included in this meta-analysis made evaluation using funnel plots of the publication bias difficult. A sensitivity analysis conducted by comparing different statistical models (fixed versus random effects) yielded the same results.

## Discussion

Current evidence does not support that ginger exerts a positive effect on the incidence of acute CINV or the severity of acute nausea. The few studies that have investigated the effect of ginger in CINV control have provided incongruent results. The characteristics of the participants, chemotherapy regimens, antiemetic use, preparation of ginger capsules, dose of ginger administered, and duration of ginger treatment all could have influenced the results of the studies.

The antiemetic control of ginger trials was considered less than optimal. Inadequate antiemetic coverage makes it difficult to evaluate the benefits of nonpharmacologic interventions (e.g., ginger consumption). Only two trials used 5-HT<sub>3</sub> RA as an antiemetic control, and they yielded conflicting results (Ryan et al., 2012; Zick et al., 2009). The hypothesis that ginger exerts an antiemetic effect through weak inhibition of 5-HT<sub>3</sub> receptors (Abdel-Aziz et al., 2006; Pertz et al., 2011) was difficult to test using data obtained in the analyzed ginger trials. Sontakke et al. (2003) only partly supported the hypothesis because the ginger was less effective than ondansetron; however, whether the effect of ginger was attributable to the inhibition of 5-HT<sub>3</sub> receptors was unclear. The weak inhibitory effect of ginger might not be strong enough to exert an antiemetic effect to control the incidence or severity of CINV; additional investigation is required to establish that idea. Zick et al. (2009) was the only trial that used the NK-1 RA aprepitant as an antiemetic; the use of aprepitant with ginger increased the severity of nausea, suggesting an interaction between ginger and prescribed antiemetics and aprepitant in particular, which warrants additional investigation. Although they were not clearly explained in the included ginger trials, the potential antiemetic mechanisms of ginger (i.e., the inhibition of 5-HT<sub>3</sub> receptors and possible interaction with NK-1 receptors) could comprise a comprehensive feature of antiemetics that advocates ginger as an attractive antiemetic for the control of CINV.

Only Ryan et al. (2012) used formulated ginger capsules, whereas the other studies used unformulated powdered ginger root or dry extract of ginger root. That made it difficult to evaluate whether the ginger formulation influenced the results of the trials. A daily ginger dose of 0.5–3.5 g had positive effects in controlling acute nausea (Pace, 1986; Ryan et al., 2012; Sontakke et al., 2003) and acute vomiting (Sontakke et al., 2003). However, a daily ginger dose of 1 g had no effect on nausea severity or vomiting incidence in the acute and delayed phases (Manusirivithaya et al., 2004). The daily ginger dose of 2 g increased the severity of nausea in the study of Zick et al. (2009). Future trials should be performed with low-dose ginger (e.g., 0.5 g per day), as suggested by Ryan et al. (2012), because daily doses of 1 g and 2 g in combination with aprepitant have resulted in more severe delayed nausea (Zick et al., 2009). The dose-specific effects of ginger and possible interactions with recommended antiemetics require further investigation.

The question remains as to when to initiate ginger therapy. Ryan et al. (2012) started ginger treatment three days prior to the start of chemotherapy, which induced a faster decrease in acute nausea in the ginger arms. Zick et al. (2009) did not provide prechemotherapy ginger, but started ginger within one hour of the completion of chemotherapy, and the result was negative. Studies in which ginger treatment was commenced 20–30 minutes before the start of chemotherapy yielded both positive and negative results (Manusirivithaya et al., 2004; Pace, 1986; Sontakke et al., 2003). Additional study is warranted to determine whether providing ginger prior to the start of chemotherapy achieves better protection from CINV.

The finding of Ryan et al. (2012) that ginger facilitated a faster decrease in acute nausea severity introduces a different aspect regarding the benefit of ginger in CINV control. However, the idea that ginger promotes a faster decrease in nausea severity requires careful consideration. Ryan et al. (2012) did not provide data regarding the incidence of CINV, so it was not possible to include their findings in the meta-analysis. The meta-analysis excluding that study did not support the effect of ginger in the control of acute nausea severity. Ryan et al. (2012) used average nausea and worst nausea as variables: a ginger dose of 1 g resulted in a significantly faster decrease in worst nausea, but not in average nausea. The different end points, which did not include the incidence of CINV, and different analytic approaches in that study hindered comparative evaluations regarding the effect of ginger in the control of acute nausea severity.

Lack of blinding in the ginger trials also could have influenced the results. In the double-blind trial by Zick et al. (2009), patients were able to determine which arm

they were assigned by the way the capsule worked and tasted. The double encapsulation and nitrogen cap used by Ryan et al. (2012) could at least mask the smell and color of the content. None of the other trials provided information regarding the maintenance of the blinding.

Although the effectiveness of ginger requires more investigation, it was safe and well tolerated by the participants as a nonpharmacologic modality. Only a few participants experienced significant side effects from ginger use, such as grade 2 heartburn and bruising. The adherence rate to consumption of the prescribed ginger was high.

## Limitations

This systematic review was limited by the small number of available studies and the use of different study end points regarding the effect of ginger in CINV control. The inclusion of data from crossover trials in the meta-analysis might have influenced the results of this study, although no carryover effect was found (Manusirivithaya et al., 2004).

## Conclusion

Current evidence does not support the use of ginger for the control of CINV. Ginger did not contribute to control of the incidence of acute nausea and vomiting or of the severity of acute nausea. More methodologically rigorous studies investigating the effect of ginger for the control of CINV are required. Controlling the chemotherapy regimen, antiemetic use, risk factors of CINV development, preparation of ginger capsules, dose of ginger administered, and duration of ginger treatment in future trials would increase understanding of the effect of ginger in CINV control.

Ginger has long been regarded as a traditional antiemetic modality, but the findings of this study should inform healthcare providers that its effectiveness remains to be established. These findings could be incorporated into clinical guidelines, such as the Oncology Nursing Society Putting Evidence Into Practice resources. Current evidence supports the need for more methodologically rigorous studies of the effectiveness of ginger in the control of CINV, and this systematic review could be used as a practical guide for such studies.

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Digital Object Identifier: 10.1188/13.ONF.163-170



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