Ginger (Zingiber officinale) and chemotherapy-induced nausea and vomiting

A systematic literature review

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is a common side-effect of cytotoxic treatment. It continues to affect a significant proportion of patients despite the widespread use of anti-emetic medication. In traditional medicine, ginger (*Zingiber officinale*) has been used to prevent and treat nausea in many cultures for thousands of years. However, its use has not been confirmed in the chemotherapy context. To determine the potential use of ginger as a prophylactic or treatment of CINV, a systematic literature review was conducted. Reviewed studies comprised randomised controlled trials or cross-over trials that investigated the anti-CINV effect of ginger as the sole independent variable in chemotherapy patients. Seven studies met the inclusion criteria. All studies were assessed on methodological quality and their limitations were identified. Studies were mixed in their support of ginger as an anti-CINV treatment in patients receiving chemotherapy, with three demonstrating a positive effect, two in favour but with caveats and two showing no effect on measures of CINV. Future studies are required to address the limitations identified before clinical use can be recommended.

Key words: nausea, ginger, chemotherapy, CINV

Introduction

Chemotherapy is one of medicine's key interventions in the treatment of cancer. While cytotoxic interventions for cancer are efficacious, they are often accompanied by a variety of adverse effects. Chemotherapy-induced nausea and vomiting (CINV) is a relatively common side effect of this treatment. A combination of different classes of anti-emetic medications such as 5-HT_3 antagonists, neurokinin 1 (NK_1) receptor antagonists, corticosteroids and anti-anxiolytics have been shown to have additive effects and are commonly prescribed for patients having chemotherapy. Vomiting has now been largely controlled but efforts to control nausea have been less successful; affecting upwards of 60% of patients.[1] Persistent nausea is also considered the most distressing symptom for patients in this setting.[2,3] This is of particular concern in oncology patients as nausea and vomiting can adversely affect food intake, increasing the risk of malnutrition during treatment. Previous studies report one in two patients in this setting as malnourished.[4] The cumulative effect of pre-treatment and treatment-related malnutrition can be one of compromised immune function, decreased performance status, poor response to treatment, and sometimes, treatment discontinuation.[5-7]

The use of integrative or complementary therapies has been steadily increasing in western countries.[8] This wide-spread use of integrative therapies has resulted in an increased interest in the investigation of these therapies as either stand-alone or adjuvant treatments for treating clinical conditions. Ginger (*Zingiber officinale*) has a long history in many cultures as a folk-remedy for nausea and gastrointestinal discomfort. Empirical research has demonstrated that ginger may be effective as an

anti-nausea agent and in particular, it has been proposed as a possible candidate for anti-CINV therapy.

While the exact mechanism of action is unknown, multiple active constituents within ginger (i.e. gingerols, shogoals, zingiberene, zingerone, and paradol) have been identified as potentially exerting beneficial effects on multiple areas implicated in the pathophysiology of CINV. Cell culture and animal studies suggest that these constituents stimulate oral and gastric secretions, regulate gastrointestinal motility,[9,10] interact with the 5-HT_3 receptors implicated in the CINV reflex,[11] and assists in rescuing intracellular redox.[12,13] Furthermore, animal studies provide preliminary support for the role of ginger supplementation in the prevention of cisplatin-induced emesis.[14,15]

Few adverse effects from the ingestion of ginger are reported in the literature.[16] Oral ginger is generally well tolerated, with mild gastrointestinal adverse effects including abdominal discomfort, heartburn, and diarrhoea being the most commonly reported. Theoretically, ginger inhibits platelet aggregation which could result in excessive bleeding, however this has not been reported in practice.[17] When added to conventional anti-emetics used in the prophylaxis and treatment of CINV, ginger does not appear to increase adverse effects.[18] Indeed, conventional anti-emetics appear to have a more varied adverse effect profile (including more severe adverse effects) compared to ginger. For example, steroids such as dexamethasone used for short durations commonly cause gastrointestinal adverse effects such as dyspepsia and psychological effects such as insomnia, while 5-HT_3 receptor antagonists such as ondansetron commonly cause constipation and headache.[19,20]

Whilst direct cost comparison between ginger and standard anti-emetic therapies is difficult due to lack of dose equivalency, it is likely that ginger would compare well, given its low ingredient cost and accessibility. Ginger is already readily available in several commercial non-prescription formulations, and requires little technical innovation in terms of cultivation and preparation.[21]

Ernst et al.[16] published a review on the effect of ginger on nausea and vomiting in a variety of settings, including only one paper that specifically investigated its effects on CINV. The review found that ginger was generally beneficial; however, firm conclusions could not be made due to the low number of studies in each setting. Multiple papers have since been published in this area and therefore, our review aims to detail the current published research from randomised, controlled trials (RCTs) and evaluate the efficacy of ginger in the prevention of CINV, highlighting areas for future investigation.

Method

A systematic search of the literature was conducted using PubMed, the Cochrane Library, and CINAHL, as well as bibliographies of past research on the subject (see Figure 1). Search terms were not limited by timeframe and therefore all searches were between April 2012 and the date of the databases inception. Articles were identified using the search terms "("*Zingiber officinale*" OR "ginger") AND ("cancer" or "chemotherapy") AND ("nausea" OR "emesis" OR "vomit" OR "CINV")". Inclusion criteria for this review were: 1) RCT and/or cross-over trials that used either placebo or current anti-CINV treatment as a control; 2) In human participants, undergoing chemotherapy; 3) The use of ginger as the main intervention and specifically investigating its effects on nausea and vomiting; and 4) Published in English.

All studies included in this review were analysed for common characteristics and methodologies, major findings, and potential limitations. Additionally, all studies were individually rated for evidence level using the National Health and Medical Research Council (NHMRC) Hierarchy of Evidence guidelines (IV-I, with I being the strongest level of evidence) as well as assessed in terms of quality (positive, neutral, negative) using the American Dietetic Association's quality criteria checklist. [22,23]

The overall body of evidence (based on a summary of the individual studies) evaluated within this review was assessed using a separate tool, the NHMRC's body of clinical evidence assessment matrix, an assessment tool that assigns a letter grade (A: strongest to D: weakest) based on the strength of the literature included in a review. [22]

Results

The search strategy identified seven studies (Table 1) that provided Level II evidence and all had a positive quality rating. Hence, all studies included in this review possessed attributes consistent with rigorous scientific method, such as randomised group allocation and clear inclusion and/or exclusion criteria. Of note, two studies did not meet the inclusion criteria as they were unpublished literature (Pecoraro et al.[24], Pace et al.[25]) and two studies (Levine et al.[26], Meyer at al.[27]) were excluded as they utilised an ineligible study design.

Study characteristics

All seven studies included in this review were RCTs, three of which were cross-over trials. Two cross-over trials used current anti-CINV treatment as the control group rather than placebo.[28,29] Five of the seven studies had relatively small sample sizes (approximately 30-70 participants in total). Zick et al.[18] and Ryan et al.[30] were the

exceptions, with 129 and 576 participants completing each trial respectively. The length and timeframe of symptom assessment varied between studies, with assessment of CINV symptoms conducted anytime from three days prior to chemotherapy treatment and up to 10 days post-treatment. The outcomes measured in the majority of studies (5/7) were acute nausea and vomiting (24 hours post-chemotherapy) and delayed nausea and vomiting (between two and ten days post-chemotherapy); however, Ryan et al.[30] did not measure vomiting symptoms and Sontakke et al.[28] measured acute nausea and emetic events only.

Typical dosing regimens were 1g to 2g of ginger, divided into four to eight capsules and consumed over a period of one to ten days. The majority of studies used powdered ginger preparations, while two studies used extracts that were standardised to either their gingerol content or to a combination of active compounds (shogoals, gingerols and zingerone). Zick et al.[18] independently verified the preparations using high-performance liquid chromatography to ensure the potency of the intervention and found their extract contained “5.38 mg (2.15%) 6-gingerol, 1.80 mg (0.72%) 8-gingerol, 4.19 mg (1.78%) 10-gingerol, and 0.92 mg (0.37%) 6-shogaol”. Ryan et al.[30] reported that the ginger preparation used within their study contained 8.5mg of active constituents per capsule; however, it was unclear whether this was independently analysed or from the manufacturers’ analysis. None of the studies that used a powdered formulation reported an analysis of active constituents. The timing of doses did not vary greatly between studies, with the initial dose generally given +/-1 hour of the first chemotherapy session. Ryan et al.[30] was the exception to this in providing ginger supplementation for the three days prior to chemotherapy.

Five of the seven studies used standard anti-CINV medication in conjunction with ginger. In the two studies that did not use ginger as an adjuvant to standard therapy, ginger was compared to ondansetron and metoclopramide as a stand-alone treatment in a cross-over trial[28] or combined with standard anti-CINV treatment in the acute phase, but compared as a stand-alone treatment in the delayed phase of the study.[29] Participants in four of the seven of studies were adults of mixed gender, with the exceptions of Panahi et al.[31] and Manusirivithaya et al.[29] who studied females and Pillai et al.[32] who studied children.

Study results

The results of the included studies were mixed. Two of the seven studies reported no benefit,[18,33] three determined some benefit on measures of CINV (measures of either acute nausea[30,31] or both acute and delayed nausea and vomiting[32]) and two reported that ginger performed equally as well as metoclopramide (Table 2).[28,29] Zick et al.[18] found that higher doses (2g) of ginger had a negative effect on delayed-CINV in participants prescribed aprepitant (p=0.01).[16]

Sontakke et al.[28] found 2g of ginger effective in reducing acute CINV equal to metoclopramide; Pillai et al.[32] determined that 1-2g of ginger was effective in reducing the severity of both acute and delayed CINV by 37-47%; while Ryan et al.[30] reported that all doses used in the intervention successfully reduced symptoms of acute nausea by 0.16-0.44 on a 1-7 Likert scale in patients experiencing mild baseline-CINV (p=0.003), with 0.5g and 1g (p=0.017 and p=0.036, respectively) being the most effective doses;~~,~~ however, delayed nausea and quality of life were not affected by ginger supplementation. A 16% reduction in acute nausea during the

first 6-24 hours post-chemotherapy was also found by Panahi et al.[31] using 1.5g of ginger (p=0,04).

Manusirivithaya et al.[29] reported that during the acute phase of chemotherapy, 1g of ginger did not further reduce CINV when combined with metoclopramide therapy. It did, however, perform equally to metoclopramide during the delayed phase (2-5 days post-chemotherapy). Zick et al.[18] and Fahimi et al.[33] found no additional benefit when ginger was used as an adjuvant therapy to standard nausea and emetic control.

A variety of tools were used to assess nausea and vomiting in the studies reviewed. Two studies measured symptoms using a modified version of the Morrow Assessment of Nausea and Emesis (MANE),[18,33] a validated instrument for assessing nausea in cancer patients[34]; Pillai et al.[32] employed the Edmonton Symptom Assessment Scale and the National Cancer Institute Guidelines for Nausea and Vomiting, respectively; two studies used an unspecified tool[28,29]; Panahi et al. [31] employed the Rhodes Index of Nausea, Vomiting, and Retching; and Ryan et al.[30] utilized a tool developed by Burish and Carey.[35]

Five of the seven studies specifically included patients receiving highly emetogenic chemotherapy regimens; however, while all being highly emetogenic regimens, there was little consistency in the agent and protocol used. The remaining two studies included patients undergoing combination chemotherapy containing agents with different degrees of emetogenicity.[18,30]

Adverse events and adherence

Despite previous research indicating that ginger supplementation could theoretically cause excessive bleeding in susceptible patients due to the inhibition of platelet aggregation,[36] all adverse events that were attributed to the intervention were non-

serious in nature. The most common reactions reported included heartburn, bruising or flushing, rash, and gastrointestinal discomfort. Adverse events were generally not significantly higher in the ginger group compared to the control group in any study.

Most studies (5/7) reported some degree of non-adherence during their investigations. Studies that included information regarding adherence found a rate between 75-90%.[18,30,31,33] The exact method for determining adherence was not stated in five of the seven studies, however, Ryan et al.[30] reported that adherence was measured by counting the amount of remaining pills at the end of each study cycle while Panahi et al.[31] measured self-reported adherence.

Discussion

The evidence is mixed in its support of ginger as an adjuvant or stand-alone treatment for CINV. Of the seven RCTs published to date; five reported favourable results while two were unfavourable. Of the five favourable studies, three studies reported ginger as improving some measure of CINV when combined with standard anti-CINV treatment, with Ryan et al.[30] and Panahi et al.[31] reporting a reduction in acute nausea and Pillai et al.[32] reporting a reduction in acute and delayed nausea and vomiting. The two other favourable studies found ginger reduced some measure of CINV equal to metoclopramide but due to the lack of a placebo group in both studies, it is difficult to determine the clinical significance of these results[28,29]. This is due to the fact that in both of these trials, the percentage of individuals that reported symptoms in the ginger group was still within the predicted emetic risk for the chemotherapy regimen used and therefore, without a placebo group, it is difficult to determine the intervention's true impact. Results from positive trials have found ginger to reduce measures of CINV by 16-47% and while these findings need to be

reconciled with the negative findings from other studies in this review, this magnitude of reduction could provide meaningful relief to patients experiencing CINV.

Using the NHMRC body of evidence assessment matrix, our review indicates that there is C level evidence for the use of ginger as an anti-nausea agent in this context. Therefore while there is some supporting evidence for its use, the considerable inconsistency in study methods and outcomes reported here reflect genuine uncertainty about its use in the chemotherapy setting. Until this uncertainty is resolved, professional opinion will continue to guide the healthcare team when choosing ginger as a treatment option.

Confounding factors within current literature

There are multiple factors that explain the mixed results reported in the literature. One possible explanation is that some ginger preparations have higher levels of certain active compounds when compared to the preparations used in other studies. Research investigating the concentration of active compounds in commercial ginger products indicates that the levels of these compounds can vary greatly between products, demonstrating a need to analyse ginger interventions for their active compounds and to utilise standardised extracts rather than powdered formulations.[37,38] In order to improve the significance of future trials in this area, dose-finding studies using varied standardised extracts are required to determine the effective dose and preparation of ginger.

Recent studies have also determined that once a patient undergoing chemotherapy develops any form of nausea or vomiting (i.e. anticipatory, acute, delayed), regardless of the emetogenicity of that treatment, the likelihood of that patient experiencing nausea for the remainder of their treatment regimen is significantly

higher and more difficult to treat with standard anti-CINV medication. [39] This is due to the complex aetiology of CINV, a response that is initiated by varying stimuli within the central and peripheral nervous systems. These include the effects of chemotherapy on both the central nervous system and gastrointestinal tract as well as the effect of sensory input (e.g. smell, sight) and the psychological conditions of the individual (e.g. fear, anxiety).[40] These stimuli activate peripheral and central nerve signals which are then received by the chemoreceptor trigger zone an area within the brain, which coordinates the body's emetic response base. Anticipatory nausea and vomiting is thought to be a conditioned response to previous chemotherapy exposure. Anticipatory CINV is mediated by the central nervous system and is caused by the coupling of neutral stimuli (such as the smell or sight of the hospital environment) with the undesirable effects of chemotherapy, which then results in the initially neutral stimuli eliciting a similar response to the cytotoxic treatment.[41] Since many studies in this review included patients who had previously experienced CINV, the participants within these studies might have had an increased resistance to the intervention due to conditioning. This is of particular concern in the studies that used a cross-over design, as patients who were initially in the control group could have had established resistance to the intervention when subsequently crossed-over. Conducting statistical analysis to ensure that the sequence of intervention does not influence the results, as undertaken by Manusirivithaya et al.[29] and Zick et al.[18], will help monitor this effect. Alternatively, Roscoe and colleagues[30,42] were able to determine that a self-assessed susceptibility to nausea and vomiting by chemotherapy patients was a predictor of CINV and might be a viable method of screening in future trials.

Research has found that female patients are significantly more likely to experience CINV than their male counterparts.[43] The majority of studies (5/7) included a sample that was predominantly female, of which four studies reported benefits from ginger treatment. This suggests that gender may have influenced the patients' response to ginger treatment, possibly by decreasing the threshold at which CINV is experienced and thereby increasing the efficacy of anti-CINV treatments. In light of this, the null results reported by Fahimi et al,[33] may be partially explained by the male-dominant sample. In this study, the severity of nausea in both the intervention and control group was rated as low at all time points which indicates that the patients within this study may not have been experiencing CINV at a sufficiently high level of severity to have responded to anti-CINV intervention. This may also explain the results found by Pillai et al.[32] When the gender distributions between the control and treatment group were compared, there was a greater proportion of men within the experimental group compared to the control, which almost reached statistical significance (p=0.055). This may have also resulted in the experimental group being more resistant to CINV compared to the control group regardless of ginger treatment. Therefore, similarly to anticipatory nausea, future trials should either include screening protocols or conduct statistical analyses to account for gender variations within the study sample.

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Additionally, because of the subjective nature of nausea, direct comparison of findings can be difficult and therefore investigators should aim to use validated tools such as the MANE, which would ensure that results are both validated and easily comparable to other studies. It should be noted that the two studies that failed to find any benefit from ginger supplementation both used the MANE as the assessment tool, which suggests that the use of different assessment tools used within each

study might have been a factor contributing to the mixed results of the reviewed literature.[18,33]

Another concern is that due to the distinctive aroma of ginger, it is important to ensure that studies are properly blinded. For example, Zick et al.[18] tested the effectiveness of the blinding in their investigation. While they had taken steps to ensure adequate blinding, the participants were able to discern the intervention group from the placebo at a statistically significant rate (p=0.01). To overcome this problem, Ryan et al.[30] utilised a combination of double encapsulation with a nitrogen cap to mask the odour and colour of the ginger. While this is an example of a potentially effective blinding technique, they did not test its effectiveness. Interestingly, Ryan et al's.[30] was one of the two studies that reported positive results when ginger was used as an adjuvant therapy; effective blinding may, at least in part, help explain the disparity of results between studies within this review. Future clinical trials should incorporate more stringent blinding procedures to avoid a potential placebo or nocebo effect from occurring.

Possible drug-interactions at high doses

An interesting result reported within two studies in this review is that when subjects were given higher doses (1.5-2g) of ginger, there was a statistically significant decline in CINV control when compared to the participants that either received lower doses or the placebo. Zick et al.[18] reported that when subjects received a combination of 2g ginger plus aprepitant (an NK_1 inhibitor), the severity of delayed nausea increased when compared to control (p=0.01). Similarly, Ryan et al.[30] concluded that while all doses of ginger were effective in reducing acute CINV, 1.5g of ginger was less effective when compared to the 0.5g and 1g of ginger preparations. These findings corroborate previous studies in this field, which

reported that higher doses of ginger were less effective when treating nausea from causes other than chemotherapy.[44,45] This led Zick et al.[18] to hypothesise that ginger reduces absorption of medication by increasing gastric emptying and intestinal motility, which has been demonstrated in animal models. However, research in human trials has not determined that ginger affects gastric emptying rates.[46,47] Another hypothesis is that ginger competitively interacts with the same receptors that standard anti-CINV medication acts upon; thereby reducing the binding rate of medications when used in combination.[30] Animal studies support this hypothesis, indicating that gingerols and shoagoals are able to bind to both 5-HT_3 and substance *P* receptors, which are the receptors that medications such as aprepitant and ondansetron interact with.[48,49] It should also be noted that these studies showed that different ginger compounds bound to these receptors with varying strengths and therefore, different preparations of ginger could exert differing effects on nausea. This highlights further limitations in our current understanding in this area, as there are multiple active compounds in ginger that appear to be responsible for these interactions. This poses a significant limitation to the current research as the majority of studies, excluding Zick et al.[18] and Ryan et al.[30], used ginger preparations with unknown levels of these active constituents.

Clinical Implications

The feasibility of ginger supplementation has not been extensively or rigorously studied in chemotherapy populations. Fatigue, mouth sores and taste sensitivities are all common symptoms that chemotherapy patients experience while undergoing treatment. Given that some studies included in this review have used up to 8 capsules, consumed at multiple times throughout the day, this could place a significant burden on a population group who might already be compromised. Future

research is required to investigate areas of practice such as participant tolerability and adherence to the intervention, in addition to its effect on quality of life and patient satisfaction with the intervention, in order to determine its real-world efficacy.

Review limitations

The exclusion of unpublished literature may have affected this review by introducing a publication bias; however, the two unpublished studies that were identified and excluded from this review both reported positive results and therefore this seems unlikely.[24,25]

Conclusion

Despite the widespread use of ginger in the treatment of nausea in other contexts such as gestational nausea, the current literature provides mixed support for the use of ginger as a standard part of anti-CINV control for patients undergoing chemotherapy. Hence standard recommendations for such use are premature. This review has discussed some of the limitations in our current understanding of the area and highlights the need for further investigation. In particular, issues regarding rigorous blinding procedures, patient screening, timing of the intervention to encompass the range of CINV, and ginger preparation should be considered in future research in this area. Our analysis of the evidence using NHMRC grading indicates that ginger may be useful for some patients but also that care needs to be taken in its application until further studies are conducted.

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Declaration of Interest

Nil

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Figure 1. Flow of information for systematic review.

Table 1. Studies reviewed							
Author	Study Design	Population	Type of cancer	Chemotherapy Protocol	Country	Level of evidence	Quality
Ryan et al. (2012)[30]	Randomized, double-blind, placebo-controlled, dose-finding trial	576 adult cancer patients. Mean age of 53 years. 93% women.	72% Breast, 28% Alimentary Genitourinary, Gynaecologic, Hematologic, Lung.	Not specified.	USA	II	Positive
Panahi et al. (2012)[31]	Randomized, open-label, pilot clinical trial	78 women. Mean age: 51.83 years.	Advanced breast cancer	Predominately, the TEC regimen (docetaxel, epirubicin, and Cyclophosphamide).	Iran	II	Positive
Pillai et al. (2011)[32]	Prospective, double-blind, randomized controlled trial	58 children, cancer patients. Mean age: 15 years. 40 men,	Bone sarcoma.	Combination of cisplatin (40 mg/m^2/day) and doxorubicin (25 mg/m^2/day).	India	II	Positive

		20 women.					
Fahimi et al. (2010)[33]	Randomized, cross-over, double-blinded, placebo-controlled trial	36 adult cancer patients. Mean age of 50.23 years. 10 women, 26 men.	50% Lung cancer, 50% Unspecified.	Cisplatin with at least one of the following agents: Etoposide, Docetaxel, Gemcitabine, Docetaxel, Vinorelbine Cyclophosphamide, Paclitaxel, Doxorubicin, 5-FU, Pemetrexed.	Iran	II	Positive
Zick et al. (2009)[18]	Randomized, double-blind, placebo-controlled trial	129 adult cancer patients. Mean age of 55.5-58 years. Approximately 75% female.	Unspecified.	Multiple regimens of varying emetogenicity.	USA	II	Positive
Manusirivithaya et al. (2004)[29]	Randomized, double-blind	43 female cancer patients. Mean	76% Ovary, 23% Cervix.	Cisplatin with one of the following agents:	Thailand	II	Positive

	crossover trial	age of 43 years.		cyclophosphamide, ifosfamide, etoposide & bleomycin, 5-fluorouracil.			
Sontakke et al. (2003)[28]	Randomized, prospective, cross-over, double-blind trial	50 cancer patients. Median age of 46 years. 39 female, 11 male.	Unspecified.	Cyclophosphamide (500-1000mg) with at least one of the following agents: vincristine, methotrexate, 5-fluorouracil, actinomycin D.	India	II	Positive

Table 2. Study results					
Author	Ginger regimen	Duration of intervention	Endpoint measured	Results and adherence	Comments
Ryan et al. (2012)[30]	Placebo, 0.5g ginger, 1g ginger or 1.5g ginger (6 capsules, combination of ginger and placebo).	Received regimen for 2 X 6 day periods. Measured for 3 X 4 day periods.	Primary objective: acute nausea. Secondary objectives: delayed nausea, anticipatory nausea, and quality of life.	All doses reduced acute nausea (p=0.003) but not delayed, using an assessment tool developed by Burish and Carey.[35] 77.4% of participants completed the trial (n=576/744), 83-93% adherence rate depending on treatment arm.	0.5 and 1g doses were most effective in reducing acute CINV. Largest study to date.
Panahi et al. (2012)[31]	1.5g (3 X 500mg)	4 days post-chemotherapy	Prevalence, score, and severity of nausea, vomiting, and retching	Reduction in nausea 6 to 24 hours post-chemotherapy (p = 0.04) using a simplified version of the Rhodes Index of Nausea, Vomiting, and	Non-blinded. Sample group relatively homogenous compared to other studies in this review.

				Retching. All other measures were non-significant. 78% of participants completed the trial (n=78/100), 18 participants were withdrawn due to lack of adherence or were lost to follow-up.	
Pillai et al. (2011)[32]	1g ginger (6 X 167mg) or 2g (5 X 400mg) determined by participants weight, or placebo.	Received regimen for 3 days post-chemotherapy, measured symptoms for 10 days post-chemotherapy.	Incidence and severity of acute and delayed nausea and emetic events.	Reduction in moderate and severe acute nausea and emesis (p=0.003, p=0.002, respectively) and reduction in moderate and severe delayed nausea and emesis (p<0.001, p=0.022, respectively), using Edmonton's Symptom Assessment Scale and National Cancer Institute	Experimental group contained a larger proportion of males, almost reaching statistical significance. Gender may influence susceptibility to nausea and vomiting.

				guidelines. 95% of participants completed the trial (n=57/60), 2 participants were withdrawn due to non-adherence with data collection protocol.	
Fahimi et al. (2010)[33]	1g (4 X 250mg) or placebo then crossed over.	2 X 3 day periods with a 3 week washout period in between.	Prevalence, severity and duration of acute and delayed nausea and emetic events.	No benefit in any measure of acute or delayed CINV, using MANE assessment tool. Prevalence: Day 1 (p=0.14). Day 2 (p=0.31). Day 3 (p=0.73). 72% of participants completed the trial (n=36/50), 13 participants were withdrawn due to non-adherence.	

Zick et al. (2009)[18]	1g (4 X 250mg, 4x placebo) or 2g (8 X 250mg) per day or placebo.	3 days post-chemotherapy	Primary objective: Severity and prevalence of delayed nausea and emetic events. Secondary objectives: Severity and prevalence of acute nausea and emetic events as well determine safety and blinding of study.	No benefit in any measure of acute or delayed CINV, using MANE assessment tool. Prevalence: Acute: *p*=0.86 Delayed: 0.16 Severity: Non-Appretiant group: Acute: *p*=0.47, Delayed: *p*=0.69. 80% of participants completed the trial (n=129/162). Authors reported 79% of participants reported consuming 80% of all study medication.	Delayed nausea was more severe in participants receiving 2g ginger with aprepitant. Blinding assessment found that participants were more likely to correctly determine which treatment group they were assigned to.
Manusirivithaya et al. (2004)[29]	1g ginger (4 X 250mg) or placebo then	2 X 5 day periods with 3-4 week washout period	Acute and delayed nausea and emetic	No benefit in acute nausea. Reduction in delayed CINV equal to standard treatment.	The name of assessment tool in this study was not identified.

	crossed over.	in-between	events.	90% of participants completed the trial (n=43/48). No data on adherence rate specified.	In delayed phase, ginger was compared as a stand-alone treatment to metoclopramide, not placebo.
Sontakke et al. (2003)[28]	2g (4 X 500mg) ginger, crossed over with two control groups	3 X 24 hour periods with 21 days between sessions	Control of acute nausea and emesis.	Complete control of vomiting was achieved in 68% of patients with ginger, 64% with metoclopramide and 86% with ondansetron Complete control of nausea was achieved in 62% of patients with ginger, 58% with metoclopramide and 86% with ondansetron. No data on withdrawals or adherence was specified.	Compared ginger to standard emetics as a standalone therapy. The name of assessment tool in this study was not identified.

147 *Abbreviations*: MANE, Morrow Assessment of Nausea and Emesis; CINV, Chemotherapy-induced Nausea and Vomiting.