RESEARCH
Research Paper

Effect of a Standardized Ginger Root Powder Regimen on Chemotherapy-Induced Nausea and Vomiting: A Multicenter, Double-Blind, Placebo-Controlled Randomized Trial

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ABSTRACT

Background There is substantial interest in the role of ginger as an adjuvant therapy for chemotherapy-induced nausea and vomiting (CINV). However, available evidence lacks robust methodology.

Objective To assess the effect of adjuvant ginger compared with placebo on chemotherapy-induced nausea-related quality of life (QoL) and CINV-related outcomes.

Design A parallel, double-blind, placebo-controlled randomized trial with 1:1 allocation was conducted.

Participants/setting One hundred three chemotherapy-naïve adults scheduled to receive moderately to highly emetogenic chemotherapy at two hospitals in Australia were enrolled and analyzed.

Intervention Four standardized ginger capsules (totaling 84 mg/day active gingerols/shogaols), or placebo, were administered commencing the day of chemotherapy and continuing for 5 days for chemotherapy cycles 1 through 3.

Main outcome measures The primary outcome was chemotherapy-induced nausea-related QoL. Secondary outcomes were vomiting- and CINV-related QoL; anticipatory, acute, and delayed nausea and vomiting; fatigue; nutritional status; depression and anxiety; health-related QoL; and adverse events.

Statistical analyses performed Intention-to-treat analysis was performed. Mixed analysis of variance with repeated measures determined differences between groups. The null hypothesis was no difference between groups. After applying a Bonferroni multiple testing correction, evidence against the null hypothesis was considered at $P = 0.003$.

Results One hundred three participants (ginger: n = 52; placebo: n = 51) were enrolled and analyzed. There was clinically relevant evidence against the null hypothesis, favoring ginger, in change scores for nausea-related QoL (F[df] = 9.34[1,101]; $P = 0.003$; partial $\eta^2 = 0.09$), overall CINV-related QoL (F[df] = 12.26[1,101]; $P < 0.001$; partial $\eta^2 = 0.11$), delayed nausea severity (F[df] = 9.46[1,101]; $P = 0.003$; partial $\eta^2 = 0.09$), and fatigue (F[df] = 10.11[1,101]; $P = 0.002$; partial $\eta^2 = 0.09$). There was a clinically meaningful lower incidence of delayed nausea and vomiting in the ginger group at Cycle 2 (53% vs 75%; $P = 0.020$ and 4% vs 27%; $P = 0.001$, respectively) and Cycle 3 (49% vs 79%; $P = 0.002$ and 2% vs 23%; $P = 0.001$, respectively). There was a clinically meaningful lower incidence of malnutrition in the ginger group at Cycle 3 (18% vs. 41%; $P = 0.032$) and in change scores for Patient-Generated Subjective Global Assessment (F[df)] = 4.32 [1,100]; $P = 0.040$; partial $\eta^2 = 0.04$). Change scores between groups favored ginger for vomiting-related QoL and number of vomiting episodes; however, findings were not clinically meaningful. There was no effect of ginger on anticipatory or acute CINV, health-related QoL, anxiety, or depression. No serious adverse events were reported.

Conclusions Ginger supplementation was a safe adjuvant to antiemetic medications for CINV that enhanced QoL during chemotherapy treatment. Future trials are needed to examine dose-dependent responses to verify optimal dosing regimens.

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CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV) is a highly distressing treatment side effect for many people undergoing chemotherapy.[1,2] CINV can worsen symptoms of cancer-related fatigue, anxiety, and depression as well as reduce food intake leading to an increased risk of malnutrition, which cumulatively compromise quality of life (QoL), cancer treatment outcomes, and overall survival.[3-6] Despite ongoing advances in antiemetic medications, moderately to highly emetogenic chemotherapy results in acute (within 24 hours of chemotherapy) and delayed (>24 hours to up to 7 days postchemotherapy) CINV in 30% to 55% and 25% to 60% of people, respectively.[7,8] Research also suggests that chemotherapy-induced nausea is more common and problematic than vomiting, particularly in the delayed phase.[7-9] Due to the persistent prevalence of CINV, the use of novel adjuvant interventions, such as ginger supplementation, has attracted both research and clinical interest.[2,10,11]

Gingerol and shogaol compounds are the primary bioactive compounds within ginger and possess inhibitory effects on serotonin (5-HT_3), muscarinic, and histaminergic receptors involved in nausea and vomiting pathways.[12,13] Ginger compounds bind to different receptor sites than antiemetic medications, suggesting that adjuvant ginger has an added benefit to antiemetic regimens.[12-14] Furthermore, ginger regulates gastric emptying and gastrointestinal motility that is dysregulated with nausea and vomiting as well as reduces the oxidative stress and inflammation that is involved in triggering CINV pathways.[15,16] Recently, the mechanisms of action of ginger are understood to extend to beneficial effects on the gut microbiota, where ginger positively influences the bacteria involved in the production of neurotransmitters involved in CINV pathways.[17,18]

Clinically, ginger is associated with benefits in managing and preventing CINV and related outcomes. The most recent systematic review and meta-analysis[10] of 18 studies exploring the effect of ginger on CINV in adults with any cancer type found that ginger supplementation reduced the likelihood of acute vomiting by 60% and fatigue by 80% when compared with placebo. However, no association was found between ginger and delayed vomiting, nausea, or other outcomes related to CINV.[10] The quality of the evidence likely contributes to this because the studies lacked robust methodology, warranting trials that clearly specify the type of ginger, standardized active constituent composition, dose, frequency, and duration of supplementation to confirm efficacy of ginger and optimal dosing regimens.[10] The pilot trial (N = 53) of the current study[19] addressed the aforementioned study limitations, confirmed feasibility of the study design, and was the first to find positive effects on CINV-related QoL.[19] Subsequent fully powered and rigorous trials are required to further validate these results. Therefore, in adults undergoing single-day moderately to highly emetogenic chemotherapy, this trial aimed to assess the effect of a standardized adjuvant ginger root powder supplement compared with placebo on chemotherapy-induced nausea-related QoL and secondary outcomes of vomiting-related QoL, overall CINV-related QoL, health-related QoL, incidence and severity of CINV, fatigue, nutritional status, and mental health.

RESEARCH SNAPSHOT

Research Question: In adults undergoing single-day moderately to highlyemetogenic chemotherapy, what is the effect of a standardized adjuvant ginger root powder supplement compared with placebo on chemotherapy-induced nausea-related quality of life (QoL) and secondary outcomes of vomiting-related QoL, overall chemotherapy-induced nausea and vomiting-related QoL, health-related QoL, incidence and severity of chemotherapy-induced nausea and vomiting, fatigue, nutritional status, and mental health?

Key Findings: This parallel, double-blind, placebo-controlled randomized trial of 103 participants found adjuvant ginger, compared with placebo, was safe and was associated with clinically relevant improvements in QoL, delayed nausea, and vomiting, fatigue, and nutritional status.

MATERIALS AND METHODS

The protocol for this multisite, double-blind, placebo-controlled randomized trial with two parallel arms is published in detail elsewhere.[20] The methodology was deemed feasible with a previous pilot study on 53 participants.[19] This trial was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12616000416493p) and Therapeutic Goods Administration in Australia (CT-2017-CTN-02280-1 v2). Ethics approval was obtained from the Metro South Human Research Ethics Committee (reference: HREC/17/QPAH/333), Mater Misericordiae Ltd Human Research Ethics Committee (reference: MML/39964), and the Bond University Human Research Ethics Committee (reference: 0000016144).

Participant Selection

Eligible participants attending the cancer care units at 2 metropolitan hospitals in Queensland, Australia, were invited to participate via written informed consent from October 18, 2017, to December 31, 2019. Participant recruitment continued over the shelf-life of 2 sequential batches of test product (Batch 1 shelf-life: January 2017-2019; Batch 2 shelf-life: May 2018-2020). Data collection continued until March 2020.

Eligible chemotherapy-naïve adult participants were physically and cognitively functional and scheduled to undergo single-day moderately to highly emetogenic chemotherapy (Table 1, available at www.jandonline.org). Participants were excluded in the case that they received concurrent radiotherapy; were pregnant or lactating; planned to use self-prescribed nausea therapies, including any type and amount of ginger or ginger-containing products; had history of adverse reactions to ginger or swallowing difficulties; were experiencing significant nausea and vomiting for reasons other than chemotherapy; consumed >14 standard alcohol drinks per week; had thrombocytopenia, gall stones, or liver disease; and were prescribed warfarin, anticoagulant therapy, hypoglycemics, insulin, cyclosporine, tacrolimus, and nonsteroidal anti-inflammatory drugs.

Power calculations based on pilot data[19] suggested a sample size of 246 participants was required for the primary

outcome and a target sample size of 300 was desirable to ensure adequate power for both primary and secondary outcomes, allowing for 30% attrition. Post hoc analysis was conducted to determine the statistical power for the primary outcome using Statistical Package for the Social Sciences software.[21]

Randomization and Blinding

Participants were randomized following enrolment with a 1:1 allocation using the method of minimization, stratified by chemotherapy emetogenicity (moderate or high), sex (male or female), age (younger than age 55 years or age 55 years or older), and research site (A or B). An independent third party (National Health and Medical Research Council Clinical Trials Centre, University of Sydney) managed the randomization process and were not involved in the design or conduct of the study.

All study personnel involved in recruitment, implementation, data collection, and analysis were blinded to the group allocation until the final study data were collected. Study supplements were overencapsulated to support blinding of participants and were identical in appearance. To evaluate the adequacy of blinding procedures, participants were asked for their perceptions of which group they were allocated to at the end of each chemotherapy cycle.

Intervention

The intervention group received nonsynthetic standardized ginger root capsules for oral consumption that were manufactured by an independent company that had no involvement in the study (Bluebonnet Nutrition Corporation; ginger root sourced from India). The 300-mg ginger capsules were standardized to contain 21 mg bioactive compounds per capsule (5% gingerols and 2% shogaols), with a total daily dose of 1.2 g ginger root powder containing 84 mg active ingredients (64 mg gingerols, 20 mg shogaols) (Table 2, available at www.jandonline.org). The selected dose and gingerol/shogaol concentration were based on that used in pharmacokinetic studies,[22,23] as well as the pilot trial,[19] and other previous trials[10] that reported significant positive effects and no serious adverse events. High-performance liquid chromatography analysis was carried out on the ginger supplements according to methodology previously used by this research team.[24] The high-performance liquid chromatography analysis was conducted at two time points during the trial and was compared with supplements that had passed their expiration date, confirming that the active constituents were stable throughout the study period. Placebo capsules contained 150 to 200 mg microcrystalline cellulose filler with no therapeutic agents.

Participants in the ginger and placebo groups were advised to consume one capsule four times daily with food where possible. The dosing schedule was based on the pharmacokinetics of ginger, particularly the relatively short biological half-life of 1.5 to 3 hours.[22,23] Supplementation begun on the day of chemotherapy before chemotherapy administration and continued for 4 days postchemotherapy (ie, a total of 5 days, from Day 1 to Day 5) during Cycle 1, repeated for Cycles 2 and 3. Participants were advised to continue their usual diet; however, were also advised to consume no fresh ginger or ginger-containing products in any amount for the duration of the study. There were no restrictions on prescribed antiemetics during the trial.

Outcomes

Group allocation (standardized ginger regiment vs placebo) was the independent variable. Chemotherapy-induced nausea-related QoL, measured by the Functional Living Index Emesis 5-Day Recall (FLIE-5DR),[25] was chosen as the primary outcome because it represented the influence of nausea, vomiting, and overall CINV on participants' activities of daily living.[25] The FLIE-5DR subgroups of vomiting-related QoL and overall CINV-related QoL were considered secondary outcomes.[25] Other secondary outcomes were health-related QoL (health status), nausea incidence and severity, vomiting incidence and number of episodes, fatigue, nutritional status, anxiety, and depression. Participant adverse events were measured to evaluate safety.

Participant characteristics and potentially confounding variables were risk factors for CINV (ie, age, sex, chemotherapy emetogenicity, antiemetic regimen, history of motion and morning sickness, alcohol intake, cancer stage [presence of metastases]) and research site.[26,27]

Data Collection

Participant characteristics were assessed at baseline (T0; before chemotherapy) (Table 3). Valid and reliable tools for use in people with cancer measured primary and secondary outcomes 1 day before chemotherapy (T1), 12 to 24 hours after chemotherapy (T2), 4 days after chemotherapy (T3), and 5 to 8 days after chemotherapy (T4). Time points 1 through 4 were repeated for three chemotherapy cycles (Cycles 1 through 3). Data were collected in person or via telephone consultation with the research assistant or via a participant booklet.

CINV-Related QoL. The FLIE-5DR[25] measured the primary outcome of chemotherapy-induced nausea-related QoL at T1 (1 day before chemotherapy) and T3 (5 to 8 days after chemotherapy). The primary outcome of nausea-related QoL was chosen due to the higher prevalence and burden of chemotherapy-induced nausea in comparison to vomiting reported elsewhere,[7,8] and for consistency with the study protocol publication[20] and pilot study.[19] The FLIE-5DR also measured secondary outcomes of CINV-related QoL and vomiting-related QoL. The FLIE-5DR comprised two domains (nausea and vomiting), each with nine identical 7-point Likert scale items. The first item rated the overall amount of nausea/vomiting. Six items assessed the influence of nausea/vomiting on enjoyment of meals and liquids, meal preparation and household tasks, daily functions, recreation and leisure activities, and time spent with family and friends. The remaining two items measured the personal hardship and hardship on others caused by nausea/vomiting. Higher scores indicated less hardship and less influence of nausea and/or vomiting.[25] No minimal clinically important difference was determined; however, using the parameters specified by Martin and colleagues[28] no influence on QoL was defined as a nausea/vomiting subscale score of $\geq$54 (score range = nine to 63) or total CINV score $\geq$108 (score range = 18 to 126).[25] Table 4 (available at www.jandonline.org) presents additional information on outcome assessment tools.

Table 3. Outcome measures, supplementation schedule, and time points for the trial assessing the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea (CIN) and vomiting (CINV)

Study procedure	T0	T1	T2	T3	T4
Time in CTx[a] cycle	Pre-CTx	1 d pre-CTx[b]	12-24 h post-CTx	4 d post-CTx	5-8 d post-CTx
CTx cycle[c]	1	1, 2, 3	1, 2, 3	1, 2, 3	1, 2, 3
Supplement consumed[d]		✓	✓	✓	✓
Participant characteristics	✓				
CIN-, CINV-, and CINV-related QoL[e] (FLIE-5DR[f])		✓		✓	
Nausea and vomiting symptoms (MAT[g])		✓	✓	✓	
Health-related QoL (EQ-5D-5L[h])		✓		✓	
Fatigue (FACIT-F[i])			✓		✓
Nutritional status (PG-SGA[j])		✓			
Depression and anxiety (HADS[k])			✓		
Adverse events					✓

[a]CTx = chemotherapy.
[b]If data collection 1 day before chemotherapy was not possible (eg, for PG-SGA), data were collected on the day of presenting for their chemotherapy before chemotherapy administration.
[c]Refers to each subsequent CTx cycle.
[d]Supplement consumed from the day of chemotherapy (before chemotherapy administration) to 4 days postchemotherapy (ie, Day 1 to Day 5).
[e]QoL = quality of life.
[f]FLIE-5DR = Functional Living Index Emesis 5-Day Recall.
[g]MAT = Multinational Association of Supportive Care in Cancer Anti-emesis Tool.
[h]EQ-5D-5L = European Quality of Life Five Dimension Five Levels Tool.
[i]FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.
[j]PG-SGA = Patient-Generated Subjective Global Assessment.
[k]HADS = Hospital Anxiety and Depression Scale.

Additional Secondary Outcomes. The Multinational Association of Supportive Care in Cancer Anti-emesis tool[29] measured nausea and vomiting symptoms (nausea incidence and severity, vomiting incidence, and number of episodes). The Multinational Association of Supportive Care in Cancer Anti-emesis tool was administered at T1 (1 day before chemotherapy) to capture anticipatory nausea and vomiting (used as baseline measures), T2 (12 to 24 hours after chemotherapy) to capture acute CINV, and at T3 (4 days after chemotherapy) to capture delayed CINV. No minimal clinically important difference was established; however, using parameters defined by Gilmore and colleagues[30] clinically significant nausea was considered as a severity score ≥3 (score range = zero to 10), whereby higher scores indicated worse symptoms.[29]

The European Quality of Life Five Dimension Five Levels tool[31] measured health-related QoL at T1 (1 day before chemotherapy) and T3 (4 days after chemotherapy). Higher total global well-being scores indicated poorer QoL (score range = five to 25). Participants also rated their health on a visual analogue scale ranging from zero (worst health imaginable) to 100 (best health imaginable).[31] The minimal clinically important difference in people with cancer has been predicted as 0.1 point for global well-being scores and 7 points for visual analogue scale rating.[32,33]

The Functional Assessment of Chronic Illness Therapy Fatigue Scale[34,35] measured cancer-related fatigue and its influence on activities of daily living at T2 (12 to 24 hours after chemotherapy) and T4 (5 to 8 days after chemotherapy). Lower scores indicated more severe fatigue and clinically significant fatigue was classified as a score ≤34 (score range = zero to 52).[34,35] The minimal clinically important difference in people with cancer has been predicted as 3.0 points.[36]

The validated Patient-Generated Subjective Global Assessment (PG-SGA)[37] measured nutrition status on the day of chemotherapy. Scores generated a numerical score and a global rating of A (well nourished), B (clinically significant suspected or moderate malnutrition), or C (clinically significant severe malnutrition).[37] A total numerical score was also calculated, whereby higher scores indicated greater risk of malnutrition and more critical need for nutrition intervention (score of zero to one = no need for intervention, two to three = education, four to eight = dietitian referral, and nine to 35 = critical need for nutrition intervention).[37] The minimal clinically important difference has been predicted as a 3-point change in PG-SGA score.[38]

The Hospital Anxiety and Depression Scale[39] assessed anxiety and depression at T2 (12 to 24 hours after chemotherapy). Higher scores indicated worst symptoms and a score ≥11 (score range = zero to 21) represented clinically significant abnormal anxiety or depression.[39] The minimal clinically important difference has been predicted as 1.7 points.[40]

Participant Adherence. Collection of the supplement containers at the end of the study to count the number of unused supplements indicated adherence to the supplement regimen. Consumption of ginger and ginger-containing products was recorded in participant diaries at each time point.

Adverse Events. Adverse events were monitored by observation of medical records as well as discussion with participants. Adverse events were classified according to the National Institutes of Health Adverse Event and Serious Adverse Event Guidelines[41] and rated in terms of severity (mild, moderate, or severe), expectedness (unexpected or expected), and relatedness to the study procedures (definitely related, possibly related, or not related).

Data Analysis

Intention-to-treat analysis was conducted using multiple imputation for missing data with SPSS software.[21] Parametric data were described as means ± SD and nonparametric data were presented as medians (25th and 75th) percentiles. After applying a Bonferroni multiple testing correction based on a total of 16 outcomes, statistical significance was considered at the P value of 0.003.

The primary outcome was analyzed by comparing the difference in nausea-related QoL change scores between ginger and placebo groups from T1 (12 to 24 hours after chemotherapy) to T3 (5 to 8 days after chemotherapy). Differences in secondary outcome change scores between groups were assessed from T1 to T3 (vomiting-related QoL, overall CINV-related QoL, health-related QoL, delayed nausea severity and vomiting episodes, and fatigue) and T1 to T2 (12 to 24 hours after chemotherapy; acute nausea severity and vomiting episodes). The difference between groups in anxiety and depression scores at T2 and PG-SGA score at T1 were also assessed. Mixed analysis of variance with repeated measures (RMANOVA) was used to determine the main group effect, main time effect, and interaction effect between group and time (over the three chemotherapy cycles), whereby the null hypothesis was no difference between groups. Post hoc pairwise t test comparisons determined the effect at each cycle, whereby P values were adjusted using the Bonferroni multiple testing correction method. Partial η^2 was the effect size used to estimate analysis of variance, whereby 0.01 represented a small effect, 0.06 a medium effect, and 0.14 a large effect.[42] Potentially confounding variables were considered for inclusion in the RMANOVA model in the case that they met the assumptions of independent observations, normality, homogeneity of the dependent variable, homogeneity of the regression slope, and linearity.[43] Potentially confounding variables were sex, age, research site, alcohol intake, history of morning or motion sickness, and chemotherapy emetogenicity.

The difference in nausea, vomiting, and malnutrition incidence between ginger and placebo groups at T1, T2, and T3 was assessed using χ^2 tests at each chemotherapy cycle, whereby the null hypothesis was no difference between groups. Cramer's V was used as the measure of effect size, whereby 0.1 represented a small effect, 0.3 a medium effect, and 0.5 a large effect. [41]

RESULTS

Participant Selection and Characteristics

A total of 103 participants were enrolled in the study between October 2017 and December 2019. Due to lower than anticipated recruitment rates, the study did not reach the target sample size; however, post hoc power calculation of the main effect for group for the primary outcome found that the study was 94% powered, suggesting that the achieved sample size was adequate to test for evidence against the null hypothesis of no difference between groups.

Of the 103 participants, 70 (68%) completed all 3 chemotherapy cycles (see the Figure). Most participants were women (68%), had a primary cancer diagnosis of breast cancer (43%), lung cancer (18%), or lymphoma (17%), were scheduled to undergo moderately emetogenic chemotherapy (60%), and were prescribed antiemetic medications (100%) (Table 5). The 2 study groups were mostly comparable; however, compared with placebo, more participants in the ginger group had a history of moderate to severe motion sickness (72% vs 39%) and history of a previous cancer diagnosis (18% vs 6%).

CINV-Related QoL

There was evidence against the null hypothesis of no difference between groups for the main effect for group for nausea-related QoL (partial $\eta^2 = 0.09$ [medium effect]; $P = 0.003$) (Table 6), vomiting-related QoL (partial $\eta^2 = 0.09$ [medium effect]; $P = 0.002$), and overall CINV-related QoL (partial $\eta^2 = 0.11$ [medium effect]; $P < 0.001$); a main effect for time for nausea-related QoL (partial $\eta^2 = 0.07$ [medium effect]; $P < 0.001$); and an interaction effect between group and time for vomiting-related QoL (partial $\eta^2 = 0.08$ [medium effect]; $P < 0.001$).

There was evidence against the null hypothesis for ginger, compared with placebo, being associated with less decline in vomiting-related QoL and overall CINV-related QoL after Cycles 2 and 3, and nausea-related QoL at Cycle 2 only (see Table 6 for P values and effect sizes). However, a clinically meaningful effect was found for ginger supplementation improving nausea-related QoL and overall CINV-related QoL at all cycles. Clinical significance was evident by mean post-intervention scores representing no influence of nausea or overall CINV on QoL in the ginger group (nausea-QoL score $\geq$54; CINV-QoL score $\geq$108), yet substantial influence on QoL in the placebo group (nausea-QoL score <54; CINV-QoL score <108). No confounding variables met assumptions for inclusion in the RMANOVA model.

Nausea and Vomiting Symptoms

Anticipatory nausea occurred in 8% of all participants; there were no differences between groups (Cycle 1: ginger = 8%, placebo = 8%; Cycle 2: ginger = 12%, placebo = 4%; Cycle 3: ginger = 8%, placebo = 2%). There were no differences between groups in anticipatory nausea severity at any cycle (Table 6) and no anticipatory vomiting reported at any cycle. Acute nausea and vomiting occurred in 43% and 1% of all participants, and delayed nausea and vomiting occurred in 64% and 16% of all participants, respectively.

In the ginger group compared with placebo group, there was a 22% lower incidence of delayed nausea at Cycle 2 (Cramer's $V = 0.5$ [large effect]; $P = 0.020$) (Table 7) and 30% lower incidence at Cycle 3 (Cramer's $V = 0.7$ [large effect]; $P = 0.002$). Although only the effect at Cycle 3 was statistically significant after adjusting P values for multiple comparisons, both were considered clinically meaningful by the investigators. Delayed nausea incidence at Cycles 2 and 3 did not differ between participants with history of moderate to severe motion sickness and none to mild motion sickness in either group.

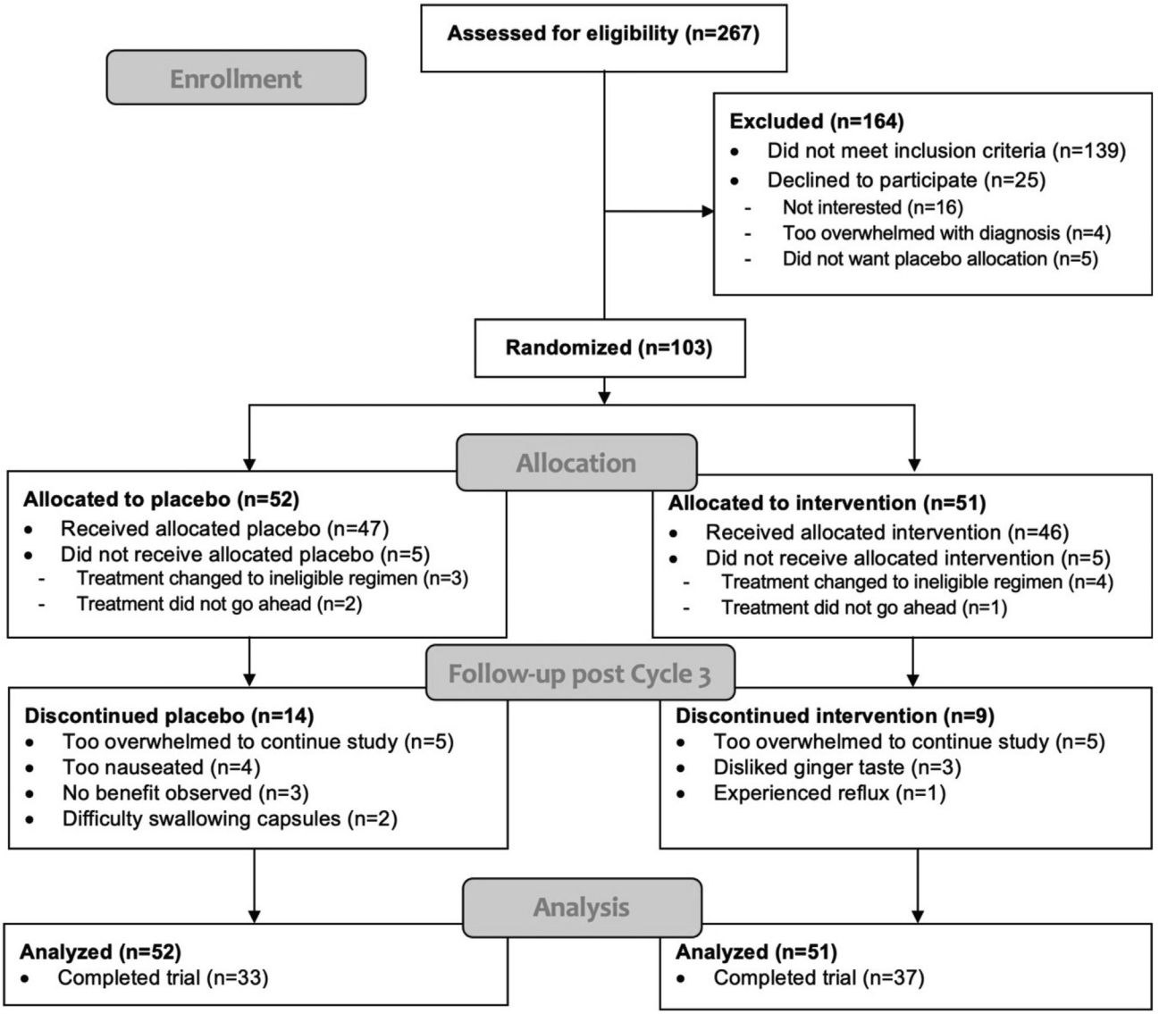

Figure. Consolidated Standards of Reporting Trials flow diagram outlining selection and flow of participants for the trial assessing the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea and vomiting.

There was a main effect for group for delayed nausea severity (partial $\eta^2 = 0.09$ [medium effect]; $P = 0.003$) (Table 6). Evidence against the null hypothesis was found at Cycle 2 only (partial $\eta^2 = 0.09$ [medium effect]; $P = 0.002$); however, the lower severity of delayed nausea in the ginger group at all cycles was clinically meaningful, indicated by mean post-intervention severity scores representing clinically significant nausea (severity score ≥ 3) only in the placebo group.

At Cycles 2 and 3, there was a 22% to 23% lower incidence of at least one episode of delayed vomiting in the ginger group compared with placebo group (Cycle 2: 4% vs 27% and Cycle 3: 2% vs 23%; Cramer's $V = 0.7$ [large effect]; $P = 0.001$), which was considered clinically meaningful by investigators. Delayed vomiting incidence at Cycles 2 and 3 did not differ between participants with history of moderate to severe motion sickness and none to mild motion sickness in either group.

For number of delayed vomiting episodes, there was a main effect for group (partial $\eta^2 = 0.08$ [medium effect]; $P = 0.003$) and time (partial $\eta^2 = 0.22$ [large effect]; $P < 0.001$), as well as an interaction effect between group and time (partial $\eta^2 = 0.11$ [medium effect]; $P < 0.001$). Ginger was associated with less delayed vomiting episodes at Cycles 2 (partial $\eta^2 = 0.10$ [medium effect]; $P = 0.001$) and Cycle 3 (partial $\eta^2 = 0.09$ [medium effect]; $P = 0.002$). Despite medium effect sizes, the mean number of vomiting episodes was low in each group (Cycle 2: 0.5 ± 0.7 vs 1.3 ± 1.7 episodes and Cycle 3: 0.5 ± 0.7 vs 1.5 ± 2.1 episodes), and thus this finding was not considered clinically meaningful.

No confounding variables met assumptions for inclusion in the RMANOVA models assessing nausea and vomiting symptoms. There was insufficient evidence against the null hypothesis and no clinically meaningful findings for the effect

Table 5. Baseline characteristics of participants enrolled in the trial assessing the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea and vomiting

Characteristic	Total (N = 103)	Ginger group (n = 51)	Placebo group (n = 52)
	←——————————*mean ± SD*——————————>		
Age (y)	59 ± 8	59 ± 8	58 ± 9
	←——————————*n (%)*——————————>		
Female sex	70 (68)	36 (71%	34 (65)
Research site			
Site A	85 (83)	43 (84)	42 (81)
Site B	18 (17)	8 (16)	10 (19)
Place of birth			
Oceania	79 (77)	40 (78)	39 (75)
Europe	18 (17)	7 (14)	11 (21)
Asia	4 (4)	3 (6)	1 (2)
Africa	2 (2)	1 (2)	1 (2)
English as first language, yes	98 (95)	48 (94)	50 (96)
Highest level of education			
Primary	9 (9)	5 (9)	4 (8)
Secondary	54 (52)	27 (53)	27 (52)
Tertiary	21 (20)	10 (20)	11 (21)
Trade	19 (19)	9 (18)	10 (19)
Previous cancer diagnosis, yes	12 (12)	9 (18)	3 (6)
Primary diagnoses			
Breast	44 (43)	25 (49)	19 (36)
Lymphoma	18 (17)	9 (18)	9 (17)
Digestive	5 (5)	0 (0)	5 (10)
Lung	19 (18)	8 (16)	11 (21)
Urogenital	5 (5)	1 (2)	4 (8)
Gynecological	5 (5)	3 (6)	2 (4)
Other	7 (7)	5 (9)	2 (4)
Metastases, yes	27 (26)	12 (24)	15 (29)
Chemotherapy emetogenicity			
Moderate	62 (60)	32 (63)	30 (58)
High	41 (40)	19 (37)	22 (42)
Alcohol use			
None	31 (30)	12 (24)	19 (37%)
1-4 standard drinks per week	45 (44)	25 (48)	20 (38%)
5-8 standard drinks per week	19 (18)	11 (22)	8 (15%)
9-14 standard drinks per week	8 (8)	3 (6)	5 (10%)
History of motion sickness			
Strong or severe	17 (17)	11 (22)	6 (12)
Moderate	40 (39)	26 (50)	14 (27)
Mild	22 (21)	5 (10)	17 (32)
None	24 (23)	9 (18)	15 (29)

(*continued on next page*)

Table 5. Baseline characteristics of participants enrolled in the trial assessing the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea and vomiting (*continued*)

Characteristic	Total (N = 103)	Ginger group (n = 51)	Placebo group (n = 52)
History of morning sickness			
Strong or severe	5 (5)	0 (0)	5 (10)
Moderate	34 (33)	17 (33)	17 (33)
Mild	22 (21)	14 (27)	8 (15)
None	9 (9)	5 (10)	4 (8)
Not applicable (no pregnancy history)	33 (32)	15 (30)	18 (34)
Antiemetics prescribed at baseline			
5-HT_3 RA[a] and steroid	2 (2)	1 (2)	1 (2)
5-HT_3 RA and steroid and rescue D2 RA[b]	11 (11)	6 (12)	5 (10)
D2 RA and steroid	26 (25)	8 (16)	18 (35)
5-HT_3 RA and NK_1 RA[c] and steroid and rescue D2 RA	48 (46)	24 (46)	24 (46)
5-HT_3 RA and NK_1 RA and steroid	5 (5)	4 (8)	1 (2)
D2 RA	10 (10)	8 (16)	2 (4)
NK_1 RA and steroid and rescue D2 RA	1 (1)	0 (0)	1 (2)

[a]5-HT_3 RA = serotonin (5-HT_3) receptor antagonist.
[b]D2 RA = dopamine receptor antagonist.
[c]NK_1 RA = neurokinin-1 receptor antagonist.

of ginger on acute nausea and vomiting at all chemotherapy cycles ($P > 0.003$).

Effect of Intervention vs Placebo on Secondary Outcomes

Clinically significant fatigue occurred in 68% of all participants (69% with metastases and 66% without metastases). There was a main effect for group (partial $\eta^2 = 0.09$ [medium effect]; $P = 0.002$), time (partial $\eta^2 = 0.07$ [medium effect]; $P = 0.001$) as well as interaction effect between group and time for fatigue (partial $\eta^2 = 0.12$ [medium effect]; $P < 0.001$). There was evidence against the null hypothesis for ginger being associated with less change in fatigue following chemotherapy at Cycle 1 only (partial $\eta^2 = 0.18$ [large effect]; $P < 0.001$), which was considered clinically meaningful (>3 point difference in mean difference between groups).

A total of 37% of all participants were malnourished at one or more time points throughout the study period (32% moderately malnourished and 5% severely malnourished). The 23% lower incidence of malnutrition observed in the ginger group compared with the placebo group at Cycle 3 was not statistically significant after adjusting P values (Cramer's $V = 0.3$ [small effect]; $P = 0.032$) (Table 3), but was considered clinically meaningful by the investigators. There was a main effect for time for PG-SGA score (partial $\eta^2 = 0.11$ [medium effect]; $P < 0.001$) (Table 4, available at www.jandonline.org). Compared with placebo, ginger was associated with clinically meaningful lower PG-SGA scores at Cycle 3; however, this was not statistically significant after adjusting P values for multiple comparisons (partial $\eta^2 = 0.07$ [medium effect]; $P = 0.009$).

No confounding variables met assumptions for inclusion in the RMANOVA models assessing fatigue and nutritional status. There was insufficient evidence against the null hypothesis and no clinically meaningful findings for the effect on health-related QoL, anxiety, and depression ($P > 0.003$).

Participant Blinding and Compliance

A greater number of participants in the ginger group correctly identified their group allocation compared with those in the placebo group (34% vs 11%; $P = 0.013$). All participants who completed the intervention consumed at least 84% of the study supplements and 79% of all participants consumed at least 3 of the 4 capsules per day (ginger group: 73% and placebo group: 85%). A total of 92% of all participants were adherent to consuming no additional ginger or ginger-containing products for the duration of the study (ginger group: 88% and placebo group: 96%; $P = 0.124$).

Adverse Events

There were no reported serious adverse events that were possibly or directly related to the intervention. There were 19 mild adverse events and one moderate adverse event possibly related to the intervention (ginger group n = 13 and placebo group n = 7). This included reflux (n = 10), constipation (n = 5), diarrhea (n = 2), and abdominal pain (n = 3). The most prevalent adverse event possibly related to the intervention was reflux with or without heartburn, reported by 10% of all participants (ginger group 18% and placebo group 2%), which was mostly infrequent but in one case from the ginger group led to study withdrawal (Table 8, available at www.jandonline.org).

Table 6. Findings from repeated measures mixed analysis of variance (RMANOVA) examining the effect of ginger supplementation (n = 51) compared with placebo (n = 52) on quality of life, nausea severity, vomiting episodes, fatigue, anxiety, depression, and nutritional status

	Cycle 1						Cycle 2						Cycle 3					
	Within groups			Between groups			Within groups			Between groups			Within groups			Between groups		
	Pre mean (SD)	Post mean (SD)	Within group MD[a] (95% CI)	Between group MD (95% CI)	p η^{2}[b]	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^{2}	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^{2}	*P* value[i]
QoL[c]																		
Nausea-related QoL																		
Placebo	60.11 (8.17)	48.62 (12.73)	−11.50 (−14.14 to −8.58)	4.98 (0.84 to 9.13)	.05	0.019	60.53 (4.44)	44.72 (14.18)	−15.82 (−18.99 to −12.64)	7.17 (2.65 to 11.69)	.09	**0.002**	59.37 (6.99)	45.18 (14.42)	−14.19 (−17.39 to −10.99)	6.25 (1.70 to 10.80)	0.07	.008
Ginger	61.12 (3.98)	54.61 (10.33)	−6.51 (−9.46 to −3.57)				61.18 (2.64)	52.54 (10.54)	−8.65 (−11.86 to −5.44)				60.75 (3.52)	52.81 (10.88)	−7.94 (−11.17 to −4.71)			
RMANOVA		**Group[d]**		***F* (df)**				Time[e]		***F* (df)**				**Time x group[f]**		***F* (df)**		
				9.34 (1, 101)	.09	**0.003**				7.81 (2, 182)	.07	**0.001**				0.88 (2,182)	0.01	.405
Vomiting−related QoL																		
Placebo	63.00 (0.00)	57.68 (8.95)	−5.32 (−7.17 to −3.46)	3.44 (0.81 to 6.1)	.06	0.011	62.98 (0.07)	56.23 (9.58)	−6.75 (−8.78 to −4.72)	4.43 (1.54 to 7.31)	.08	**0.003**	62.15 (1.21)	54.89 (12.01)	−7.26 (−9.72 to −4.80)	6.13 (2.63 to 9.63)	0.11	**<.001**
Ginger	63.00 (0.00)	61.13 (3.21)	−1.87 (−3.75 to 0.00)				62.94 (0.28)	60.62 (4.09)	−2.32 (−4.38 to −0.27)				61.80 (2.95)	60.66 (3.70)	−1.13 (−3.62 to 1.35)			
RMANOVA		**Group**		***F* (df)**				Time		***F* (df)**				**Time x group**		***F* (df)**		
				9.96 (1, 101)	.09	**0.001**				4.14 (2,192)	.04	0.019				8.39 (2, 192)	0.08	**<.001**
CINV[g]−related QoL																		
Placebo	123.11 (8.17)	104.87 (19.26)	−18.25 (−22.47 to −14.03)	8.64 (2.64 to 14.64)	.08	0.005	123.43 (4.47)	100.95 (20.71)	−22.49 (−27.10 to −17.88)	11.57 (5.02 to 18.13)	.11	< **0.001**	121.49 (7.34)	100.06 (24.79)	−21.43 (−26.63 to −16.24)	12.40 (5.02 to 19.79)	0.10	**.001**
Ginger	124.11 (3.98)	114.50 (13.12)	−9.61 (−13.87 to −5.34)				124.05 (2.72)	113.14 (13.33)	−10.92 (−15.58 to −6.26)				122.50 (5.59)	113.57 (13.43)	−9.03 (−14.28 to −3.78)			

(*continued on next page*)

Table 6. Findings from repeated measures mixed analysis of variance (RMANOVA) examining the effect of ginger supplementation (n = 51) compared with placebo (n = 52) on quality of life, nausea severity, vomiting episodes, fatigue, anxiety, depression, and nutritional status (*continued*)

	Cycle 1						Cycle 2						Cycle 3					
	Within groups			Between groups			Within groups			Between groups			Within groups			Between groups		
	Pre mean (SD)	Post mean (SD)	Within group MD[a] (95% CI)	Between group MD (95% CI)	p η^{2}[b]	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^{2}	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^{2}	*P* value[i]
RMANOVA		**Group**		***F* (df)**				**Time**		***F* (df)**				**Time x group**		***F* (df)**		
				12.26 (1, 101)	.11	< **0.001**				5.35 (2, 202)	.05	0.007				3.42 (2, 202)	0.03	.035
Health-related QoL rating (VAS[h])																		
Placebo	75.75 (16.03)	68.20 (15.76)	−7.54 (−11.54 to −3.54)	4.32 (−1.37 to 10.00)	.02	0.135	72.37 (16.19)	64.83 (19.30)	−7.54 (−11.21 to −3.87)	0.98 (−4.24 to 6.20)	.00	0.709	72.71 (16.47)	66.63 (19.11)	−6.08 (−9.07 to −3.09)	−1.04 (−5.29 to 3.21)	0.00	.630
Ginger	77.65 (15.76)	74.43 (15.98)	−3.22 (−7.26 to 0.82)				82.07 (13.55)	75.52 (16.32)	−6.55 (−10.26 to −2.85)				83.66 (12.28)	76.54 (14.08)	−7.12 (−10.14 to −4.10)			
RMANOVA		**Group**		***F* (df)**				**Time**		***F* (df)**				**Time x group**		***F* (df)**		
				0.53 (1, 101)	.01	0.470				0.72 (2, 168)	.01	0.462				1.79 (2, 168)	0.02	.177
Health-related QoL score																		
Placebo	6.1 (2.40)	8.50 (2.34)	1.99 (1.39 to 2.58)	−9.10 (−1.76 to −0.07)	.04	0.035	7.28 (1.47)	8.55 (2.91)	1.27 (0.62 to 1.91)	0.47 (−0.45 to 1.39)	.01	0.311	7.23 (1.37)	8.86 (2.76)	1.62 (1.06 to 2.19)	0.06 (−0.75 to 0.86)	0.00	.884
Ginger	6.53 (1.69)	7.60 (1.97)	1.08 (0.47 to 1.68)				6.27 (1.40)	8.01 (2.05)	1.74 (1.08 to 2.39)				6.18 (1.13)	7.86 (2.05)	1.68 (1.11 to 2.25)			
RMANOVA		**Group**		***F* (df)**				**Time**		***F* (df)**				**Time x group**		***F* (df)**		
				0.14 (1, 101)	.00	0.708				0.23 (2, 158)	.00	0.741				4.47 (2, 158)	0.04	.020

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Table 6. Findings from repeated measures mixed analysis of variance (RMANOVA) examining the effect of ginger supplementation (n = 51) compared with placebo (n = 52) on quality of life, nausea severity, vomiting episodes, fatigue, anxiety, depression, and nutritional status (*continued*)

	Cycle 1						Cycle 2						Cycle 3					
	Within groups			Between groups			Within groups			Between groups			Within groups			Between groups		
	Pre mean (SD)	Post mean (SD)	Within group MD[a] (95% CI)	Between group MD (95% CI)	p η^2[b]	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^2	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^2	*P* value[i]
Acute CINV																		
Acute nausea severity																		
Placebo	0.34 (0.72)	2.18 (2.56)	1.84 (1.21 to 2.47)	−0.10 (−1.00 to 0.79)	.00	0.817	0.57 (1.02)	1.96 (1.96)	1.34 (0.97 to 1.81)	−0.01 (−0.61 to 0.59)	.00	0.979	0.48 (1.04)	1.88 (1.97)	1.40 (1.00 to 1.81)	−0.18 (−0.76 to 0.40)	0.00	.548
Ginger	0.50 (1.20)	2.24 (2.33)	1.74 (1.10 to 2.37)				0.48 (0.74)	1.87 (1.91)	1.38 (0.94 to 1.81)				0.43 (0.62)	1.66 (1.62)	1.23 (0.82 to 1.64)			
RMANOVA		**Group**		***F* (df)**				**Time**		***F* (df)**				**Time x group**		***F* (df)**		
				0.10 (1, 101)	.001	0.753				5.20 (1, 149)	0.05	0.013				0.14 (1, 149)	0.00	.803
Delayed CINV																		
Delayed nausea severity																		
Placebo	0.34 (0.72)	3.05 (2.52)	2.71 (2.13 to 3.29)	−1.16 (−1.99 to −0.34)	.07	0.006	0.57 (1.02)	3.53 (2.52)	2.96 (2.41 to 3.51)	−1.24 (−2.03 to −0.46)	.09	**0.002**	0.48 (1.04)	3.17 (2.52)	2.69 (2.11 to 3.27)	−1.00 (−1.83 to −0.18)	0.05	.018
Ginger	0.50 (1.20)	2.05 (2.06)	1.55 (0.96 to 2.13)				0.48 (0.74)	2.20 (2.05)	1.71 (1.16 to 2.27)				0.43 (0.62)	2.11 (2.07)	1.69 (1.10 to 2.27)			
RMANOVA		**Group**		***F* (df)**				**Time**		***F* (df)**				**Time x group**		***F* (df)**		
				9.46 (1, 101)	.09	**0.003**				0.99 (2, 238)	.01	0.353				0.33 (1, 238)	0.00	.656
Delayed vomiting episodes																		
Placebo	0.00 (0.00)	0.43 (0.82)	0.43 (0.24 to 0.62)	−0.15 (−0.42 to 0.13)	.01	0.285	0.00 (0.00)	1.33 (1.70)	1.34 (0.97 to 1.70)	−0.86 (−1.37 to 0.35)	.10	**0.001**	0.00 (0.00)	1.48 (2.06)	1.48 (1.01 to 1.90)	−0.99 (−1.59 to −0.38)	0.09	**.002**
Ginger	0.00 (0.00)	0.28 (0.55)	0.28 (0.09 to 0.48)				0.00 (0.00)	0.48 (0.73)	0.48 (0.11 to 0.84)				0.00 (0.00)	0.49 (0.71)	0.49 (0.06 to 0.92)			
RMANOVA		**Group**		***F* (df)**				**Time**		***F* (df)**				**Time x group**		***F* (df)**		
				9.14 (1, 101)	.08	0.003				27.68 (1, 130)	.22	< **0.001**				12.14 (1, 130)	0.11	<**0.001**

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Table 6. Findings from repeated measures mixed analysis of variance (RMANOVA) examining the effect of ginger supplementation (n = 51) compared with placebo (n = 52) on quality of life, nausea severity, vomiting episodes, fatigue, anxiety, depression, and nutritional status (*continued*)

	Cycle 1						Cycle 2						Cycle 3					
	Within groups			Between groups			Within groups			Between groups			Within groups			Between groups		
	Pre mean (SD)	Post mean (SD)	Within group MD[a] (95% CI)	Between group MD (95% CI)	p η^{2b}	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^2	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^2	*P* value[i]
Physical and psychological outcomes																		
Fatigue																		
Placebo	35.96 (11.35)	26.35 (10.63)	−9.60 (−11.87 to −7.34)	−7.68 (−10.89 to −4.46)	.18	< 0.001	29.88 (12.48	26.67 (13.49)	−3.20 (−4.92 to −1.49)	−0.02 (−2.46 to 2.41)	.00	0.985	30.67 (11.71)	26.35 (11.85)	−4.32 (−5.96 to −2.69)	−2.26 (−4.58 to 0.06)	0.04	.028
Ginger	36.35 (10.38)	34.42 (11.22)	−1.93 (−4.21 to 0.35)				36.06 (9.17)	32.88 (11.01)	−3.18 (−4.91 to −1.45)				34.53 (10.15)	32.46 (11.89)	−2.07 (−3.72 to −0.42)			
RMANOVA	**Group**			***F* (df)**			**Time**			***F* (df)**			**Time x group**			***F* (df)**		
				10.11 (1, 101)	.09	0.002				7.91 (2, 163)	.07	**0.001**				13.87 (2, 163)	0.12	< **0.001**
Anxiety																		
Placebo	—	5.14 (3.31)	—	−0.84 (−2.05 to 0.37)	.02	0.171	—	4.79 (3.66)	—	−0.28 (−1.59 to 1.03)	.00	0.674	—	5.41 (4.28)	—	−0.63 (−2.15 to 0.89)	0.01	.764
Ginger	—	4.30 (2.87)	—				—	4.51 (3.00)	—				—	4.78 (3.41)	—			
RMANOVA	**Group**			***F* (df)**			**Time**			***F* (df)**			**Time x group**			***F* (df)**		
				0.83 (1, 101)	.01	0.364				2.88 (2, 172)	.03	0.067				1.02 (2, 172)	0.01	.352
Depression																		
Placebo	—	3.78 (3.11)	—	0.16 (−0.97 to 1.28)	.00	0.784	—	5.44 (4.14)	—	−1.17 (−2.60 to 0.25)	.03	0.105	—	5.66 (4.28)	—	−0.69 (−2.22 to 0.85)	0.01	.377
Ginger	—	3.94 (2.61)	—				—	4.26 (3.05)	—				—	4.97 (3.53)	—			

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Table 6. Findings from repeated measures mixed analysis of variance (RMANOVA) examining the effect of ginger supplementation (n = 51) compared with placebo (n = 52) on quality of life, nausea severity, vomiting episodes, fatigue, anxiety, depression, and nutritional status (*continued*)

	Cycle 1						Cycle 2						Cycle 3					
	Within groups			Between groups			Within groups			Between groups			Within groups			Between groups		
	Pre mean (SD)	Post mean (SD)	Within group MD[a] (95% CI)	Between group MD (95% CI)	p η^{2b}	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^2	*P* value[i]	Pre mean (SD)	Post mean (SD)	Within group MD (95% CI)	Between group MD (95% CI)	p η^2	*P* value[i]
RMANOVA		**Group**		***F* (df)**				**Time**		***F* (df)**				**Time x group**		***F* (df)**		
				0.79 (1, 101)	.008	0.377				21.84 (2, 153)	.18	**< 0.001**				4.49 (2, 153)	0.04	**.021**
Nutrition status score																		
Placebo	—	3.94 (5.53)	—	−0.43 (−1.65 to 0.78)	.01	0.483	—	5.56 (4.78)	—	−1.50 (−3.23 to 0.23)	.03	0.088	—	6.73 (5.53)	—	−2.59 (−4.53 to −0.66)	0.07	.009
Ginger	—	3.51 (3.09)	—				—	4.06 (4.46)	—				—	4.14 (4.27)	—			
RMANOVA		**Group**		***F* (df)**				**Time**		***F* (df)**				**Time x group**		***F* (df)**		
				4.32 (1, 100)	.04	0.040				12.29 (2, 153)	.11	**< 0.001**				4.72 (2, 151)	0.05	.018

[a]MD = mean difference.
[b]p η^2 = partial eta squared.
[c]QoL = quality of life.
[d]Group = between-group effect.
[e]time = time effect.
[f]time x group = interaction effect for group and time.
[g]CINV = chemotherapy-induced nausea and vomiting.
[h]VAS = visual analogue scale.
[i]Bold text represents statistically significant findings.

Table 7. Effect of ginger supplementation compared with placebo on incidence of nausea, vomiting, and malnutrition

Outcome	Cycle 1				Cycle 2				Cycle 3			
	Placebo (n = 52)	Ginger (n = 51)		*P*	Placebo (n = 52)	Ginger (n = 51)		*P*	Placebo (n = 52)	Ginger (n = 51)		*P*
	n (%)		*V*[a]	value[a]	n (%)		*V*[a]	value[a]	n (%)		*V*[a]	value[a]
Acute CINV[b]												
Nausea incidence	19 (37)	24 (47)	0.2	0.279	22 (42)	22 (43)	0.0	0.932	20 (38)	19 (37)	0.0	0.900
Delayed CINV												
Nausea incidence	29 (56)	25 (49)	0.1	0.493	39 (75)	27 (53)	0.5	0.020	41 (79)	25 (49)	0.7	**0.002**
Vomiting incidence	3 (6)	2 (4)	0.1	0.662	14 (27)	2 (4)	0.7	**0.001**	12 (23)	1 (2)	0.7	**0.001**
Nutritional status												
Well-nourished	39 (77)	41 (80)	0.1	0.630	29 (56)	38 (74)	0.133	0.2	31 (59)	42 (82)	0.3	0.032
Moderate malnutrition	12 (23)	10 (20)			21 (40)	12 (24)			17 (33)	8 (16)		
Severe malnutrition	0 (0)	0 (0)			2 (4)	1 (2)			4 (8)	1 (2)		

V = Cramer's *V* (0.1 = small effect, 0.4 = medium effect, and 0.5 = large effect).
[a]Bold text represents statistically significant findings.
[b]CINV = chemotherapy-induced nausea and vomiting.

DISCUSSION

The findings suggest that adjuvant ginger is associated with clinically relevant improvements in nausea-related QoL, overall CINV-related QoL, incidence and severity of delayed nausea, incidence of delayed vomiting, fatigue, and malnutrition. With the exception of fatigue, which showed benefit only at Cycle 1, all improvements in outcomes were mostly seen in later chemotherapy cycles (Cycle 2 and/or 3). Ginger was also associated with improvements in vomiting-related QoL and number of delayed vomiting episodes; however, these findings were not clinically meaningful. Minimal clinically important differences are not defined for nausea and vomiting incidence, number of vomiting episodes, and malnutrition; therefore, professional judgments were made by the investigators regarding clinical relevance of these outcomes. There was insufficient evidence against the null hypothesis for the effect of ginger on anticipatory or acute CINV, health-related QoL, anxiety and depression; potentially confounding variables did not influence results. Ginger appeared safe for use with no serious adverse events related to the intervention.

This study and its previous pilot[19] are the only trials that have examined whether or not ginger-mediated improvements in CINV are associated with improved QoL. Unlike the pilot study,[19] this randomized controlled trial found larger effect sizes for the positive effect of ginger on the primary outcome of nausea-related QoL. Evidence against the null hypothesis supporting the positive effect of ginger on QoL confirms the clinical importance, with optimized QoL often being more highly valued by people with cancer than improved treatment outcomes or survival.[44] However, future well-powered trials measuring both CINV- and health-related QoL are needed to confirm these findings and gain a valid understanding of the widespread influences of improved CINV on daily living. The clinically meaningful finding that ginger was positively associated with reduced cancer-related fatigue was consistent with previous systematic review findings[10] and pilot data.[19]

Similar to existing literature, incidence of fatigue among this study population was high (70%) and further research is warranted to confirm ginger as a promising intervention to assist in the management of this common, debilitating, and difficult to treat side-effect.[45,46] Mechanisms of cancer-related fatigue are multifactorial and complex, with numerous pathways having the potential to be influenced by ginger.[46] Convincing evidence exists for the anti-inflammatory properties of ginger,[16] which might benefit fatigue because inflammation is a key biological characteristic of fatigue in populations with cancer.[46-48] Fatigue is also characterized by widespread physiological changes in the brain and subsequent brain functioning, which have inflammatory involvement.[49] Worsening fatigue is associated with advanced stages of disease.[50] Thus, it is important to note that there were no differences between groups in presence of metastases at baseline or in fatigue between those who had metastases compared with those who did not. Because CINV can also exacerbate fatigue,[2] the observed positive effect could be due to improved CINV. Therefore, future studies that measure inflammatory and oxidative stress markers and stratify for disease stage are warranted.

Unlike findings of the pilot trial,[19] ginger improved nutritional status in this study. Nutritional status declined with subsequent chemotherapy cycles in the placebo group; however, remained stable in the ginger group. Maintenance

of nutritional status is considered a clinically important achievement in this patient group who are at high risk of decline.[51,52] This finding supports the association between reduced CINV and better nutritional status, likely improved through increased food intake and/or decreased nutrition losses that assists weight management and everyday functioning.[3-6] This confirms current recommendations that nutritional status in patients with CINV should be routinely monitored and managed to reduce risk of malnutrition, particularly as the course of chemotherapy progresses.[6] Ginger as a method of improving nutrition-influencing symptoms of CINV should be further explored in future research as an intervention for malnutrition prevention and management.

Consistent with previous systematic review[10] and pilot data,[19] ginger supplementation in this sample was safe with no serious adverse events reported. However, the findings of this study cannot be extrapolated to all populations, especially those who were ineligible for inclusion due to concurrent radiotherapy; liver disease; blood clotting disorders; or use of anticoagulant, hypoglycemic, and nonsteroidal anti-inflammatory medications. Some participants experienced reflux, which was inconsistent with other research suggesting ginger improves reflux symptoms.[53,54] Ginger use is not contraindicated for people with history of reflux but should be closely monitored in an oncology setting. Ginger supplementation might also be unsuitable for participants who are highly burdened with their cancer diagnosis and treatment schedule because this was the most common reason for study withdrawal. Despite possibly not being a feasible intervention for all, the participation rate in this study was high, indicating that ginger supplementation was well accepted as a method to improve CINV and QoL during cancer treatment.

This study advances current knowledge on optimal dosing regimens for ginger supplementation for CINV. Ginger could be most effective in later chemotherapy cycles and in the delayed phase for both CINV incidence as well as nausea severity, thus longer-term supplementation (ie, 5 days over 3 or more cycles) might be optimal. However, it is unclear if the greater effects in later cycles remain if ginger is not supplemented during the first cycle. The finding that ginger might be most effective in the delayed phase is contrary to the most well-understood mechanism of action; that is, the antagonistic effect of ginger on peripheral serotonin (5-HT3) receptors, which is most relevant to acute phase CINV.[55,56] Our findings suggest that ginger could have more of an effect on delayed phase central CINV pathways: antagonism of neurokinin receptors.[55,56] This is noteworthy as delayed CINV is difficult to manage in clinical practice in comparison to acute CINV.[57,58] Ginger, therefore, is of particular benefit as a supportive care option for chemotherapies with known delayed symptoms, such as cisplatin, carboplatin, cyclophosphamide, and doxorubicin.[59]

The novel beneficial effects of ginger observed in this study and the pilot data[19] also suggest that the frequency of ginger consumption (four times daily) might be optimal as most other trials that reported conflicting results have only administered ginger once or twice daily.[10] Given that the biological half-life of ginger is only 1.5 to 3 hours, the need for more frequent ginger consumption is also suggested. Regular consumption assists in maintaining peak serum concentrations of ginger bioactives.[22,23] The total ginger dose of 1.2 g/day containing 64 mg (3%) gingerols and 20 mg (1%) shogaols appeared beneficial in this trial and the pilot study[19]; however, future trials would benefit from investigating the dose-dependent response of standardized ginger supplements using compositional analysis to confirm stability of active ingredients.

Study Strengths, Limitations, and Implications for Future Research

The novelty of this study lies in its use of robust methodology and stringent adherence to the Consolidated Standards of Reporting Trials Statement[60] and Template for Intervention Description and Replication Checklist[61] to address the methodical limitations of previous trials and increase reproducibility and translation to practice.[10] This included detailed reporting of intervention and control conditions and outcome measurements, use valid and reliable outcome assessment tools, strict eligibility criteria and randomization minimisation to limit effects of confounders, double-blinding and supplement overencapsulation, and intention-to-treat analysis using multiple imputation to give an unbiased estimate of the effect of group allocation. Furthermore, this study is novel in being among the largest rigorous randomized controlled trials to confirm safety and efficacy of ginger supplementation for delayed phase CINV, which is particularly difficult to manage in clinical practice. The results also demonstrate novel effects on cancer-related fatigue, for which there are minimal treatment options,[62] as well as nutritional status and improved quality of life. Finally, it is the first trial to use analytical methods to confirm manufacturer's certificate of analysis as well as ensure the stability of active antiemetic constituents in the ginger supplements throughout the trial period.

Numerous limitations also require consideration when translating findings into clinical practice. The study was unable to recruit the prespecified sample size. Lower than anticipated recruitment rates were attributable to the number of eligible participants being much smaller than that observed in the pilot trial,[19] likely due to changes over time in chemotherapy regimens prescribed. However, post hoc power calculation found the study to be adequately powered. There were more participants with history of moderate to severe motion sickness in the ginger group, a known risk factor for CINV[26]; however, this had no effect on the results of this study. Despite double encapsulation, a higher number of participants in the ginger group correctly identified their group allocation, mainly due to ginger-tasting burps. Not only does this inadequacy of blinding imply potential bias and perceived improved outcomes due to knowing group allocation, but the intervention could exacerbate CINV in people who dislike ginger. Some trials have reported relief of reflux and ginger taste when consumed with food[10,16] and although this recommendation was made in this study, it might not be achievable, especially in people with CINV and low food intake.

This study has highlighted numerous additional areas for consideration in future research. Participants were asked to report their adherence to antiemetic regimens on discussion with the research assistant following each chemotherapy cycle. However, most participants had difficulty recalling this information and therefore was not deemed reliable or

meaningful to the results of this study. Future trials would benefit from including surveys on antiemetic use at each of the study time points because it is possible that participation in this trial led to improved adherence to antiemetic prescription. However, this was unlikely as CINV incidence in the placebo group was comparable to that reported in other trials.[7,8] It is also possible that changes in antiemetic use influenced CINV outcomes, although such changes should likely be equally distributed between groups due to the effective randomization process. Future trials considering these limitations are warranted and should be well powered and rigorously designed to confirm clinical significance as well as explore the perspectives and supportive care needs of people undergoing chemotherapy. There is a need to establish minimal clinically important differences for CINV and CINV-related outcomes to assist in the interpretation of the clinical relevance of future findings. The effect of ginger on broader outcomes is also required, including cost-effectiveness, cost-benefit, and treatment outcome.

CONCLUSIONS

In a sample of adults with cancer undergoing moderately to highly emetogenic chemotherapy, convincing evidence against the null hypothesis was found suggesting that adjuvant ginger, compared with placebo, is associated with clinically relevant improvements in QoL, delayed nausea and vomiting, fatigue, and nutrition status. Ginger supplementation is a promising, safe, and feasible adjuvant to standard antiemetic medications for CINV that enhances QoL during chemotherapy treatment. However, future well-powered, robust trials should use and report on standardized ginger formulations and examine dose-dependent responses to verify optimal dosing regimens.

PRACTICE IMPLICATIONS

What Is the Current Knowledge on this Topic?
There is substantial interest in the role of ginger as an adjuvant therapy for chemotherapy-induced nausea and vomiting. However, available evidence lacks robust methodology.

How Does this Research Add to Knowledge on this Topic?
This rigorous trial further validates current knowledge that adjuvant ginger, compared with placebo, is associated with clinically relevant improvements in quality of life, delayed nausea and vomiting, fatigue, and nutritional status.

How Might this Knowledge Influence Current Dietetics Practice?
Ginger supplementation is a promising, safe, and feasible adjuvant to standard antiemetic medications for nausea and vomiting that enhances quality of life during chemotherapy treatment.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

All third parties, including Bluebonnet Nutrition Corporation and The University of Sydney, were not affiliated with the study beyond commercial services. A. Molassiotis declares grants and honoraria from Helsinn.

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AUTHOR CONTRIBUTIONS

M. Crichton, S. Marshall, E. Isenring, A. Lohning, A. L. McCarthy, A. Molassiotis, R. Bird, C. Shannon, I. McPherson, and W. Marx designed the research; M. Crichton, A. Lohning, and A. Koh conducted the research; M. Crichton performed statistical analysis; M. Crichton drafted the paper and all other authors reviewed manuscript drafts; and W. Marx had primary responsibility for final content. All authors read and approved the final manuscript.

Table 1. Participant eligibility criteria for the trial assessing the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea and vomiting (as reported elsewhere)[20]

Inclusion criteria	Exclusion criteria
• Chemotherapy-naïve (no prior history of chemotherapy) • Scheduled for chemotherapy classed as moderately to highly emetogenic[a] • Scheduled for single or combined agent single-day chemotherapy regimen repeated in 2-, 3-, or 4-wk cycles[b] • Age >18 y • Adequate physical function: baseline Karnofsky score >60	• Concurrent radiotherapy • Severe cognitive impairment preventing ability to fully understand the purpose of the study, adhere to the intervention, and complete data collection forms • Pregnant or lactating women • Concurrent use of other ginger-containing supplements and ingestion of any amount of fresh or dried ginger from 24 hours before chemotherapy to 7-d postchemotherapy (Cycle 1-3) • History of adverse reactions to ginger • Experiencing significant nausea and vomiting for reasons other than chemotherapy, including o Prescribed medications with nausea-related side-effects (eg, newly-prescribed opioids) o Diagnosed with malignancies that might cause nausea and vomiting due to the position of the cancer (eg, gastrointestinal cancer) o Metabolic risk factors for nausea (eg, electrolyte imbalances) o Mechanical risk factors for nausea (eg, intestinal obstruction) • Chronic alcohol use as indicated by >14 standard drinks per week (exceeding Australian Guidelines to Reduce Health Risks from Drinking Alcohol; predictive factor for decreased chemotherapy-induced nausea risk)[21,22] • Severe thrombocytopenia or likely to experience severe thrombocytopenia (platelets <50 x 10^9/L) (medical note observation)[23] • Gallstones or liver disease (including liver cancer) • Prescribed warfarin, anticoagulant therapy, hypoglycemics, insulin, cyclosporine, tacrolimus, and nonsteroidal anti-inflammatory drugs • Swallowing difficulties preventing supplement ingestion • Self-prescribed nausea therapies or complementary products

[a]Moderate to highly emetogenic chemotherapy regimens informed by the Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology guideline from the Perugia consensus conference[24] and the most recent American Society of Clinical Oncology Antiemetic Guideline Update.[25]

[b]Includes regimens with more than one type of chemotherapy agent delivered in single day doses ≥7 days apart (eg, as with doxorubicin hydrochloride (Adriamycin), cyclophosphamide, and paclitaxel (taxol) regimens used in the treatment of breast cancer whereby cyclophosphamide and doxorubicin are administered on Day 1 of the treatment cycle and paclitaxel is administered on Day 1, Day 8, and Day 15 of a 21-day cycle).

Table 2. Manufacturer's compositional analysis of interventional ginger supplements used in the trial assessing the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea and vomiting

Active ingredient	Amount per 300-mg capsule (mg) (% of total weight)
6-gingerol	10.8 (3.6)
8-gingerol A	1.6 (0.5)
8-gingerol B	0.7 (0.2)
10-gingerol	2.4 (0.8)
6-gingerdiol	0.3 (0.1)
6-gingerdione	Not detected
8-gingerdione	Not detected
Total gingerols	15.8 (5.2)
6-shogaol	4.7 (1.6)
8-shogaol	0.6 (0.2)
10-shogaol	Not detected
Total shogaols	5.3 (1.8)
Total gingerols and shogaols	21.1 (7.0)

Table 4. Additional information about primary and secondary outcome measurement tools used to determine the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea and vomiting (CINV) and related outcomes

Outcome	Tool	Time point[a]	Assessment	Interpretation
Nausea-related QoL[b], vomiting-related QoL, CINV-related QoL	FLIE-5DR[c]: total score and subscale scores (nausea and vomiting)	T1, T3	There were 9 questions in each nausea and vomiting subscale, which used a 7-point Likert scale. A score ranging from 9 to 63 was generated for each nausea and vomiting subscale and a total CINV-related QoL score was summed from all 18 questions, with scores ranging from 18 to 126	Higher scores indicated less hardship and less influence of nausea and/or vomiting. No or minimal influence on daily living was defined as a subscale score of ≥54/63 or total score of ≥108/126
Nausea and vomiting symptoms[d]	MAT[e]	T1, T2, T3	Questions measured the incidence of nausea and vomiting as well as the severity of nausea and number of episodes of vomiting using a Likert scale (0-10)	Higher scores indicated more severe nausea and frequent vomiting. Clinically significant nausea was considered as a severity score of ≥3
Health-related QoL	EQ-5D-5L[f]: total score and VAS[g] rating	T1, T3	A total global wellbeing score ranging from 5 to 25 was generated by summing responses to the 5 questions. Participants were also asked to rate their health on a VAS from 0 to 100	Higher global well-being scores indicated poorer QoL. VAS health rating score ranged from 0 (worst health imaginable) to 100 (best health imaginable)
Fatigue	FACIT-F[h]	T2, T4	The 13-item scale using a 5-point Likert scale generated a total score ranging from 0 to 52	Lower scores indicated more fatigue. Clinically significant fatigue was classified as a score of ≤34 and a difference of 3 points between groups was considered a clinically meaningful difference
Anxiety and depression	HADS[i]	T2	Responses to the 7 anxiety-specific and 7 depression-specific questions were summed to generate total scores ranging from 0 to 21 for anxiety and depression	Higher scores indicated worst symptoms and a score of ≥11/21 represented abnormal anxiety or depression and was flagged to nursing staff as an incidental finding for follow-up care

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Table 4. Additional information about primary and secondary outcome measurement tools used to determine the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea and vomiting (CINV) and related outcomes (*continued*)

Outcome	Tool	Time point[a]	Assessment	Interpretation
Nutritional status	PG-SGA[j]	T1	PG-SGA was conducted by the research assistant, an accredited practicing dietitian The PG-SGA generated a total score typically ranging from 0 to 30.	Higher scores indicated greater risk of malnutrition as well as a global rating of A (well nourished), B (suspected or moderately malnourished), or C (severely malnourished). Participants identified as malnourished (PG-SGA rating B or C) were flagged to nursing staff and/or usual care dietitian as an incidental finding for follow-up care

[a]Time points are T0 = before chemotherapy, T1 = 1 day before chemotherapy or day of their chemotherapy (PG-SGA), T2 = 12 to 24 hours after chemotherapy, T3 = 4 days after chemotherapy, T4 = 5 to 8 days after chemotherapy. Time points 1 through 4 were repeated for three chemotherapy cycles (Cycles 1-3).
[b]QoL = quality of life.
[c]FLIE-5DR = Functional Living Index Emesis 5 Day Recall.
[d]Incidence and severity/frequency of anticipatory, acute, and delayed nausea and vomiting.
[e]MAT = Multinational Association of Supportive in Cancer Anti-emesis.
[f]EQ-5D-5L = European Quality of Life Five Dimension Five Levels tool.
[g]VAS = visual analogue scale.
[h]FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.
[i]HADS = Hospital Anxiety and Depression Scale.
[j]PG-SGA = Patient-Generated Subjective Global Assessment.

Table 8. Adverse events, classified according to the National Institute of Health Adverse Event and Serious Adverse Event Guidelines, reported by participants in the trial assessing the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea and vomiting

Adverse event	Incidence n (%)	Severity[a]	Expectedness[b]	Relatedness[c]
Reflux	10 (10) Ginger: 9 (18) Placebo: 1 (2)	Mild (n = 9) Moderate (n = 1, ginger group)	Expected	Possibly related
Constipation	5 (5) Ginger: 2 (4) Placebo: 3 (6)	Mild	Unexpected	Possibly related
Diarrhea	2 (2) Ginger: 1 (2) Placebo: 1 (2)	Mild	Unexpected	Possibly related
Abdominal pain	3 (3) Ginger: 1 (2) Placebo: 2 (4)	Mild	Unexpected	Possibly related
Mucositis	2 (2) Ginger: 1 (2) Placebo: 1 (2)	Mild	Unexpected	Not related
Peripheral neuropathy	1 (1) Ginger: 0 (0) Placebo: 1 (2)	Mild	Unexpected	Not related
Wound infection	3 (3) Ginger: 1 (2) Placebo: 2 (4)	Moderate	Unexpected	Not related
Oral thrush	1 (1) Ginger: 0 (0) Placebo: 1 (2)	Moderate	Unexpected	Not related
Urinary tract infection	1 (1) Ginger: 0 (0) Placebo: 1 (2)	Moderate	Unexpected	Not related
Upper respiratory tract infection	2 (2) Ginger: 2 (4) Placebo: 0 (0)	Moderate	Unexpected	Not related
Neutropenic	4 (4) Ginger: 3 (6) Placebo: 1 (2)	Moderate	Unexpected	Not related
Emergency room admission due to neutropenic fever	2 (2) Ginger: 0 (0) Placebo: 2 (2)	Severe	Unexpected	Not related
Emergency room visit due to fever	3 (3) Ginger: 1 (2) Placebo: 2 (4)	Severe	Unexpected	Not related

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Table 8. Adverse events, classified according to the National Institute of Health Adverse Event and Serious Adverse Event Guidelines, reported by participants in the trial assessing the effect of ginger supplementation, compared with placebo, on chemotherapy-induced nausea and vomiting (*continued*)

Adverse event	Incidence n (%)	Severity[a]	Expectedness[b]	Relatedness[c]
Pneumonia	2 (2) Ginger: 0 (0) Placebo: 2 (4)	Severe	Unexpected	Not related

[a]Severity was described as mild (tolerable, transient symptoms, minor irritant, no interference with normal activities, symptoms do not require therapy), moderate (low level of inconvenience, might interfere with normal activities and functioning, usually improved with simple therapeutic measures), or severe (interruption to normal activities, generally require systemic drug therapy, incapacitating).

[b]Expectedness was described as either expected (event known to be associated with the intervention) or unexpected (nature or severity of the event is not consistent with information about the intervention).

[c]Relatedness was described as definitely related (event clearly related to the investigational agent/protocol), possibly related (event shows some consistency with the onset of the study procedure but could have been produced by a number of other factors), or not related (clearly not related to investigational agent/protocol and another cause of the event is plausible).