Effects of Food-based Interventions in the Management of Chemoradiotherapy-Induced Nausea and Vomiting: A Systematic Review

Authors:
Molassiotis A[1], Zhao IY[2], Crichton M[3], Olver I[4], Fleury M[5], Giusti R[6], Scotte F[7], Affronti ML[8]

Affiliations:
[1]College of Arts, Humanities & Education, University of Derby, Derby, UK

[2]School of Nursing, The Hong Kong Polytechnic University, Hong Kong SAR, China

[3]Bond University Nutrition and Dietetics Research Group, Faculty of Health Science & Medicine, Bond University, Robina, Queensland, Australia.

[4]Olver I, University of Adelaide, Adelaide, South Australia, Australia.

[5]Department of Oncology, Lausanne University Hospital (CHUV), Faculty of Biology and Medicine, Lausanne, Switzerland

[6]Faculty of Medicine and Psychology, Sapienza University, Rome, Italy

[7]Interdisciplinary Patient Pathway Division, Institute Gustave Roussy, 94208 Villejuif, France

[8]School of Nursing, Duke University, Durham, North Carolina, USA

Corresponding author:

Prof. Alex Molassiotis
College of Arts, Humanities & Education,
University of Derby,
Derby, UK

Email: a.molasiotis@derby.ac.uk

Disclosures
All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Author contributions
Who had the idea for this article: AM
Who performed the literature search: AM , IYZ
Who performed the analysis: AM, IYZ, MC
Who drafted the paper: AM, IYZ, MC
Who critically revised the work: All authors
All authors confirm that they have approved the work submitted.

Declarations:
Ethical approval: NA as this is a review study
Consent to participate: NA
Consent to publish: NA.

Funding
No funding were obtained for this work.

Abstract

Background: Cancer treatment-related nausea and vomiting continue to be common and distressing symptoms for patients, despite improvements in antiemetics. Dietary modifications could potentially improve this symptom experience. Clinicians frequently provide dietary advice to patients, although the evidence base of such suggestions or recommendations is not clear.

Purpose: This systematic review aimed to examine the current literature on food interventions associated with improvements in cancer treatment-related nausea and vomiting.

Methods: Eight electronic databases were searched with a specific search term strategy covering trials without time or language limitations. Eligible studies focused on a food substance, defined as any nutritious substance that people eat or drink to maintain life and well-being. Trials in children and adults during chemotherapy or radiotherapy were included. Cochrane Risk of Bias Tool was used to assess trial quality and GRADE was used to assess the certainty in the effect of each outcome.

Results: Seventeen trials were included, 3 focusing on children and 14 on adults. Two trials included patients receiving radiation. Ten out of 17 trials (59%) had a high risk of bias. Strongest evidence with highest certainty was found for dietary counselling to meet macronutrient requirements in reducing incidence of radiotherapy-related nausea and vomiting in adults (n=2 studies; n=124 participants; GRADE level: moderate). There was also moderate certainty in the beneficial effect of protein supplementation on nausea and vomiting incidence in adults during radiotherapy (n=2 studies; n=124 participants; GRADE level: moderate). A significant positive effect on CINV inci dence and/or severity in adults was also found for dietary counselling to meet macronutrient requirements during chemotherapy, a peppermint drink, scaly wood mushroom, chamomile, protein with ginger, and a colorless odorless diet (GRADE level: low to very low).

Conclusions: The review identified food-based approaches that could improve the nausea and vomiting experience in patients with cancer and provide guidance to clinicians. However, confidence in these findings was low and studies were heterogeneous and mostly of low quality, requiring further investigation before stronger recommendations can be made. Future research is needed to confirm efficacy and safety.

Trial registration: PROSPERO CRD42022341154

Keywords: Diet; cancer; chemotherapy; radiotherapy; dietary counselling; food; nutrition

INTRODUCTION

Chemoradiotherapy-related toxicity remains a significant clinical problem in both adult and pediatric oncology, despite advances in antiemetic therapy and supportive care. Gastrointestinal toxicities, such as chemoradiotherapy-induced nausea or vomiting (CINV) are the most feared and the most common adverse effects in patients undergoing cancer treatment [1]. CINV are nutrition impacting symptoms experienced by patients with cancer, which may lead to decreased food intake, and may compromise both nutritional status and functional ability [2, 3], subsequently resulting in diminished quality of life [4] and treatment toxicity, and potentially deterring patients from further treatment [5].

The management of CINV has been improved over the past years with newer antiemetic medications [6]. Vomiting can be significantly prevented in the majority of patients by using combination guideline antiemetic medications [7]. However, strategies to control nausea have been less effective, with up to 60% of patients reporting nausea despite the use of antiemetics [8]. Furthermore, the administration of combination antiemetic medications for treating CINV can lead to side effects, such as headache, diarrhea, insomnia, epigastric discomfort, agitation, weight gain, and hyperglycemia [9, 10], which are exacerbated in pediatric patients [11]. Therefore, there is growing interest in the role that diet may play the prevention and management of CINV [12].

Nutritional status is closely associated with the toxicity of chemotherapy [13]. Patients with CINV may have added benefits from the implementation of nutritional support [14]. A clinical review, focusing on dietary management in gastrointestinal complications from chemotherapy, suggested patients avoid overly fatty and sweet foods [15] and Mardas' study [16] found that more than 10% of patients indicated oily foods had significantly increased the incidence of their nausea. Several self-care strategies were suggested by Williams et al. [17], including using green mint tea, lime juice, and garlic,

to relieve the symptoms of CINV. However, while guidelines for CINV treatment and prevention recommend specific pharmacological interventions, there is lack of information regarding dietary modification [16]. There is limited evidence regarding effective dietetic interventions for CINV. Only one recent systematic review, focusing on dietary strategies and including both clinical trials and observational studies, has provided some evidence that nutrition education specific to these symptoms with support from health care professionals has a positive effect on CINV [18]. Gala and colleagues state that non-restrictive dietary patterns, and the Mediterranean diet, could positively impact CINV [18]. However, the confidence in these results was low due to methodological issues with the primary studies, and nutraceuticals as well as children and patients undergoing radiotherapy were not considered. To inform clinical decisions about the impact of nutritional interventions during chemoradiotherapy, it is essential to review the evidence base for dietary support in this context, particularly around specific dietary modifications that have not been explored in past reviews. The aim of this review was to examine the current literature on the effect of food-based interventions on any nausea and vomiting outcome in patients of any age undergoing chemotherapy and/or radiotherapy, compared to any control conditions.

METHODS

Design

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: CRD42022341154). To enhance the rigor of the review, our approach followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Figure 1) [19] and the PRISMA 2020 update [20].

Search strategy and selection criteria

We searched broad search engines with no time restriction. EBSCO (comprising of MEDLINE, CINAHL and Global Health), PubMed, ProQuest, Cochrane Library, EMBASE, Web of Science and Google Scholar were searched systematically from database inception to June 2022. Manual searches were conducted from June to July 2022 by examining reference lists of included studies and previous reviews to identify any additional studies. The search strategies were based on the following combination of terms: (Cancer OR oncology OR carcinoma OR neoplasm* OR tumor* OR malignant*) AND (chemotherapy* OR chemoradiotherapy*) AND (nausea OR vomiting OR CINV OR emetics OR emesis) AND (dietary OR diet OR nutrition OR food OR supplement OR nutrient OR dietetics OR eat* OR malnutrition).

Inclusion and exclusion criteria

Studies that assessed the efficacy of specific food-based approaches for the management of cancer treatment-related nausea and vomiting were included. Food, for the purposes of the current analysis, is defined as any nutritious substance that people eat or drink to maintain life and well-being. We included such studies that met the following criteria: 1) Patients with cancer of any age (both adult and pediatric populations); 2) Patients receiving chemo(radio)therapy treatment (i.e., chemotherapy, radiotherapy, or both); 3) any type of controlled study with no restrictions on comparator; 4) Included any nausea and vomiting outcome (primary outcomes for this review); and 5) Studies in any language or geographical location. Studies with specific food intake combined with another dietary strategy (i.e., dietary counselling) were also included. Studies were excluded if patients were receiving parenteral nutrition or enteral tube feeding or nutrition intervention in combination with pharmaceutical intervention. We also excluded studies with ginger, as there are many systematic reviews on the topic already [21-25], unless the use of ginger was combined with another food.

Selection of literature and outcomes

Following the search, all identified citations were collated and uploaded into EndNote 20 (Clarivate Analytics, PA, USA) and duplicate checking of full records from the initial search was performed. Two investigators independently screened the titles and abstracts of all citations then full texts using Endnote. Any discrepancies were resolved with input from a third investigator.

Data extraction, quality appraisal and data synthesis

Data were extracted by two independent investigators using a predetermined data extraction tool developed by the research team. The data extracted included specific details about the author, publication year, country, participants, study design, sample size and sample characteristics, components of the intervention and the comparator, outcome measures, and main findings relevant to the review question(s). Discrepancies were addressed through discussions among the research team.

The internal validity and risk of bias for the included trials were independently assessed by two investigators using the appraisal Risk of Bias (RoB 2) tool from the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [26]. This assessment has seven criteria, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, in addition to other bias. Each of them could be classified as yes ('low risk of bias'), no ('high risk of bias'), or unclear ('moderate risk of bias'). The overall risk of bias rating for each trial was 'low' when all seven items were defined as of 'low risk of bias', 'high' when one or more items were evaluated as 'high risk of bias', and 'unclear' in any other case. Discrepancies were discussed, and if required, a third investigator was consulted. Data were reported via narrative synthesis in tables and text. The sources of funding for the studies as well as the declarations of conflicts of interest were systematically identified.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method [21] was used to evaluate the certainty in the effect of each outcome for which there were significant findings. Assessments were conducted using GRADEpro GDT software (GRADEpro Guideline Development Tool, McMaster University, 2015). Four levels of certainty for the estimated effect were possible: high (very confident in the effect), moderate (moderately confident in the effect), low (little confidence in the effect) and very low (very little confidence in the effect) [21]. One investigator independently determined the GRADE level f evidence, which was reviewed and confirmed by a second investigator.

RESULTS

Search results and study quality

Of the 18,237 titles and abstracts reviewed, we excluded 18,214 articles that did not meet our eligibility criteria, resulting in 23 articles for full-text review. Additionally, six articles were excluded because there was no comparator to examine the effect of different dietary strategies on CINV. In all, 17 papers satisfied our eligibility criteria and were included by consensus agreement (see Figure 1). Of the 17 interventional studies, 10 studies (59%) had an overall high risk of bias [4, 13, 14, 27-33], five studies (29%) had low risk of bias [34-38], and two studies (12%) had unclear risk of bias (see Table 2) [39, 40]. The main reasons for bias were the lack of personnel and outcome assessment blinding, and other sources of bias, (small sample size, short follow-up time, and poor participant compliance), which were acknowledged limitations in most studies. GRADE ratings were low to very low for most outcomes (see Table 3). We report on the sources of funding for the studies included in the review in Supplementary Table 1.

Population and study characteristics

The 17 studies (15 randomized controlled trials (RCTs) and two non-randomized trials [28, 33]) included 23 interventions and were published between 1992 and 2021 (see Table 1). Three studies focused on

adolescents and children (n=270) [14, 28, 39], while the remaining studies were undertaken with adults (n=1134). Four studies were conducted in Iran [27, 31, 36, 38], three in the United States [29, 37, 40], two in Portugal [34, 35], two in Brazil [4, 32] and one each in Mexico, Singapore, China, Poland, the Netherlands, and Germany [13, 14, 28, 30, 33, 39] respectively. All studies reported gender ratios and provided age ranges (1.3-84 years old). Research participants were patients with hematological malignancies, central nervous system tumors, head and neck cancers, colorectal cancer, breast cancer or other types of cancer. Two of studies focused on radiotherapy [14, 39] with one in head and neck and the other in colorectal patients with cancer, one on radiotherapy combined with chemotherapy [28], and the remaining 14 studies focused on chemotherapy. Nine different tools were used to assess CINV: Memorial Symptom Assessment Scale (MSAS) [14], CTCAE [4, 13, 28, 33], Ottery's Subjective Global Assessment [34, 35], McGill Questionnaires [31], EORTC-QLQ-C30 [30], RD tool [40], INV-R [37], VAS [38] and self-designed questionnaires [27, 36]. Interventions were administered as adjuvants to standard antiemetic regimens.

Dietary strategies for CINV and related outcomes

Specific food intake

Two (67%) of the three studies [28, 39] on children and adolescents examined the effect of probiotic intake on CINV during chemotherapy with or without radiotherapy. Incidence of nausea and vomiting was significantly decreased with Lacticaseibacillus rhamnosus (previously known as *Lactobacillus rhamnosus;* n=60 participants) [39] and *Bacillus licheniformis* preparation (n=160 participants) [28] compared to placebo or usual care (GRADE level: very low).

In adults during chemotherapy, four (29%) RCTs examined the effect of specific nutrition supplements on CINV: *Agaricus sylvaticus* (scaly wood mushroom) tablets [32], *Matricaria chamomilla* (chamomile)

extract capsules [36], Concord® grape juice drink [37], and *Mentha piperita* (peppermint) extract consumed in water [38]. Patients consuming scaly wood mushroom tablets reported less incidence of nausea and vomiting than patients in the placebo group (15% vs. 85%); however, statistical significance was not tested (n=46 participants; GRADE level: very low) [32]. Chamomile in capsule form was significantly more effective in reducing the frequency of vomiting compared to antiemetics alone (GRADE level: very low), but was not more effective than ginger (*Zingiber officinale)* supplements (n=65 participants) [36]. Similarly, grape juice flavonoid treatment reduced nausea frequency 0.64 times, nausea distress by 0.98 units, vomiting distress by 0.11 units, and vomiting volume by 0.33 units [37], all of which, however, did not reach statistical significance possibly due to high attrition (50%). Consumption of peppermint water in comparison to unflavored water significantly reduced nausea severity at 24 and 48 hours after chemotherapy (n=84 participants; GRADE level: low) [38].

Specific nutrient intake

Seven (50%) [4, 13, 27, 29, 31, 34, 35] of the 14 studies on adults examined the effect of specific nutrients on CINV: protein supplementation [13, 29, 34, 35] and dietary counselling to achieve macronutrient requirements [4, 27, 31, 34, 35]. During chemotherapy, nausea was significantly less prevalent in patients who received a high protein drink (32g/day) with ginger capsules (1g/day), compared to those who had less protein (17g/day) with ginger (1g/day) and those who received usual care (n=28 participants; GRADE level: very low) [29]. However, in another study during chemotherapy that administered protein supplements (36g/day) without ginger, there was no effect on CINV incidence nor severity (n=114 participants) [13]. During radiotherapy, protein supplementation significantly reduced incidence of nausea and vomiting compared to usual care (n=2 studies; n=124 participants; GRADE level: moderate) but was not as effective as dietary counselling to meet macronutrient requirements [34, 35].

All five studies that assessed dietary counselling with or without a personalized diet plan to achieve macronutrient and thus energy requirements found significant benefits [4, 27, 31, 34, 35]. Dietary counselling to meet macronutrient requirements and specific to CINV significantly reduced CINV incidence during radiotherapy compared to usual care or protein supplements (n=2 studies; n=124 participants; GRADE level: moderate) [34, 35] and significantly reduced CINV severity during chemotherapy compared to usual care (n=3 studies; n=334 participants; GRADE level: low) [4, 27, 31].

Dietary patterns

One (33%) [14] of the three studies on adolescents and children and three (21%) [30, 33, 40] of the 14 studies on adults examined dietary patterns for CINV: a colorless and odorless diet [40] and fasting with or without a ketogenic diet [30, 33]. In adolescents and children, assessing food preference and managing energy, hydration and nutritional intake were significantly associated with lower fatigue in the intervention group, while no difference were identified on CINV outcomes between the two groups [14]. In adults during chemotherapy, patients who were adherent to a 4-day plant-based low amino-acid substitution diet, consisting of soups, broths, liquids, vitamin tablets and tea, reported less complaints of nausea (n=129) [30]. Patients who had a colorless, odorless, predetermined meal exhibited higher overall food intake and decreased vomiting incidence and volume compared to a regular inpatient diet; however, statistical significance was not tested (n=20 participants; GRADE level: very low) [40]

Dietary counseling combined with specific food intake

Five studies (5/14) were conducted among adult patients to examine the effect of combining dietary counseling and specific food intake on CINV. The reduction in the incidence and severity of nausea and vomiting was distinctly showed in the intervention group of providing dietary counseling, individual diet plan, and energy and protein supplement after radiotherapy [34, 35] and chemotherapy [4, 27, 31].

DISCUSSION

The current review is the first to synthesize evidence focus on specific food intake for the prevention and management of CINV in adults as well as children and adolescents. Strongest evidence with highest certainty was found for dietary counselling to meet macronutrient requirements in reducing incidence of radiotherapy-related nausea and vomiting in adults. There was also moderate certainty in the beneficial effect of protein supplementation on nausea and vomiting incidence in adults during radiotherapy. A significant positive effect on CINV severity in adults was also found for dietary counselling to meet macronutrient requirements during chemotherapy and a peppermint drink; however, certainty in these effects was low. There was very low certainty in the positive effect of scaly wood mushroom, chamomile, protein with ginger, and a colorless odorless diet for reducing CINV incidence in adults. In children and adolescents, probiotics reduced CINV incidence during chemotherapy with or without radiotherapy, but the certainty in this effect was very low. There was no significant effect of grape juice, fasting, nor a ketogenic diet on CINV.

Findings of this review complement previous (except for reviews specifically on ginger [21-25]) and dietary strategies, behaviors, and education that included observational studies [18]. The combined results from the two reviews of Gala et al [18] and the current review provide useful evidence for clinicians to improve their practice, both in terms of nutritional approaches and food intake. Although, the level of confidence in most studies is low due to methodological issues, such as small sample sizes and risk of bias, and heterogeneity in terms of interventions, populations, and outcome measures that precludes meta-analysis.

Two studies (one during chemotherapy and one during chemoradiotherapy) have shown that supplementation with specific probiotics can significantly improve nausea and vomiting during treatment

in children and adolescents [39, 28]. Although complex and not yet well understood, probiotic supplementation causes beneficial changes in gastrointestinal bacteria composition, which might influence CINV pathways. The gut microbiota is thought to modulate the response to chemotherapy drugs; therefore, gut microbiota composition is suggested to play a role in chemotherapy efficacy and toxicity [36]. Preliminary evidence also suggests that the release of serotonin from enterochromaffin cells, an initiating step of CINV pathways, can be modulated by gut microbiota [37, 38]. Probiotics can also promote bile salt hydrolase-producing bacteria that in turn decrease bile acid, which is linked with exacerbating nausea and vomiting [41, 42]. However, it should be kept in mind that, as with any intervention, while probiotics are generally well tolerated, some preparations contain live and therefore active microorganisms, which also have adverse effects that could call into question their benefit-risk balance. Bacteremia and sepsis have been reported in immunocompromised patients with central lines, and colonization by pathogens, even in healthy humans, should prompt us to exercise great caution. As more and more chemotherapies are accompanied by immunotherapy, the benefit-risk balance must be carefully weighed, as indications of a deleterious effect on the gut microbiome cannot be ruled out. Nevertheless, the focus on probiotics for the management of CINV is novel and of growing research interest, and thus necessitates careful attention and the identification of patients who could benefit from this type of intervention in future research.

Dietary counselling with regular foods or nutritional advice and energy and protein supplements have also been effective in alleviating nausea and vomiting during radiotherapy. One study [34] found more improvement with dietary counselling (90% improvement) with the group with energy/protein supplementation had a 67% improvement, while the usual intake group had an improvement of 51%. Hence, both study groups had clinically important improvements. The second similar study in another

group of patients with cancer from the same authors [35] found that both dietary counselling and energy/protein supplementation improved symptoms of nausea and vomiting, alongside other outcomes such as energy or protein intake and quality of life scores, with the dietary counselling group being the more effective one too. A third trial with nutritional advice and an individualized meal plan focusing on guideline-based energy and protein intake [4] also showed positive effects along similar results from another trial where the same approach was used in addition to education and a pamphlet given to patients [31]. In addition to the above studies where a diet based on higher levels of energy and protein supplementation had positive clinically relevant effects albeit lower than with dietary counselling, another trial of high protein meals (using ProSure) plus ginger [29] had significantly better results for delayed nausea than a protein diet group or antiemetics only. The same was the case for a trial using nutritional education with specific percentage of calories coming from protein, fat and carbohydrates [27], also finding positive outcomes in relation to the severity of nausea.

Consistent with Gala et al [18], this review found strongest evidence for dietary strategies implemented with dietary counselling. While some of these trials used more than one component in the intervention and hence a clear single effect cannot be discerned for them, the evidence that individualized dietary counselling to achieve adequate macronutrient and thus energy intakes is valid. Future research delineating the effect of adequate macronutrient and energy intakes from dietary counselling support would be useful in determining the cause of effect.

A novel finding of this review is the possible benefit of protein supplementation for CINV, particularly during radiotherapy. Gastrin, a hormone secreted in response to protein ingestion, is involved in maintaining normal stomach rhythm, which is dysregulated with nausea and vomiting [39]. Protein is also acknowledged to be important during cancer treatment to maintain muscle mass, immunity, healing

and recovery, and fluid balance, improving overall health, quality of life, as well as response and tolerance to cancer treatment. Therefore, findings of this review support the most recent European Society for Clinical Nutrition and Metabolism (ESPEN) Practice Guideline for Clinical Nutrition in Cancer [40], which strongly recommends a high protein diet for people with cancer (1.5g/kg/day rather than 1.0g/kg/day for the general healthy population) [40].

Another trial with intriguing results related to nausea and vomiting during chemotherapy has used an extract of a mushroom in the form of a pill [32] and showed a very large difference between the experimental and control group in a small study of 46 patients with breast cancer. This merits further investigation in the future; the effect on CINV may be indirect, as the main medicinal functions obtained from eating mushrooms are a type of polysaccharides (â-Glucan) and a large amount of other dietary fibre that can improve bowel function [43]. Once again, a weighing of the benefit-risk balance and counseling of patients who would like to experiment with this type of product is essential, as case reports of hepatic toxicity have been reported.

Two different types of diet modification have been shown to improve chemotherapy-related nausea and vomiting. One was a 4-day low amino-acid diet consisting of broths, liquids, vitamin tablets and tea [30], while the other used a colorless, odorless predetermined meal based on cottage cheese, apple sauce, vanilla ice cream and other selected foods [40]. These are low-cost and easily implemented approaches that could be used in clinical practice considering patient preferences too. However, the evidence obtained from these two trials was of very low quality, and from a dietetics perspective experts would advise against overly restrictive eating habits.

Both chamomile and ginger decreased the *frequency of vomiting* although neither improved the *intensity of nausea*. There were no significant differences between the chamomile and the ginger group, except

for ginger being linked with lower *frequency of nausea*. Both substances are remedies that are traditionally used to improve gastrointestinal disorders, improve gastric emptying and aid digestion. Another substance traditionally used to smooth the stomach and has abdominal spasmolytic effects is peppermint, which showed a decrease in nausea severity in one trial, using 40 drops of peppermint in a glass of water during chemotherapy [38]. A trial using 4oz of grape juice during chemotherapy [37] also found beneficial effects in relation to nausea frequency, nausea distress, vomiting distress and vomiting amount. However, it also showed higher levels of vomiting in the experimental group than the control group, perhaps linked with the sweetness of the juice, which also may explain the higher attrition rate in the experimental group. While there is no previous related work on chamomile or grape juice and limited work on peppermint (primarily on peppermint as an essential oil [44-46]), the role of ginger in managing CINV is well established [21-25], at least in the form of capsules and powders, with work needed to be done on ascertain how this translates into dietary consumption. Such substances could all be used complementary to dietary modifications and antiemetics, although further research work is required to confirm efficacy and safety.

A few trials showed no evidence of effect in relation to chemotherapy-related nausea and vomiting, including an educational programme managing energy, hydration and nutritional intake in children and adolescents with cancer (although this programme improved fatigue) [14]; an intervention with oral nutritional support and high protein (although nutrition status overall improved) [13], and fasting with or without ketogenic diet [33]. This is important information for clinicians who are intervening to manage nausea and vomiting and hence can focus their approaches to other areas with stronger evidence base.

This review, along with that conducted by Gala et al [18], highlight that most recommendations for managing CINV provided by many organisations and hospitals, including information clinicians

regularly provide to patients as education for managing CINV (ie. to eat toast or crackers; have carbonated drinks; avoid fatty, greasy, fried, spicy or sweet food; eat small amounts more often) have no research evidence base [41-43]. While evidence-based practice is ideal, the aforementioned strategies are safe, feasible, and in line with general healthy eating guidelines [40], and thus should continue to be provided on a case-by-case basis until research refutes them. In addition to current patient educational material, nutritional advice can be offered as a key component of managing treatment-induced nausea and vomiting, either by a dietician, another health professional or in writing, depending on available resources. Adequate energy and macronutrient intakes, particularly protein, can be introduced in patient education, alongside healthy eating practices or advice on choice of foods (e.g. colourless, odourless, predetermined meals). The Multinational Association of Supportive Care in Cancer will introduce the above key points related to nutritional advice in their updated 2023 clinical antiemetic guidelines together with other non-pharmacological approaches. Dietary practices with lower level of evidence can be proposed to patients if other options are not preferred or appropriate.

Limitations

Many of the trials used for the review were small-scale studies, often underpowered and with methodological limitations. Doses and approaches differed significantly. For most interventions only a single trial was found, and hence meta-analysis was not possible. Outcome measurements were also variable and at times crude, and assessment tools used were mostly unvalidated and differed greatly between studies. Most studies had high risk of bias and there was little confidence in the effect of most outcomes, evident by GRADE ratings being mostly low to very low. Most of the findings presented in the review need further methodologically robust investigation before conclusive recommendations can be made.

CONCLUSION

This systematic review identified several foods that can be used to prevent and manage CINV. The strongest evidence was found for dietary counselling to meet macronutrient requirements and address CINV, with protein supplementation also showing promise. There is preliminary evidence for peppermint, probiotics, chamomile, and scaly wood mushroom for CINV. Future research is warranted to increase confidence in the effect of food-based interventions for CINV and to confirm efficacy.

References

1. Limon-Miro AT, Lopez-Teros V, Astiazaran-Garcia H: Dietary guidelines for breast patients with cancer: A critical review. *Adv Nutr* 2017, 8(4):613–623.
2. Marx W, Kiss N, McCarthy AL, McKavanagh D, Isenring L. Chemotherapy-Induced Nausea and Vomiting: A Narrative Review to Inform Dietetics Practice. J Acad Nutr Diet. 2016; 116(5):819-27.
3. Sari DK, Dewi R, Daulay W: Association Between Family Support, Coping Strategies and Anxiety in Patients with cancer Undergoing Chemotherapy at General Hospital in Medan, North Sumatera, Indonesia. *Asian Pac J Cancer Prev* 2019, 20(10):3015-3019.
4. Souza A, Silva L, Fayh A: Nutritional Intervention Contributes to the Improvement of Symptoms Related to Quality of Life in Breast Patients with cancer Undergoing Neoadjuvant Chemotherapy: A Randomized Clinical Trial. *Nutrients* 2021, 13(2):589.
5. Krikorian S, Pories S, Tataronis G, et al.: Adherence to oral chemotherapy: challenges and opportunities. *J Oncol Pharm Pract* 2019, 25(7):1590-1598.
6. Amirifard N, Sadeghi E, Payandeh M, et al.: Relationship between HER2 proto-oncogene status and prognostic factors of breast cancer in the west of Iran. *Asian Pac J Cancer Prev* 2016, 17:295-298.
7. Jordan K, Jahn F, Aapro M: Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. *Ann Oncol* 2015, 26:1081-1090.
8. Hsieh RK, Chan A, Kim HK: Baseline patient characteristics, incidence of CINV, and physician perception of CINV incidence following moderately and highly emetogenic chemotherapy in Asia Pacific countries. *Support Care Cancer* 2015, 23:263-227.
9. Vardy J, Chiew KS, Galica J, Pond GR, Tannock IF: Side effects associated with the use of dexamethasone for prophylaxis of delayed emesis after moderately emetogenic chemotherapy. *Br J Cancer* 2006, 94(7):1011-1015.
10. Rao KV, Faso A: Chemotherapy-induced nausea and vomiting: optimizing prevention and management. *Am Health Drug Benefits* 2012, 5(4):232-240.
11. Merrow M, King N: Optimizing antiemetic therapy for children undergoing chemotherapy. *J Pediatr Nurs* 2022, 66:136–142.
12. Kim AJ, Hong DS, George GC: Dietary influences on symptomatic and non-symptomatic toxicities during cancer treatment: A narrative review. *Cancer Treat Rev* 2022, 108:102408.
13. Ziętarska M, Krawczyk-Lipiec J, Kraj L, Zaucha R, Małgorzewicz S: Chemotherapy-Related Toxicity, Nutritional Status and Quality of Life in Precachectic Oncologic Patients with, or without, High Protein Nutritional Support. A Prospective, Randomized Study. . *Nutrients* 2017, 9(10):1108.
14. Cheng KK, Tan L: A pilot study of the effect of a home-based multimodal symptom-management program in children and adolescents undergoing chemotherapy. *Cancer Rep (Hoboken, NJ)* 2021, 4(3):e1336.
15. Calixto-Lima L, Martins de Andrade E, Gomes AP, Geller M, Siqueira-Batista R: Dietetic management in gastrointestinal complications from antimalignant chemotherapy. *Nutricion hospitalaria* 2012, 27(1):65–75.
16. Mardas M, Madry R, Stelmach-Mardas M: Link between diet and chemotherapy related gastrointestinal side effects. *Contemporary oncology (Poznan, Poland)* 2017, 21(2):162–167.
17. Williams PD, Piamjariyakul U, Ducey K, Badura J, Boltz KD, Olberding K, Wingate A,

Williams AR: Cancer treatment, symptom monitoring, and self-care in adults: pilot study. *Cancer Nurs* 2006, 29(5):347–355.

18. Gala D, Wright HH, Zigori B, Marshall S, Crichton M. Dietary strategies for chemotherapy-induced nausea and vomiting: A systematic review. Clin Nutr. 2022; 41(10):2147-2155. doi: 10.1016/j.clnu.2022.08.003.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group. TP: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PloS Med* 2009, 6(7).
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021, 372:n71.
21. Marx, W.M., et al., Ginger (Zingiber officinale) and chemotherapy-induced nausea and vomiting: a systematic literature review. Nutr Rev, 2013. 71(4): p. 245-254.
22. Marx, W., N. Kiss, and L. Isenring, Is ginger beneficial for nausea and vomiting? An update of the literature. Curr Opin Support Palliat Care, 2015. 9(2): p. 189-95.
23. Marx, W., et al., Ginger—Mechanism of action in chemotherapy-induced nausea and vomiting: A review. Crit Rev Food Sci Nutr, 2017. 57(1): p. 141-146.
24. Crichton, M., et al., Efficacy of ginger (Zingiber officinale) in ameliorating chemotherapy-induced nausea and vomiting and chemotherapy-related outcomes: a systematic review update and meta-analysis. J Acad Nutr Diet, 2019. 119(12): p. 2055-2068.
25. Saneei Totmaj, A., et al., The effect of ginger (Zingiber officinale) on chemotherapy-induced nausea and vomiting in breast patients with cancer: A systematic literature review of randomized controlled trials. Phytotherapy Res, 2019. 33(8): p. 1957-1965.
26. Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. UK: John Wiley & Sons: The Cochrane Collaboration; 2011.
27. Abdollahi R, Najafi S, Razmpoosh E, Shoormasti RS, Haghighat S, Raji Lahiji M, Chamari M, Asgari M, Cheshmazar E, Zarrati M: The Effect of Dietary Intervention Along with Nutritional Education on Reducing the Gastrointestinal Side Effects Caused by Chemotherapy Among Women with Breast Cancer. *Nutr Cancer* 2019, 71(6):922–930.
28. Du SX, Jia YR, Ren SQ, Gong XJ, Tang H, Wan-Shui W, Li-Ming S: The protective effects of Bacillus licheniformis preparation on gastrointestinal disorders and inflammation induced by radiotherapy in pediatric patients with central nervous system tumor. . *Adv Medi Sci* 2018, 63(1):134–139.
29. Levine ME, Gillis MG, Koch SY, Voss AC, Stern RM, Koch KL: Protein and ginger for the treatment of chemotherapy-induced delayed nausea. *J Altern Complement Med* 2008, 14(5):545–551.
30. Lugtenberg RT, de Groot S, Kaptein AA, Fischer MJ, Kranenbarg EM, Carpentier MD, Cohen D, de Graaf H, Heijns JB, Portielje J *et al*: Quality of life and illness perceptions in patients with breast cancer using a fasting mimicking diet as an adjunct to neoadjuvant chemotherapy in the phase 2 DIRECT (BOOG 2013-14) trial. *Breast Cancer Res Treat,* 2021, 185(3):741–758.
31. Najafi S, Haghighat S, Raji Lahiji M, RazmPoosh E, Chamari M, Abdollahi R, Asgari M, Zarrati M: Randomized Study of the Effect of Dietary Counseling During Adjuvant Chemotherapy on Chemotherapy Induced Nausea and Vomiting, and Quality of Life in Patients With Breast Cancer. *Nutr Cancer* 2019, 71(4):575–584.
32. Valadares F, Garbi Novaes MR, Cañete R: Effect of Agaricus sylvaticus supplementation on nutritional status and adverse events of chemotherapy of breast cancer: a randomized, placebo-

controlled, double-blind clinical trial. *Indian J Pharm* 2013, 45(3):217–222.

33. Zorn S, Ehret J, Schäuble R, Rautenberg B, Ihorst G, Bertz H, Urbain P, Raynor A: Impact of modified short-term fasting and its combination with a fasting supportive diet during chemotherapy on the incidence and severity of chemotherapy-induced toxicities in patients with cancer - a controlled cross-over pilot study. *BMC Cancer* 2020, 20(1):578.
34. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME: Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck* 2005, 27(8):659–668.
35. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME: Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal patients with cancer undergoing radiotherapy. *J Clin Oncol* 2005, 23(7):1431–1438.
36. Sanaati F, Najafi S, Kashaninia Z, Sadeghi M: Effect of Ginger and Chamomile on Nausea and Vomiting Caused by Chemotherapy in Iranian Women with Breast Cancer. *Asian Pac J Cancer Prev.* 2016, 17(8):4125–4129.
37. Ingersoll GL, Wasilewski A, Haller M, Pandya K, Bennett J, He H, Hoffmire C, Berry C: Effect of concord grape juice on chemotherapy-induced nausea and vomiting: results of a pilot study. *Oncol Nurs Forum* 2010, 37(2):213–221.
38. Jafarimanesh H, Akbari M, Hoseinian R, Zarei M, Harorani M: The Effect of Peppermint (Mentha piperita) Extract on the Severity of Nausea, Vomiting and Anorexia in Patients with Breast Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. *Integr Cancer Ther* 2020, 19(1534735420967084).
39. Reyna-Figueroa J, Barrón-Calvillo E, García-Parra C, Galindo-Delgado P, Contreras-Ochoa C, Lagunas-Martínez A, Campos-Romero FH, Silva-Estrada JA, Limón-Rojas AE: Probiotic Supplementation Decreases Chemotherapy-induced Gastrointestinal Side Effects in Patients With Acute Leukemia. *J Pediatr Hem Oncolo*2019, 41(6):468–472.
40. Menashian L, Flam M, Douglas-Paxton D, Raymond J: Improved food intake and reduced nausea and vomiting in patients given a restricted diet while receiving cisplatin chemotherapy. *J Am Diet Assoc* 1992, 92(1):58–61.
41. Liu AT, Chen S, Jena PK, Sheng L, Hu Y, Wan YY. Probiotics Improve Gastrointestinal Function and Life Quality in Pregnancy. Nutrients. 2021;13(11):3931.
42. Urdaneta V, Casadesús J. Interactions between Bacteria and Bile Salts in the Gastrointestinal and Hepatobiliary Tracts. Front Med (Lausanne). 2017; 4:163.
43. Novaes MR, Valadares F, Reis MC, Gonçalves DR, Menezes Mda C. The effects of dietary supplementation with Agaricales mushrooms and other medicinal fungi on breast cancer: Evidence-based medicine. *Clinics (Sao Paulo)* 2011;66:2133–9.
44. Mohr C, Jensen C, Padden N, Besel JM, Brant JM. Peppermint Essential Oil for Nausea and Vomiting in Hospitalized Patients: Incorporating Holistic Patient Decision Making Into the Research Design. J Holist Nurs. 2021;39(2):126-134.
45. Efe Ertürk N, Taşcı S. The Effects of Peppermint Oil on Nausea, Vomiting and Retching in Patients with cancer Undergoing Chemotherapy: An Open Label Quasi-Randomized Controlled Pilot Study. Complement Ther Med. 2021;56:102587.
46. Briggs P, Hawrylack H, Mooney R. Inhaled peppermint oil for postop nausea in patients undergoing cardiac surgery. Nursing. 2016; 46(7):61-67.

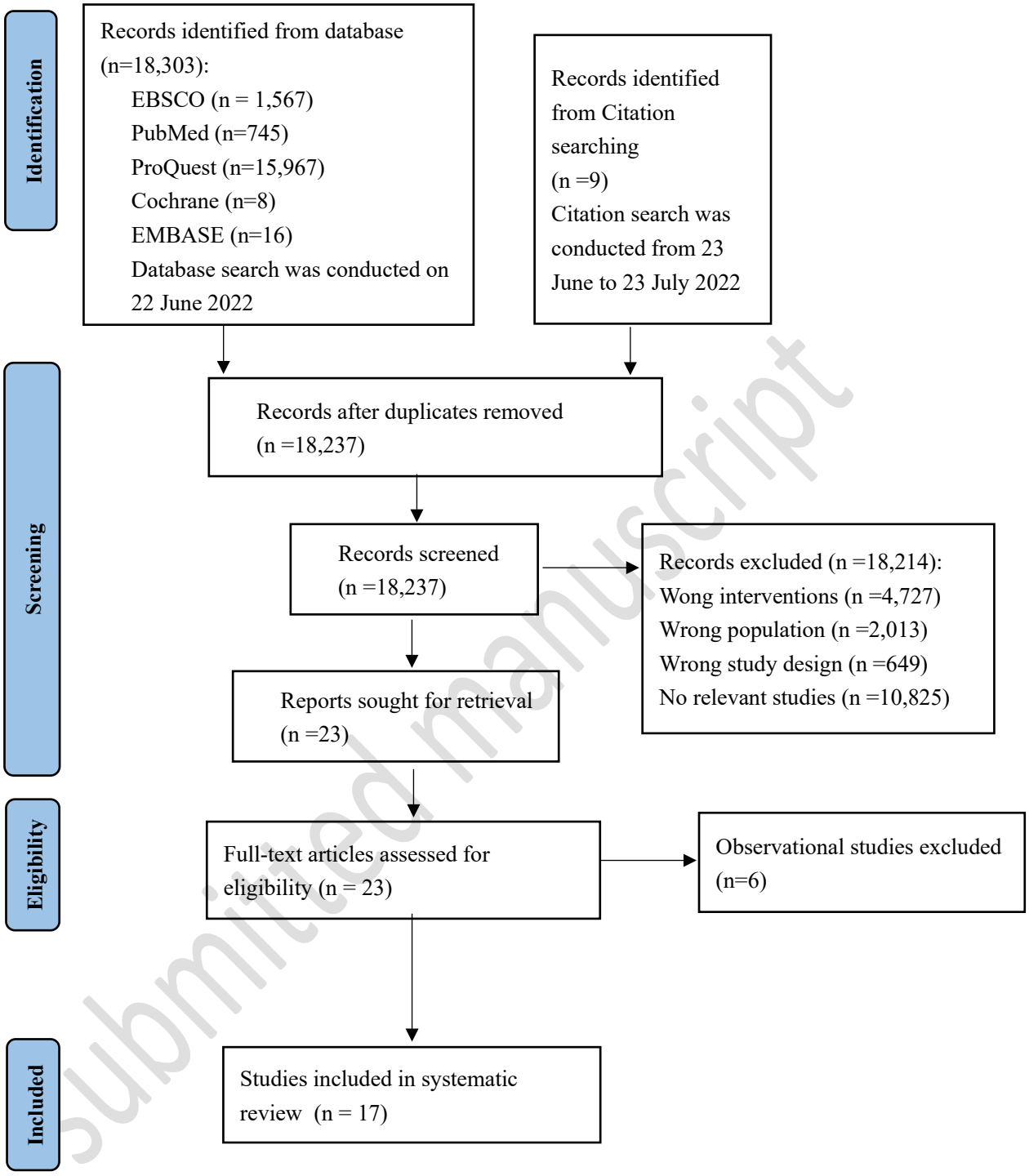

Figure 1. PRISMA Literature screening diagram and results [19, 20].

Table 1. Characteristics and findings of studies examining the effect of dietary strategies on CINV in children and adults.

Study & Population Characteristics					Dietary Strategy Characteristics [a]		Study Results	
Study Characteristics	**Country**	**Population** **1. Sample size** **2. Age** **3. Gender ratio (F:M)**	**Cancer**	**Study aims/objectives**	**Dietary Strategy**	**Comparator**	**CINV Tool**	**Primary Outcome: CINV** **Secondary Outcomes**
Adolescents and children's studies (N=3)								
Reyna-Figueroa et al., 2019 [39] RCT	Mexico	1. 60 2.10.8 yrs 3. IG: 9/21; CG:13/17	Acute leukemia on remission induction or remission reinduction chemotherapy	To assess the effects of probiotic supplementation on chemotherapy-induced gastrointestinal side effects in children with acute leukemia (AL).	Probiotic Lactobacillus rhamnosus GG (a concentration of 5×109 CFU per sachet was administered at a standard dose twice daily, by mouth) for a maximum of 7 days	No probiotics	Case Report Form	Primary outcomes Nausea and vomiting significantly decreased in the probiotic group (P<0.05); for nausea a relative risk of 0.5 (95% CI, 0.4-0.8; P=0.04) and for vomiting a relative risk of 0.4 (95% CI, 0.2-0.9; P=0.04) were observed. Secondary outcomes Abdominal distension significantly decreased in the probiotic group (P<0.05). For diarrhea a relative risk of 0.5 (95% confidence interval [CI], 0.2-1.2; P=0.04) was observed.
Cheng et al., 2021 [14] RCT	Singapore	1. 50 2. 13.7 ± 2.5 yrs 3. 19/31	Hematological malignancy or solid tumor and had planned chemotherapy	To examine the effect of a home-based multimodal symptom-management program for alleviation of nausea and vomiting in children and adolescents undergoing chemotherapy for hematological malignancies or solid tumors.	Managing energy, hydration and nutritional intake. Screening of noxious stimuli and discussing ways to avoid them, assessing children and adolescents' food preference, and discussing principles of meal preparation particularly during nausea/vomiting times + usual care for 6 months	Usual care	Memorial Symptom Assessment Scale (MSAS) 10-18	Primary outcomes No differences were found with respect to nausea and vomiting between groups. Secondary outcomes Fatigue was significantly lower across all time-points in the intervention group compared to the control group (F = 4.95, P = .034, effect-size = 0.32).
Du et al., 2018 [28] Non-randomised controlled trial	China	1. 160 2. 7.1 (1.3–15.5) yrs 3. 52/108	Central nervous system tumor with craniospinal irradiation (CSI) treatment	To assess the effect of Bacillus licheniformis preparation (ZCS) on CNST (central nervous system tumor) patients undergoing the gastrointestinal symptoms and inflammation induced by radiotherapy.	One capsule per time of Bacillus licheniformis preparation (ZCS) and 3 times a day until the end of radiotherapy, starting one day before radiotherapy	Placebo without any probiotics	CTCAE 3.0	Primary outcomes Decreased incidence for all grades of nausea (53/80) compared to the control group (66/80), x^2 =5.542, P=0.019. Decreased incidence for all grades of vomiting (28/80) compared to the control group (42/80), x^2 =4.978, P=0.026 Secondary outcomes Increased of serum ET, TNF-a, IL-1b, IL-6 and CRP after RT
Adults studies (n=14)								
Radiotherapy (n=2)								
Ravasco et al., 2005 [34] RCT	Portugal	1. 75 2. 60±11 yrs 3. 15/60	Head and neck cancer	To determine the effect of dietary counseling or oral supplements on outcome for patients with cancer, specifically, nutritional outcome, morbidity, and quality of life (QOL), during and 3 months after radiotherapy.	G 1: dietary counseling with regular foods; G 2: maintained usual diet plus energy and protein supplements;	G 3: maintained intake ad lib.	Ottery's Subjective Global Assessment	Primary outcomes At 3 months, the reduction in the incidence and severity of grade 1 + 2 nausea/vomiting was distinctly different between groups: 90% of the patients improved in group 1 versus 67% in group 2 versus 51% in group 3 (p < .0001); group 1 > groups 2 and 3 (p < .07). Secondary outcomes Energy intake after RT increased in both groups 1 and 2 (p <.05). Protein intake also increased in both groups 1 and 2 (p <.006). Both energy and protein intake decreased

								significantly in group 3 ($p < .01$). At 3 months, group 1 maintained intakes, whereas groups 2 and 3 returned to or below baseline levels. At 3 months, patients in group 1 maintained or improved overall QOL, whereas patients in groups 2 and 3 maintained or worsened overall QOL.
Ravasco et al., 2005 [35] RCT	Portugal	1. 111 2. 58±15 yrs 3. 45/66	Colorectal cancer outpatients referred for preoperative radiotherapy combined with chemotherapy	To investigate the impact of dietary counseling or nutritional supplements on outcomes in patients with cancer: nutritional, morbidity, and quality of life (QoL) during and 3 months after radiotherapy.	G1: received individualized dietary counseling based on regular foods; G2: consumed 2 cans per day of a high-protein liquid supplement in addition to their usual diet;	G3: maintained their ad libitum intake.	Ottery's Patient Generated Subjective Global Assessment	Primary outcomes After radiotherapy and at 3 months, rates of nausea, and vomiting were higher in G3 ($P < .05$). 100% patients improved in G1, 62% showed improvement in G2, and 51% showed improvement in G3 (P.0001) Secondary outcomes At radiotherapy completion, energy intake increased in G1/G2 ($P < .04$), G1 more than G2 (P =.001), and decreased in G3 ($P < .01$). Protein intake increased in G1/G2 ($P < .007$). At 3 months, G1 maintained nutritional intake and G2/G3 returned to baseline. At radiotherapy completion, in G1 all QoL function scores improved proportionally to adequate intake or nutritional status ($P < .05$); whereas in G2 only three of six function scores improved proportionally to protein intake (P = .04), and in G3 all scores worsened ($P < .05$). At 3 months, G1 patients maintained/improved function, symptoms, and single-item scores ($P < .02$); in G2, only few function and symptom scales improved ($P < .05$); in G3, QoL remained as poor as after radiotherapy. In G1/G2, respectively, improvement/deterioration of QoL correlated with better or poorer intake or nutritional status ($P < .003$)
Chemotherapy (n=12)								
Ziętarska et al., 2017 [13] RCT	Poland	1. 114 2. 40–84 yrs 3. IG: 20/27; CG: 26/22	All types of cancer in the first step of cancer cachexia-asymptomatic precachexia	To determine whether nutritional support with high protein (ONS) in adult oncologic patients in the first step of cancer cachexia-asymptomatic precachexia, has an influence on the toxicity of systemic therapy	Oral nutritional support (ONS) with high protein of 2x 125 mL pf per day (36g/day), 7 days per week for 12 weeks	Without nutritional support	NCI CTCAE Version Vomiting and nausea 4.0	Primary outcomes There were no statistical differences between groups (ONS with high protein vs. Control) in the number and severity of nausea and vomiting ($p>0.05$) Secondary outcomes In the ONS group an improvement in nutritional status was noticed (increased appetite VAS, $p = 0.05$; increased points in SGA, $p = 0.015$, and increased levels of albumin and prealbumin, $p = 0.05$). The performance status and quality of life were stable in both groups.
Souza et al., 2021 [4] RCT	Brazil	1. 34 2. IG: 44.3 ± 9.2 yrs; CG: 45.5 ± 8.6yrs 3. 34/0	Breast cancer and at the beginning of neoadjuvant chemotherapy treatment	To evaluate the effect of a nutritional intervention on QoL and on gastrointestinal and hematological toxicities resulting from chemotherapy in women with breast cancer.	Nutritional advice on healthy eating practices and individualized diet plan estimated individually by a dietitian and based on age, current weight, and height of each subject, recommending between 25 and 30 kcal/kg/day of energy and 1.5 g/kg/day of protein, according to current guidelines	Nutritional advice on healthy eating practices	Common Terminology Criteria for Adverse Events (CTCAE) | Protocol— National Cancer Institute version 5.0	Primary outcomes The nausea/vomiting scale (nausea severity) showed an interaction effect between group and time ($p < 0.001$), and the main effect of time ($p = 0.018$), without the main effect of the group ($p = 0.065$), with a large effect size measured by Cohen's ds (>0.8 for all times). Nausea and vomiting frequency $p>0.05$. Secondary outcomes The CG significantly presented a reduction (from 21.6 ± 5.9 kg to 18.8 ± 4.0 kg, p = 0.009) in handgrip strength (HGS), while the IG did not present changes in this variable.

								IG had lower frequencies of leukopenia and abdominal pain.
Levine et al., 2008 [29] RCT	US	1. 28 2. 29–83 yrs 3. 19/9	All types of cancer receiving chemotherapy for the first time	To explore the use of protein meals with ginger for the treatment of the delayed nausea of chemotherapy.	Protein Group meal: • One 237-mL ProSure® beveragea • - 300 kcal (23% whey protein (17 g), 21% fat, 57% carbohydrates) • Four 250-mg capsules of dried powdered ginger root (Zintona®)b • Standard antiemetic medication High Protein Group meal: • One 237-mL ProSure beverage • - 300 kcal (23% whey protein (17 g), 21% fat, 57% carbohydrates) • Three 6.6-g scoops of ProMod® protein powdera (added to ProSure) • - 84 calories (71% whey protein (15 g), 19% fat, 10% carbohydrate) • Four 250-mg capsules of dried powdered ginger root (Zintona) • Standard antiemetic medication	Standard antiemetic medication	Symptom diary.	Primary outcomes Nausea was significantly less common among High Protein Group patients (p <0.01). Reports of nausea being frequent were significantly less common among High Protein Group patients (p <0.01). Reports of nausea being bothersome were significantly less common among High Protein Group patients (p <0.01). Secondary outcomes The use of prescribed antiemetic medication was significantly less common among High Protein Group patients (p <0.05).
Najafi et al., 2019 [31] RCT	Iran	1. 150 2. IG: 46.9 ±12.4 yrs CG: 46±8.8 yrs 3. 150/0	Breast cancer were at stage IA to IIIB but without distant organ metastasis	To elucidate the impact of nutritional education during adjuvant chemotherapy on CINV and QoL	A personalized diet, which contained 1.2–1.5 g/kg of protein, 30% of energy from fat and 55–60% of energy from carbohydrate, a face to face nutrition education, and a pamphlet which contained beneficial nutrition information to reduce the severity of CINV before each chemotherapy session for three times or regular care.	Usual diet based on their food patterns, regular chemotherapy drug regimen without having any pamphlet, nutritional education and dietary intervention	McGill Questionnaires	Primary outcomes Nausea and vomiting severity: Patients in the intervention group experienced less nausea and vomiting (β=-20.90, $P <$ 0.001) than the control group Secondary outcomes Patients in the intervention group experienced less fatigue (β=-19.68, $P < 0.001$), pain (β=–24.36, $P < 0.001$), dyspnea (β= –12.86, $P < 0.001$), sleep loss (β= –15.06, $P < 0.001$), appetite loss (β= –21.11, $P < 0.001$), constipation (β=–16.67, $P < 0.001$), and diarrhea (β= –9.87, $P < 0.001$) than the control group
Abdollahi et al., 2019 [27] RCT	Iran	1. 150 2. IG: 46.81 ± 12.32 yrs; CG: 46.10 ± 8.91 yrs 3. 150/0	Breast cancer	To assess the effect of dietary intervention along with nutritional education on reducing GI side effects.	Dietary intervention and nutritional education for 10 weeks. The related diet consisted of 12–15% calories of protein, 30–35% of fat, and 55–60% of carbohydrates which were estimated individually based on participant's current age, weight, and height before the subsequent session of each chemotherapy	Usual care without giving pamphlet, nutritional education and dietary intervention	Self-designed questionnaire	Primary outcomes The severity of nausea (P =0.002) in the intervention group reduced significantly in the third session of chemotherapy compared to the first session Secondary outcomes The severity of GI side effects in the intervention group including reflux disorder (P =0.05), anorexia ($P < 0.001$), constipation ($P < 0.001$), and diarrhea ($P < 0.001$) reduced significantly in the third session of chemotherapy compared to the first session.
Valadares et al., 2013 [32] Non-randomized controlled trial	Brazil	1. 46 2. IG: 52.7 yrs; CG: 49.5 yrs 3. 46/0	Breast cancer, Stage II and III	To evaluate the effects of dietary supplementation of Agaricus sylvaticus on clinical and nutritional parameters in BC patients undergoing chemotherapy.	nutritional supplement (tablet format) with Agaricus sylvaticus (2.1 g/day)	Placebo	Not available	Primary outcomes Only 2 (15.3%) patients treated with A. sylvaticus reported nausea and vomiting while majority of patients 11 (84.62%) in placebo group notified nausea and vomiting. P not reported. Secondary outcomes Poor appetite decreased by 20% with no changes in bowel functions (92.8%)
Lugtenberg	Netherlands	1. 129	HER2-negative	To examine the possible side	4-day plant-based low amino acid	Regular diet	EORTC-QLQ-	Primary outcomes

et al., 2021 [30] RCT		2. IG: 49.0 (31–71) yrs; CG:51.0 (27–71) yrs 3. 129/0	stage II/III breast cancer	effects of chemotherapy and the FMD diet	substitution diet, consisting of soups, broths, liquids, vitamin tablets and tea (FMD).		C30	In both groups, patients reported significant worsening of nausea during treatment, but in the FMD group the difference was not clinically relevant (an increase in nausea score of <10). Patients who were adherent to the diet reported less complaints of nausea. Secondary outcomes Better emotional, physical, role, cognitive and social functioning scores as well as lower fatigue, and insomnia symptom scores for patients adherent to the FMD in comparison with non-adherent patients and patients on their regular diet.
Menashian et al., 1992 [40] RCT	USA	1. 20 2. 25-84 yrs 3. 11/9	All types of cancer	To evaluate nausea and vomiting, amount of food intake, and subjective assessment of well-being	A colorless, odorless, predetermined meal 3 times daily; the meal included cottage cheese, apple sauce, vanilla ice cream, and other selected foods.	Normal inpatient menu	RD tool; day of CTX	Primary outcomes Study-group patients exhibited higher overall food intake, decreased nausea and vomiting. P not reported. Secondary outcomes Not available
Zorn et al., 2020 [33] RCT	Germany	1. 51 2. 30-74 yrs 3. 51/0	Gynaecologic cancer	To investigate whether modified short-term fasting (mSTF) reduces the incidence of chemotherapy-induced toxicities and whether an initial ketogenic diet (KD) as fasting supportive diet reduces fasting-related discomfort and improves the compliance.	Strategy 1: Fasting (n=27) - Fasting (<25% of daily energy requirements) Duration: 4 days (from 3 days prior to CTX to day of CTX) Strategy 2: Ketogenic diet then fasting (n=24) - Ketogenic diet with normal energy intake (maximum of 20-40g carbohydrate per day, at least 75% of energy from fat) - Fasting (<25% of daily energy requirements) Duration: Ketogenic diet for 6 days then fasting diet for 4 days (from 3 days prior to CTX to day of CTX)	Normal diet	CTCAE	Primary outcomes For both nausea and vomiting, -no significant difference between fasting with or without KD; *p* NR Secondary outcomes During mSTF the frequency and severity score of stomatitis [− 0.16 ± 0.06; 95% CI -0.28 - (− 0.03); $P = 0.013$], headaches [− 1.80 ± 0.55; 95% CI -2.89 – (− 0.71); $P = 0.002$], weakness [− 1.99 ± 0.87; 95% CI -3.72 – (− 0.26); $P = 0.024$] and the total toxicities' score were significantly reduced [− 10.36 ± 4.44; 95% CI -19.22 - (− 1.50); $P = 0.023$]. A significantly fewer chemotherapy postponements post-mSTF, reflecting improved tolerance of chemotherapy [− 0.80 ± 0.37; 95% CI -1.53 – (− 0.06); $P = 0.034$]. A significant reduction in mean body weight by − 0.79 ± 1.47 kg during mSTF was not compensated and remained until study's conclusion *(*$P < 0.005$). On average, Insulin [− 169.4 ± 44.1; 95% CI -257.1 – (− 81.8); $P < 0.001$] and Insulin-like growth factor 1 levels [− 33.3 ± 5.4; 95% CI -44.1 – (− 22.5); $P < 0.001$] dropped significantly during fasting.
Sanaati et al., 2016 [36] RCT	Iran	1. 65 2. 20-60 yrs 3. 65/0	Breast cancer	To determine the effect of ginger and chamomile capsules on nausea and vomiting in cases undergoing chemotherapy for breast cancer (BC)	Intervention group 1: (ginger group; comparator) 5 days before and 5 days after chemotherapy was: 2 times a day and 500 mg capsules of powdered ginger root in addition to a routine antiemetic regimen consisting of dexamethasone, metoclopramide and aprepitant (DMA). Intervention group 2 (chamomile group) 5 days before and 5 days after chemotherapy was: 2 times a day and 500 mg capsules of Matricaria	Routine antiemetic regimen consisting of DMA	A self-developed, self-reporting instrument	Primary outcomes Ginger and chamomile are ineffective on intensity of nausea (P=0.238) while both are effective on the frequency of vomiting (P<0.0001). There is no significant difference in the ginger and chamomile groups. Ginger effects on the frequency of nausea (P=0.006).

					Chamomilla extract in addition to a routine antiemetic regimen consisting of DMA capsule			
Ingersoll et al., 2010 [37] RCT	US	1. 77 2. IG:54.1 ± 12.4 yrs; CG 54.5 ± 12.7 yrs 3. 62/15	All types of cancer	To provide preliminary data on effect of Concord grape juice on CINV	4 oz. of grape juice prior to meals for one week following each of four chemotherapy treatment cycles	Placebo	INV-R	Primary outcomes The grape juice treatment reduced 0.64 time of nausea frequency, 0.98 unit of nausea distress, 0.11 unit of vomiting distress, and 0.33 unit of vomiting amount. P>0.05. Secondary outcomes Low positive correlations were seen between total number of days in which nausea occurred and baseline MAACL-R anxiety (r = 0.32; p = 0.005), depression (r = 0.35; p = 0.002), hostility (r = 0.25; p = 0.03), and dysphoria (r = 0.37; p = 0.001) scores
Jafarimanesh et al., 2020 [38] RCT	Iran	1. 84 2.IG:11.78±49.6 yrs; CG:9.52±51. 90 yrs. 3. 84/0	Breast cancer	To determine the effect of peppermint extract on the severity of nausea, vomiting, and anorexia in patients with breast cancer undergoing chemotherapy	40 drops of peppermint extract mixed in 20 cc of tap water every 8 hours	40 drops of distilled water mixed in 20 cc of tap water every 8 hours.	Patients' medical records, frequency table, and the VAS	Primary outcomes The mean score of nausea severity was significantly lower in the IG than CG at 24 and 48 hours after the chemotherapy (P < .05). Secondary outcomes The mean score of anorexia in the experimental group was lower in than the control group (P = .001).

CFU: colony-forming units;

Table 2. Cochrane Risk of Bias assessment for Randomised Trials included in the review

	Q1 Random sequence generation	Q2 Allocation concealment	Q3 Blinding (participants and personnel)	Q4 Blinding (outcome assessment)	Q5 Incomplete outcome data	Q6 Other sources of bias	Q7 Selective reporting	Overall bias
Reyna-Figueroa et al. [39]	Y	Y	Y	U	U	Y	Y	U
Cheng et al. [14]	Y	Y	U	N	Y	Y	Y	N
Du et al. [28]	N	N	N	N	Y	N	Y	N
Ravasco et al. [34]	Y	Y	Y	Y	Y	Y	Y	Y
Ravasco et al. [35]	Y	Y	Y	Y	Y	Y	Y	Y
Ziętarska et al. [13]	Y	Y	N	N	Y	Y	Y	N
Souza et al., [4]	Y	Y	N	N	Y	N	Y	N
Levine et al., [29]	Y	U	N	N	Y	N	Y	N
Najafi et al., [31]	Y	Y	N	Y	Y	N	Y	N
Abdollahi et al. [27]	Y	U	N	N	Y	N	Y	N
Valadares et al. [32]	Y	Y	Y	Y	Y	Y	N	N
Lugtenberg et al. [30]	Y	Y	N	N	Y	Y	Y	N
Menashian et al.[40]	Y	Y	U	U	U	U	U	U
Zorn et al., [33]	N	N	N	N	Y	N	Y	N
Sanaati et al. [36]	Y	Y	Y	Y	Y	Y	Y	Y
Ingersoll et al., [37]	Y	Y	Y	Y	Y	Y	Y	Y
Jafarimanesh et al. [38]	Y	Y	Y	Y	Y	Y	Y	Y

'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias

Table 3. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for each outcome examining the effect of food-based interventions in the management of chemoradiotherapy-induced nausea and vomiting.

Certainty assessment							Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Lactobacillus rhamnosus GG - Nausea & vomiting relative risk							
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	⊕◯◯◯ Very low
Bacillus licheniformis preparation - Nausea & vomiting incidence							
1	randomised trials	very serious[c]	not serious	not serious	very serious[b]	none	⊕◯◯◯ Very low
Mushroom - Nausea & vomiting incidence							
1	randomised trials	very serious[c]	not serious	not serious	extremely serious[d]	none	⊕◯◯◯ Very low
Chamomile vs. antiemetics alone - vomiting frequency							
1	randomised trials	not serious	not serious	not serious	extremely serious[d]	none	⊕◯◯◯ Very low
Peppermint - nausea severity							
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ Low
Protein and ginger - nausea incidence (chemotherapy)							
1	randomised trials	very serious[c]	not serious	not serious	extremely serious[d]	none	⊕◯◯◯ Very low
Colorless and Odorless diet - vomiting incidence & volume							
1	randomised trials	serious[a]	not serious	not serious	extremely serious[d]	none	⊕◯◯◯ Very low
Protein supplements vs. usual care - nausea and vomiting incidence (radiotherapy)							
2	randomised trials	not serious	not serious	not serious	serious[e]	none	⊕⊕⊕◯ Moderate
Dietary counselling vs. usual care - nausea and vomiting incidence (radiotherapy)							
2	randomised trials	not serious	not serious	not serious	serious[e]	none	⊕⊕⊕◯ Moderate
Dietary counselling vs. usual care - nausea and vomiting severity (chemotherapy)							
3	randomised trials	very serious[c]	not serious	not serious	serious[e]	Strong association	⊕⊕◯◯ Low

CI: confidence interval

Explanations

a. Unclear risk of bias

b. ≤100 participants

c. High risk of bias

d. ≤50 participants

e. ≤400 participants