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Efficacy and Safety of Ginger (Zingiber Officinale) for Chemotherapy-Induced Nausea and Vomiting (CINV) in Breast Cancer Patients

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ABSTRACT

Background: Cancer is one of the world's leading causes of death. Cancer statistics in 2022 predict that there will be 1,918,030 new cancer cases and 609,360 cancer-related deaths. Breast cancer has the newest cases, with an estimated 287,850 patients (31%). Chemotherapy is a common intervention used in the treatment of breast cancer. Although chemotherapy is an essential conventional cancer treatment, it has a few serious side effects that can be fatal to cancer patients both during and after treatment, one of which is chemotherapy-induced nausea and vomiting (CINV). Ginger (Zingiber officinale), which is said to have anti-nausea properties, is one of the most prominent herbs used in traditional medicine. Despite new emerging studies that Ginger can help CINV symptoms, high-quality data supporting the efficacy and safety of ginger on CINV remain scarce.

Methods: We will search for electronic database that is in English from inception to July 2022. Two experienced researchers select qualified articles from the following databases: PubMed, Embase, and The Cochrane Library. The primary outcome was the number and severity of nausea and vomiting incidents. Data extraction and quality assessment will be carried out independently by two experienced researchers. RevMan 5.3 software will be used to analyze data and assess the risk of bias.

Results and Conclusion: We will get exact evidence about the safety and effectiveness of ginger in the treatment of CINV in breast cancer based on the current proof.

Abbreviations: CINV: Chemotherapy induced Nausea and Vomiting; NTS: Nucleus of the Solitary Tract; CTZ: Chemoreceptor Trigger Zone; NK1: Neurokinin-1; RCT: Randomized Controlled Trial; RR: Risk Ratio; MD: Mean Difference; SMD: Standard Mean Difference

Keywords: Ginger; Zingiber Officinale; Breast Cancer; CINV; Chemotherapy Induced Nausea and Vomiting

Introduction

Cancer is one of the leading causes of death in the world. According to cancer statistics 2022, there are expected to be 1,918,030 new cancer cases and 609,360 cancer-related deaths. Breast cancer has the highest estimated new cases of 287,850 patients (31%) [1]. Chemotherapy is a common intervention used in the treatment of breast cancer. Even though it is a necessary conventional treatment for cancer patients, it has a few serious side effects that can be fatal to cancer patients both during and after treatment [2]. Chemotherapy-induced nausea and vomiting (CINV) remains one of the most unpleasant and feared side effects of cancer treatment, despite advances in new and effective antiemetic medications [2]. Five different forms of CINV can be distinguished: acute, delayed, anticipatory, breakthrough, and refractory. Acute CINV is defined as nausea and vomiting that occur within 24 hours of the chemotherapeutic drug's initial administration, while delayed CINV begins 24 hours to 2-3 days after delivery [3]. Both acute and delayed CINV include routes in the peripheral and central neural systems with various underlying causes. In cases of acute CINV, entero-chromaffin cells in the gastrointestinal tract are stimulated by free radicals produced by toxic chemotherapy drugs, which leads to the production of serotonin. Serotonin then binds to intestinal vagal afferent nerves via 5-HT3 receptors, which triggers the vomiting reflex via the nucleus of the solitary tract (NTS) and chemoreceptor trigger zone (CTZ) in the CNS. 5-HT3 receptor signaling may also play a role in delayed CINV, but to a lesser extent than in acute CINV. Substance P is considered to be the principal neurotransmitter involved in delayed CINV [4]. Chemotherapy drugs trigger the release of substance P from neurons in the central and peripheral nervous systems, which then binds to neurokinin-1 (NK1) receptors mainly in the NTS to induce vomiting [5]. New antiemetic drug developments are emerging to treat CINV, but they are not only expensive but also have adverse effects on the digestive and nervous systems, resulting in side effects such as hypotension, diarrhea, headaches, and fatigue [6]. Therefore, there has been various approaches and researches finding alternative ways on managing CINV.

One of the most prominent herbs that is most frequently used in traditional medicine is ginger (Zingiber officinale), which is said to have anti-nausea properties [5]. A variety of compounds, including shogaols, gingerols, zingerone, and paradols, are bioactive within the ginger rhizome [7]. While the concentrations of these compounds vary greatly depending on the country of origin, storage, and preparation of the ginger product, gingerol and shogaol are most likely the primary components responsible for ginger's pharmacological effects. These compounds are thought to interact with a variety of areas involved in the development of CINV [8]. Consequently, investigation of how these components acts on the pathophysiology of CINV started to emerge. Ymahara was the first to demonstrate that the whole ginger including gingerols 6,8 and 10 can inhibit 5-HT3 induced contraction. Followed by that, the 5-HT3 antagonistic effect of ginger using four major compounds of ginger (gingerol 6,8,10 and 6-shogaol) was found in animal experiments [9,10]. These authors also noted that these substances only moderately inhibited substance P and acetyl-choline-induced contractions, suggesting alternative pathways for ginger's anti-CINV properties [10]. However, despite of these emerging studies, high-quality data supporting the efficiency and safety of ginger on CINV are still lacking. More systemic analysis is required, especially given that 60-90 percent of CINV incidences occur in breast cancer patients [11]. Therefore, the authors of this study will look at the treatment efficacy of orally administrated ginger for treating CINV in breast cancer patients to build more specific and solid clinical evidence that can be used in clinical settings.

Methods

Study Registration

This protocol has been registered on PROSPERO (CRD42022344125) and will be prepared according to the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) [12].

5Inclusion Criteria

Type of Study: All randomized controlled trials (RCTs) of ginger for the management of CINV in breast cancer will be included in English language. Observation studies, cross-over studies, conference abstracts, animal studies, and letters will be excluded.

Types of Participants: We will include participants who are diagnosed with breast cancer and underwent any type of chemotherapy. The individual with other malignancies is excluded. All eligible study participants will be included in this review regardless of their age, gender, race, sex, ethnicity, economic status, or educational background.

Types of Interventions: Interventions to be reviewed are oral intake of ginger. Ginger (Zingiber officinale) alone or ginger used with other herbs are both included. Studies where ginger is used in combination with nonpharmacologic therapy, such as acupuncture, massage, far infra-red, physical therapy, thermotherapy, or magnetic therapy, are excluded. Studies that compare the efficacy of different modifications of ginger formulas will be excluded as this is not the focus of the review.

Types of Comparator(S)/Control:

The following control groups will be considered:

1. Ginger versus placebo
2. Ginger versus conventional medicine (including

pharmaceutics and behavioral therapies)

3. Ginger + conventional medicine versus conventional medicine

Outcomes

Primary Outcome: The primary outcome will be the incidence, severity, and duration of chemotherapy-induced nausea and vomiting as measured by using any tool.

Safety Outcome: All reported side effects and adverse events, associated with ginger supplementation will be included as safety outcomes.

Search Strategy

Electronic Searches: To identify all relevant studies, a comprehensive electronic search of the following database including 3 English medical databases will be performed from their inception to June 2022: PubMed, Embase, and Cochrane Library. (Table 1) shows the searching strategy of the PubMed database, which will then be searched in the corresponding database. Our research is only focused on the aforementioned electronic searches.

Table 1: Search strategy of the PubMed database.

No.	Search Items
1	CINV[Title/Abstract]
2	Chemotherapy induced nausea and Vomiting[Title/Abstract]
3	Vomiting[Title/Abstract]
4	Nausea[Title/Abstract]
5	Vomiting[MeSH Terms]
6	Nausea[MeSH Terms]
7	1 OR 2 OR 3 OR 4 OR 5 OR 6
8	Breast neoplasms[MeSH Terms]
9	Breast cancer[Title/Abstract]
10	Breast neoplasms[Title/Abstract]
11	8 OR 9 OR 10
12	ginger[MeSH Terms]
13	ginger[Title/Abstract]
14	zingiber officinale[Title/Abstract]
15	ShengJiang[Title/Abstract]
16	Zingiberis Rhizoma Recens[Title/Abstract]
17	12 OR 13 OR 14 OR 15 OR 16
18	7 AND 11 AND 17

Data Collection and Analysis

Selection of Studies: The search results will be imported from the original databases into Endnote20.3. Two reviewers (EK and SK) will independently assess the eligibility of the retrieved studies according to the inclusion criteria. For preliminary study selection, only the title and abstract will be reviewed to exclude obviously inappropriate publications. The next step will be to further evaluate the included studies by reading their full-text version. The selection results will be cross-checked by the two reviewers. Any disagreement will be resolved by consensus. The further argument will be arbitrated by a third reviewer (MX). The process of selection will be shown by the PRISMA flowcahrt (Figure 1).

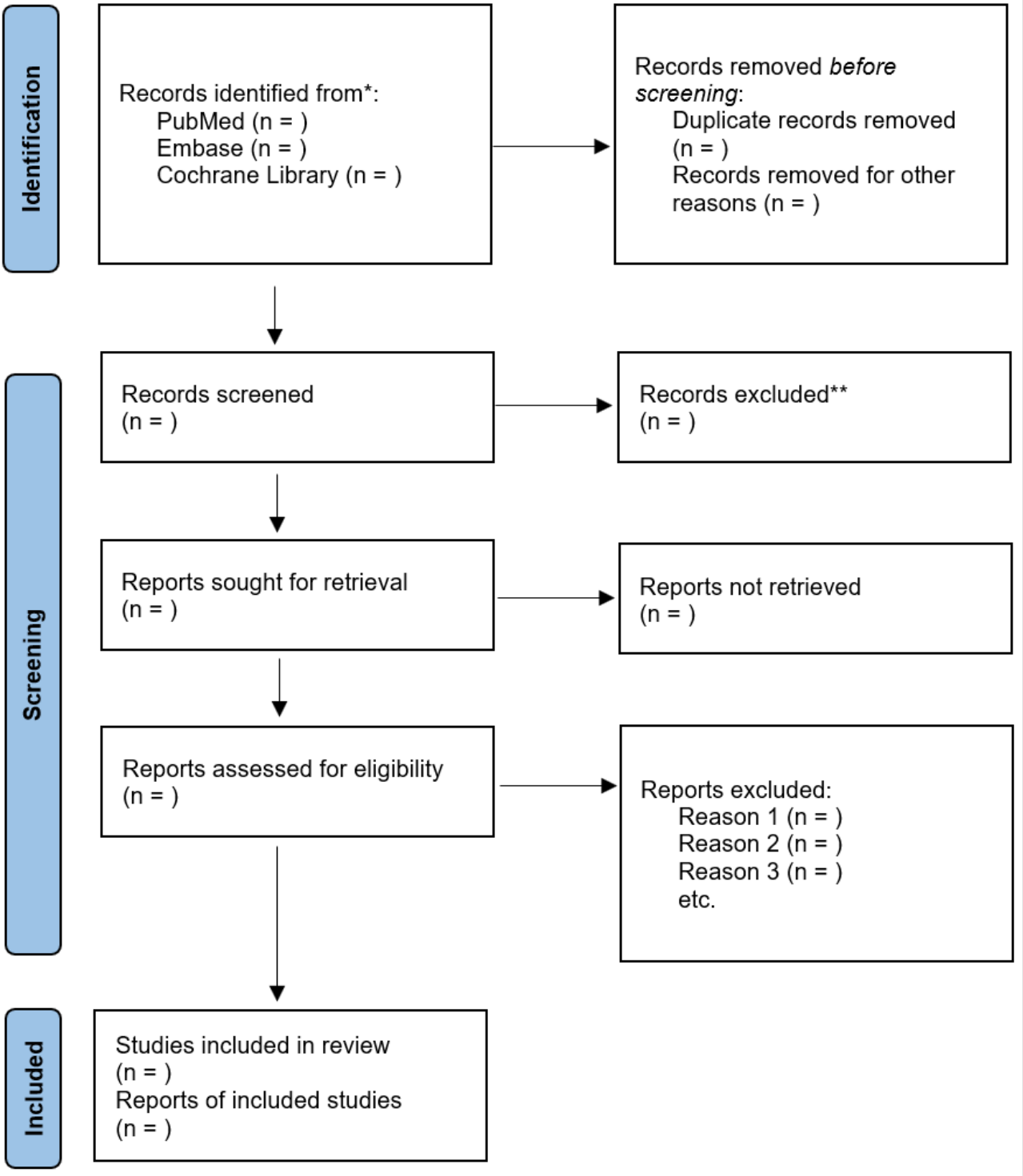

Figure 1: Flow diagram of study selection.

Data Extraction and Management: Two reviewers (SK and EK) will independently double-check the eligibility of the included studies and extract data by entering details into a predefined data acquisition form. This acquisition form will include four main domains: citation information (title, year of publication, first author's name, and country), design (design, participants, trial

methods, duration, intervention/control details), results (outcome measures, adverse events) and related data. Any discrepancy noticed in the process of data cross-checking will be resolved through discussion and the suggestion of another reviewer (MX). Review Manager (RevMan) V.5.4 will be used for data analysis and synthesis.

Assessment of Risk of Bias in Included Studies: The risk of bias for each included trial will be evaluated using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. Two reviewers (SK and EK) will input the relevant details of each trial into the RevMan software and assess the trial for at least six domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias if necessary). For each domain, the trial will be rated as high, unclear, or low risk of bias. A trial that is rated high risk of bias in one or more domains will be rated as 'high risk', while a low risk of bias in all domains will be rated as 'low risk'. If there is low or unclear risk of bias for all key domains, the trial will be rated as 'unclear risk' [13]. The contact person or corresponding author will be contacted if basic information is missing for the risk of bias assessment. The rating results will be cross-checked, and discrepancies resolved through discussion and the arbitration of a third reviewer (MX).

Measures of Treatment Effect: Efficacy data will be synthesized and statistically analyzed in RevMan V.5.4. Dichotomous data will be analyzed by using a risk ratio (RR) with 95% confidence intervals (95% CIs). For continuous outcomes, data will be analyzed by using a mean difference (MD) or a standard mean difference (SMD) with 95% CIs. The MD will be used for the same scale or same assessment instrument; SMD will be used for different assessment tools [14].

Unit of Analysis Issue: Prior to statistical analysis, the units of each outcome from several trials will be changed to the International System of Units [14].

Dealing with Missing Data: By getting in touch with the related author or another relevant author to obtain the missing data. If the authors or contact person fail to respond, we will explain the situation and use the available data to accomplish our analysis.

Assessment of Heterogeneity: To explore statistical heterogeneity in the forest plot, chi-square tests will be run using RevMan, and, in accordance with the Cochrane Handbook, a P value of less than 0.10 will be regarded as significant. To further quantify the effect of statistical heterogeneity on the meta-analysis, the I2 value will be determined. The I2 values are categorized into four groups in the Cochrane Handbook: 0–40% may not be significant; 30–60% denotes moderate heterogeneity; 50–90% denotes significant heterogeneity; and 75–100% denotes considerable heterogeneity.

Assessment of Publication Biases: A funnel plot will be generated to observe the reporting bias when more than 10 trials are included.

Data Synthesis: To undertake data synthesis, clinical data will be entered into the RevMan program. According to patient characteristic, treatment, control, and outcome assessment, efficacy data will be categorized. Depending on the degree of statistical heterogeneity, the data will be synthesized and examined. The fixed-effects model will be applied to the pooled data if the heterogeneity tests reveal minimal or no statistical heterogeneity in these trials. The random-effects model will be utilized for data synthesis if significant heterogeneity is found (if the I2 value is greater than 50%). Meta-analysis won't be carried out if the trials have a lot of heterogeneity.

Subgroup Analysis and Investigation of Heterogeneity: If data are available, a subgroup analysis based on differences in the trial participants' characteristics, ginger treatments, the kind of control arm, and outcome assessment will be carried out. If a subgroup analysis is required after a previous analysis reveals significant heterogeneity, it will be carried out.

Sensitivity Analysis: Sensitivity analysis will be performed to keep track of how reliable the main choice made throughout the review process was. To execute a sensitivity review, we will consider several decision nodes during the systematic review process, including small studies, methodological flaws, and missing data.

Quality of Evidence: Two researchers use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to evaluate the quality of evidence. The quality will be graded as very low, low, moderate, and high [10].

Discussion

Chemotherapy is an important breast cancer treatment. However, CINV affects the majority of breast cancer patients undergoing chemotherapy [2,15]. It is primarily treated with antiemetic drugs, which are not only expensive but also have adverse effects on the digestive and nervous systems, resulting in side effects such as hypotension, diarrhea, headaches, and fatigue [6] Ginger has fewer side effects, is more widely accepted, and is inexpensive [16]. Many clinical trials and systematic review studies have been conducted to assess its effect on CINV [17-20]. However, the effectiveness and safety of ginger in breast cancer patients have not been studied scientifically or systematically in recent years. As a result, the purpose of this study is to provide evidence-based medical evidence for its efficacy and safety. Of course, there will be some limitations to this study. We will only search the English database, which may result in publication biases. Furthermore, the stage of breast cancer and the different types of chemotherapeutics

can increase the risk of heterogeneity. As a result, subgroup analyses will be required to reduce inconsistency.

Author Contributions

1. Conceptualization: Soo-Dam Kim, Eun-Bin Kwag
2. Funding acquisition: Soo-Dam Kim
3. Data curation: Soo-Dam Kim, Eun-Bin Kwag
4. Investigation: Ming Xiao Yang
5. Methodology: Soo-Dam Kim, Eun-Bin Kwag, Ming Xiao Yang
6. Supervision: Hwa-Seung Yoo
7. Writing – Original Draft: Soo-Dam Kim, Eun-Bin Kwag
8. Writing – Review & Editing: Ming Xiao Yang, Hwa-Seung Yoo

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Clinical Registration Number

PROSPERO - (registration no. CRD42022344125).

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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