



The Effectiveness of Ginger in Controlling Chemotherapy-induced Nausea and Vomiting; A Review

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Abstract

Background

Chemotherapy is considered as the main part of systemic cancer treatment. Chemotherapy is associated with adverse effects such as nausea, vomiting, and diarrhea. This study was carried out to evaluate the effectiveness of oral administration of ginger in controlling chemotherapy-induced nausea and vomiting (CINV).

Materials and Methods: This review was conducted with a systematic search of electronic resources in English, including Medline, Scopus, Web of Science, Cochrane Library, and EMBASE with no time limit from inception up to January, 2021 to find research articles related to the effect of ginger on chemotherapy-induced nausea and vomiting using the following keywords: (Nausea OR Vomiting) AND (Ginger OR Herbal OR Matricaria Chamomilla) AND (Chemotherapy OR Iran OR Iranian).

Results: Thirteen studies conducted on the effectiveness of ginger in controlling chemotherapy-induced nausea and vomiting (CINV) were found and reviewed. Inconsistent results were reported about the effects of ginger on chemotherapy-induced nausea and vomiting. Nine studies have shown beneficial effects, while four studies did not report any significant difference with the control group. According to one study, ginger is as effective as metoclopramide in controlling chemotherapy-induced vomiting and nausea.

Conclusion: The present study recommends the use of ginger as a non-pharmacological and uncomplicated method to reduce postoperative nausea and vomiting.

Key Words: Effect, Ginger, Chemotherapy, Nausea, Vomiting.

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1- INTRODUCTION

Cancer, in the literal sense, is a disease of uncontrolled cell division and, if exacerbated, can invade local tissues and lead to systemic metastasis (1). According to the latest statistics reported from the American Cancer Society (ACS), about one in eight women in North America (about 13%) will develop invasive breast cancer at some point during her life (2). Surgery, radiotherapy and chemotherapy are among the primary methods of cancer treatment, with chemotherapy being one of the most effective (1).

The use of this treatment method for cancer is gaining popularity. However, the effective use of this treatment is limited due to its toxic side effects, the most common of which are nausea and vomiting, diarrhea, mucositis, and bone marrow depression (3). Chemotherapy-induced nausea and vomiting (CINV) is among the major concerns of cancer patients, with a prevalence of about 54-96% (4). Degrees of nausea and vomiting vary. The two conditions have a significant impact on patients' quality of life and are associated with serious metabolic problems such as hyponatremia, hypokalemia, and metabolic acidosis. Furthermore, malnutrition caused by nausea and vomiting reduces the patients' resistance to infection and ultimately leads to weight loss (5).

Acute nausea or vomiting may begin in the acute phase (in the first 24 hours after chemotherapy), and have a major impact on the patients' professional and personal lives. Not only is there little improvement from the widespread use of antiemetic chemicals such as serotonin receptor antagonists (5-HTS), and Neurokinin 1 (NK1) receptor antagonists, but it is also associated with unpleasant side effects such as extrapyramidal side effects (EPS), hypotension, headache, and so on. Hence, the tendency to use herbal medicines with fewer side effects has increased (6).

Several clinical trials have been performed in Iran on the effect of the ginger plant on chemotherapy-induced nausea and vomiting (CINV) (7, 8). However, articles in Persian have not been included in any of the published review articles (8-11), and it is necessary to carry out a comprehensive review including all studies in this field on the effect of ginger on chemotherapy-induced nausea. Therefore, this study was carried out with the aim of investigating the effect of ginger in controlling chemotherapy-induced nausea and vomiting.

2- MATERIALS AND METHODS

2-1. Method

A systemic search of English electronic resources such as Medline (via PubMed), Scopus, ISI Web of Science, Cochrane Library, Scopus, EMBASE, and Google Scholar up to January 1, 2021 were carried out by two researchers to conduct this review study. The following keywords were used to find research articles related to ginger on chemotherapy-induced nausea and vomiting:

(Nausea OR Vomiting) AND (Ginger OR Herbal OR Matricaria Chamomilla) AND (Chemotherapy OR Iran OR Iranian). Persian databases such as SID, CIVILICA, and Magiran were also searched with the same keywords in Persian on ginger and chemotherapy-induced nausea and vomiting, as well as references to articles included in the study to find more articles.

2-2. Inclusion criteria

All clinical trial studies that examined the effect of herbal medicines on chemotherapy-induced nausea and vomiting were included in the study.

2-3. Measured consequences

In the included studies, the effects of oral ginger on chemotherapy-induced nausea and vomiting were evaluated.

3- RESULTS

According to the results, 13 studies carried out by January 1, 2021 involved the effectiveness of ginger in controlling chemotherapy-induced nausea and vomiting.

3-1. Dose-dependent effects of ginger on CINV

One study investigated the dose-dependent effects of ginger on chemotherapy-induced vomiting nausea. According to their results, ginger has no alleviating effect on chemotherapy-induced vomiting nausea (12). Julie et al. (2012) carried out a study titled "Ginger reduces acute chemotherapy-induced nausea" on 744 patients. Of these, 576 were divided into four groups: 1) control group, 2) patients who received 0.5 mg ginger, 3) patients who received 1 mg of ginger, and 4) patients who received 1.5 mg of ginger for two cycles of chemotherapy. All patients received anti-nausea 5-HT₃ receptor antagonist once daily. The results showed that all doses of ginger reduced the severity of acute nausea compared to the control group ($p=0.003$). The largest decrease in nausea was seen in those receiving 0.5 ($p=0.017$), and 1 g ($p=0.036$) of ginger (12).

3-2. The effectiveness of ginger on cyclophosphamide-based CINV

Only one study involved a comparison of the effects of ginger with conventional medications for nausea and vomiting. In their study, Sontakke et al. randomly assigned patients to three groups of receiving ginger, metoclopramide, and ondansetron in the first cycle of chemotherapy. Complete control of nausea was achieved for 62% in the ginger group, 58% in the metoclopramide group, and 86% in the ondansetron group ($p < 0.01$). According to the results, ginger is as effective as metoclopramide in controlling vomiting; but of these three medications, ondansetron has the highest anti-nausea

effect. No side effects were observed for ginger (13).

3-3. The effectiveness of ginger on Carboplatin and Paclitaxel-based CINV

In 2019, Uthaipaisanwong et al., in their study titled "the effect of ginger as a standard prophylaxis on carboplatin and paclitaxel-induced nausea and vomiting", divided 47 patients into two groups; one receiving ginger and the other placebo twice daily. The mean score for nausea decreased in the ginger group compared to the control group ($p = 0.03$). There was no significant difference in the acute and delayed phase between the two groups. Also, no serious side effects were observed in the ginger group ($p > 0.05$) (14).

3-4. Effectiveness of ginger on doxorubicin-based CINV

In Ansari et al.'s study, carried out a study on intervention group receiving 500 g of ginger powder twice daily for three days, and the control group receiving placebo. In general, the severity of nausea in the ginger group [$1.4 (\pm 1.041)$] was lower than [$0.71 (+ 0.86)$] in the control group (15).

3-5. The effect of ginger on cisplatin-based CINV

Fahimi et al. carried out a study on the intervention group that received ginger capsules in addition to standard anti-nausea and control group that received placebo in addition to standard anti-nausea, and found no difference in prevalence, severity, and duration of acute and delayed nausea and vomiting in the two groups (16). In the study by Eghdam-Zamiri et al., the intervention group received 500 mg ginger tablets twice daily for ten days after chemotherapy (with cisplatin) and one week before mastectomy. The severity of nausea ($p=0.004$) and of vomiting ($p=0.004$) in the ginger group were significantly lower than the placebo (17).

3-6. The effect of ginger on nausea and vomiting in cancer patients treated with Docetaxel, Epirubicin and Cyclophosphamide

Panahi et al. carried out a study to evaluate the effect of ginger on acute and delayed chemotherapy-induced nausea and vomiting in 100 breast cancer patients receiving standard doses of chemotherapy, including docetaxil, epirubicin, and cyclophosphamide. Patients were divided into two intervention groups: patients receiving 0.5 g ginger every eight hours for four days from the start of chemotherapy in addition to the anti-nausea regimen (granisetron and dexamethasone); and the control group receiving solely the anti-nausea regimen. No significant effect was observed from ginger on the severity of nausea and vomiting in other courses of chemotherapy ($p > 0.05$). The effects of ginger and placebo on nausea and vomiting after chemotherapy were similar (18).

3-7. Ginger in the treatment of CINV

Ebrahimi et al. carried out a study on an intervention group receiving 250 mg of ginger capsules every six hours from three days before chemotherapy to three days after. The same regimen was applied to the control group with placebo. The severity and frequency of nausea in the predicted phase were significantly lower in the ginger group compared to the placebo ($p = 0.008$, $p = 0.0007$, respectively). Also, the severity ($p = 0.001$), and frequency of ($p = 0.001$) of nausea in the acute phase were significantly lower in the ginger group than the placebo. Ginger capsules did not produce any side effects (19).

In a study by Ghanbari et al., patients were divided based on the randomized quadruple block method into two groups; in the first cycle, the two groups received one of the anti-emetic diets (diet A: routine and one gram of ginger or diet B: routine and one gram of placebo). In the second

cycle after 28 days, the groups received another diet (A or B) together with chemotherapy drugs. The score and severity of nausea were assessed using the VAS instrument 5 times in 24 hours, in 1, 2, 3, 4 hours and after the second dose of treatment regimens and at the end of 24 hours after the onset of chemotherapy. According to the results, in all hours of the study, no statistically significant difference was observed in the frequency of nausea and vomiting between the two treatment regimens. However, there was a significant decrease in the severity and score of nausea in the ginger diet compared to placebo, and independent t-test and Mann-Whitney U test also showed a statistically significant difference in the nausea score at the third hour and the end of 24 hours ($p = 0.06$, $p = 0.01$) (20).

In 2016, Sanaati et al. carried out a study titled "the effect of ginger and chamomile on chemotherapy-induced nausea and vomiting in Iranian women with breast cancer" on 65 patients divided into three groups. The ginger group received 500 mg herbal capsules of ginger root powder plus anti-nausea regimen containing dexamethasone, metoclopramide, and aprepitant twice daily for five days before and five days after chemotherapy. The chamomile group received 500 mg capsules of chamomile extract twice a day along with the anti-nausea regimen. The routine group received solely an anti-nausea regimen. The ginger and chamomile groups showed a significantly reduced frequency of vomiting, but there was no significant difference between the two groups ($p = 0.238$). Unlike chamomile, ginger significantly reduced the frequency of nausea ($p < 0.001$) (8).

Zick et al. (2009) carried out a study titled "Phase 2 of Ginger Capsule Intervention in the Treatment of Chemotherapy-induced Nausea and Vomiting" on 162 cancer patients with chemotherapy-induced nausea and vomiting. All patients received

5-HT₃ receptor antagonist and aprepitant. The intervention group received one and two grams of ginger daily for up to three days and the control group received placebo. There was no significant difference in the prevalence of chemotherapy-induced nausea and vomiting between the groups ($p= 0.07$) (21). In their study, Li et al. divided patients into two groups. In the ginger group, 0.5 g capsules of ginger root powder were used twice a day for five days from the start of chemotherapy. According to the results, no significant difference was observed between the two groups in the incidence and severity of nausea and vomiting ($p> 0.05$) (22).

Parsa et al. investigated a group of patients receiving 250 mg ginger capsules four times a day at intervals of six hours (one gram per day for six days) as well as samples of the control group receiving placebo capsules from three days before chemotherapy to three days after. According to the results, a significant difference was observed between the intervention and placebo groups in terms of the severity of nausea resulting from chemotherapy drugs and the duration of the disease, respectively ($p= 0.01$, $p=0.06$). Also, the frequency of vomiting in acute cases was significantly lower in the ginger group (2.7 ± 1.2) compared to placebo (3.7 ± 2.5) ($p = 0.04$). Moreover, the use of ginger capsules wasn't associated with any side effects compared to placebo ($p= 0.06$) (23).

4- DISCUSSION

The present study is one of the first on clinical trial studies to evaluate the effectiveness of ginger on chemotherapy-induced nausea and vomiting. Contradictory findings on the effects of ginger on chemotherapy-induced nausea and vomiting were reported. According to the results, ginger is as effective as metoclopramide in controlling vomiting,

but the anti-nausea effect of ondansetron is higher than that of ginger or metoclopramide (8). Unlike chamomile, ginger significantly reduces the frequency of nausea (8). Ginger is considered as one of the effective herbal medicines for the treatment of nausea and vomiting and does not cause any special side effects, and is used in Germany in the preparation of anti-nausea medicines. The major pharmacological activity of ginger (scientific name: *Zingiber officinale* Rosc. from the family Zingiberaceae) is related to its active ingredients, including gingerol and shogaols. These compounds have antiemetic, antipyretic, antitussive, anti-inflammatory, and anti-cancer effects and are associated with reduced prostaglandins and digestive disorders (7).

The anti-nausea efficacy of ginger in cisplatin-induced nausea in dogs and mice has also been confirmed along with human studies. Acetone and 50% ethanolic extract in doses of 25, 50, 100, and 200 mg by weight, unlike aqueous ginger extract in similar doses, have been effective in reducing nausea induced by cisplatin. Acetone extract has been more effective than ethanolic extract. However, both have been less effective compared to the granisetron 5-HT₃ receptor antagonist granisetron. None of the ginger extract doses have been effective in reducing nausea induced by apomorphine (24).

Sharma et al. investigated the effect of acetone extract and 50% ethanolic ginger at doses of 100, 200, and 500 mg and blue ginger extract at doses of two and four mg based on weight in mice. According to the results, all three models of ginger extract significantly reduced the effect of cisplatin-induced nausea. (25).

4-1. Mechanism of the possible effect of ginger

Ginger products have an anti-emetic effect through several mechanisms. For example, gingerol and shogaols reduce gastric

contractions, but increase gastrointestinal activity. Also, these compounds have an anti-serotonin effect and are effective against free radicals (7). A study was conducted on the possible mechanism of ginger in inhibiting cisplatin-induced vomiting and nausea in mice and minks.

According to the findings of this study, ginger significantly reduced the Hydroxytryptamine and 5-Hydroxytryptamine type 3 receptors, Tryptophan hydroxylase, Substance P Neurokinin-1 receptor Preprotachykinin, dopamine, dopamine D2 receptor, and tyrosine hydroxylase damage, and increases the receptors serotonin transporter, Neutral endopeptidase, and dopamine transporter. Ginger reduces cisplatin-induced nausea by regulating the central and peripheral systems 5-Hydroxytryptamine, Substance P system, and dopamine system (26).

The observed differences between the results of the studies may be related to the differences between the types of extracts (acetone, ethanolic, and fruit juices) used. In one study, all three types of ginger extract had a significant effect on reducing cisplatin-induced nausea. However, acetone extract and fruit juice were reported to be more effective in reducing nausea than 50% ethanolic extract of ginger (25). Another study reported that acetone extract was more effective than ethanolic (24).

4-2. Study Limitations

The heterogeneity of the articles is one of the main drawbacks of this study, which can be related to the different doses of ginger, the small amount of available samples, the non-specificity of the type of cancer, or the hours of receiving ginger. Some of the reviewed studies in this systematic review had a low methodological quality. These shortcomings include the lack of or inadequate reporting of random allocation

sequences, the lack of or inadequate reporting of blinding, and the lack of intention to treat analysis. It is therefore recommended that further research be conducted and reported based on the consortium. Other limitations of this study are the small number of studies and their low sample size, which indicates the need for more studies with a larger sample size in this field.

5- CONCLUSION

Ginger can reduce the frequency of nausea and vomiting as well as the severity of nausea in patients undergoing chemotherapy. It can, therefore, be stated that ginger is a simple and safe herbal medicine for use as a supplement to antiemetic drugs in patients undergoing chemotherapy. Given that various studies have reported contradictory results in relation to the use of ginger, it is recommended to carry out further research with higher doses and longer study duration.

6- AUTHORS' CONTRIBUTIONS

Study conception or design: SS, MS, and SM; Data analyzing and draft manuscript preparation: MS, RR, MS, and SG, Critical revision of the paper: ZD, MS, MB, and SS, Supervision of the research: SS and MS; Final approval of the version to be published: SS, MS, MS, RR, MB, SG, ZD, and SM.

7- CONFLICT OF INTEREST

The authors declare no competing interests.

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