Ginger (Zingiber officinale) in the Management of Chemotherapy-Induced Nausea and Vomiting in Cancer Patients: Integrative Literature Review

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Gengibre (Zingiber officinale) no Manejo de Náuseas e Vômitos Induzidos por Quimioterapia em Pacientes com Câncer: Revisão Integrativa da Literatura

Jengibre (*Zingiber officinale*) en el Tratamiento de las Náuseas y los Vómitos Inducidos por la Quimioterapia en Pacientes con Cáncer: Revisión Integradora de la Literatura

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ABSTRACT

Introduction: Chemotherapy-induced nausea and vomiting (CINV) are important side effects of antineoplastic treatments. Some medicinal plants have been studied in the management of these effects, such as ginger (*Zingiber officinale*). **Objective:** Review the oral use of ginger in the management of CINV in cancer patients. **Method:** Integrative literature review carried out at the MEDLINE database, in September 2022, utilizing the combination of the keywords "*Zingiber officinale*" and "*Cancer*", filters were also applied to include randomized clinical trials published between 2012 and 2022. **Results:** In all, nine studies were analyzed. Ginger has the potential to reduce CINV in cancer patients, reflecting positively on quality-of-life, improved appetite and fatigue. The studies have not found any adverse effect after administering ginger. **Conclusion:** The oral use of ginger proves to be an effective strategy for the management of CINV in cancer patients, in the dosage regimen of 1 g/day of powdered ginger, and can be used as a complementary therapy along with standard antiemetic regimens.

Key words: neoplasms/drug therapy; ginger/adverse effects; plants, medicinal; phytotherapy.

RESUMO

Introdução: Náuseas e vômitos induzidos por quimioterapia (NVIQ) são importantes efeitos colaterais dos tratamentos antineoplásicos. Algumas plantas medicinais vêm sendo estudadas no manejo desses efeitos, como o gengibre (*Zingiber officinale*). **Objetivo:** Realizar uma revisão acerca do uso via oral do gengibre no manejo de NVIQ em pacientes com câncer. **Método:** Revisão integrativa da literatura realizada na base de dados MEDLINE, em setembro de 2022, adotando a combinação das palavras-chave "*Zingiber officinale*" e "*Cancer*". Foram também aplicados filtros na seleção para incluir ensaios clínicos aleatórios publicados entre 2012 e 2022. **Resultados:** Ao todo, foram analisados nove estudos. O gengibre apresenta potencial de reduzir NVIQ em pacientes com câncer, refletindo positivamente na qualidade de vida e na melhora do apetite e da fadiga. Os estudos não observaram efeitos adversos da administração do gengibre. **Conclusão:** O uso por via oral do gengibre demonstra ser uma estratégia segura para o manejo de NVIQ em pacientes com câncer, na dose de 1 g/dia do gengibre em pó, podendo ser utilizado como terapia complementar juntamente com regimes antieméticos padrões.

Palavras-chave: neoplasias/tratamento farmacológico; gengibre/efeitos adversos; plantas medicinais; fitoterapia.

RESUMEN

Introducción: Las náuseas y los vómitos inducidos por la quimioterapia (NVIQ) son efectos secundarios importantes de los tratamientos antineoplásicos. Se han estudiado algunas plantas medicinales en el manejo de estos efectos, como el jengibre (*Zingiber officinale*). **Objetivo:** Realizar una revisión integradora de la literatura sobre el uso oral del jengibre en el manejo de las NVIQ en pacientes oncológicos. **Método:** Revisión integradora de la literatura realizada en la base de datos MEDLINE, en septiembre de 2022, adoptando la combinación de las palabras clave "*Zingiber officinale*" y "*Cancer*". También se aplicaron filtros en la selección para incluir ensayos clínicos aleatorizados publicados entre 2012 y 2022. **Resultados:** En total, se analizaron nueve estudios. El jengibre tiene el potencial de reducir las NVIQ en pacientes con cáncer, lo que se refleja positivamente en la mejora de la calidad de vida, apetito y fatiga. Los estudios no han observado ningún efecto adverso por la administración del jengibre. **Conclusión:** El uso del jengibre por vía oral demuestra ser una estrategia segura para el manejo de NVIQ en pacientes con cáncer, usando una dosis de 1 g/día de jengibre en polvo, y puede usarse como terapia complementaria junto con los regímenes antieméticos estándar.

Palabras clave: neoplasias/tratamiento farmacológico; jengibre/efectos adversos; plantas medicinales; fitoterapia.

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INTRODUCTION

Cancer is a group of more than 100 different types of malignant diseases having in common the uncontrolled growth of potentially invasive cells to tissues and metastasis[1]. The International Agency for Research on Cancer estimated 18.1 million new cases of cancer worldwide in 2020, except non-melanoma skin cancer[2]. For each year of the triennium 2023-2025 it is anticipated that 704 thousand new cases will be diagnosed in Brazil[3].

Antineoplastic treatment as chemotherapy, radiotherapy, immunotherapy and surgery[4] can trigger protein-caloric malnutrition in individuals with cancer. Chemotherapy is the use of powerful chemicals to kill fast-growing cancer or non-cancer cells[5].

Maintenance and/or recovery of nutritional condition plays a key role in the quality-of-life and well-being of the patient in chemotherapy since the treatment related toxicity is associated with the appearance of side effects as nausea and vomits. These symptoms impact food intake, the efficacy of the treatment and survival[6].

Chemotherapy-induced nausea and vomits (CINV) are one of the main side effects of antineoplastic treatments, their control is necessary to allow better treatment with as much less impact as possible on the quality-of-life of patients, mainly those receiving high potentially emetogenic drugs[6].

Some medicinal plants are being studied to manage nausea and vomits as ginger (*Zingiber officinale*) due to its phenol, gingerols and shogaols components which act on the digestive tract, stimulating peristaltic and intestinal tonus[7]. Medicinal plants in clinical practice are being increasingly recognized since the implementation of the National Policy of Integrative and Complementary Practices (PNPIC) which reinforced the utilization of phytotherapy[8].

It is believed that ginger can be an intervention able to improve nausea and vomits of individuals in chemotherapy treatment described in recent studies but there are still discussions about the ideal dosage to be prescribed in conjunction with antiemetic regimens[6,9]. The objective of this article was to perform an integrative review of the literature about the oral administration of ginger (*Zingiber officinale*) to manage CINV in patients with cancer.

METHOD

Integrative review of scientific literature with randomized clinical trials published in the last ten years based in a research question, inclusion and exclusion criteria for literature search, evidences found in the articles, critical analyzes, discussion of the outcomes and presentation of the integrative review[10].

The research question was: "Is ginger able to be utilized to manage CINV in patients with cancer?". The method PICOT was adopted to define the inclusion and exclusion criteria: P (population): patients with cancer; I (intervention): administration of ginger; C (comparison): intervention group and control group (placebo); O (outcome): improvement of nausea and vomits; T (type of study): randomized clinical trials.

The articles were searched at the database MEDLINE in September 2022 with the keywords "*Zingiber officinale*" and "Cancer" through the Boolean operator AND, forming the term: "Z*ingiber officinale* AND Cancer". Filters to select only randomized clinical trials published from 2012 to 2022 were applied as well.

The inclusion criteria were: fully available randomized clinical trials with oral intervention of ginger to manage nausea and vomits in individuals with cancer in chemotherapy. Articles not fully available, those adopting interventions with other complementary and integrative health practices, not published in Portuguese and English and ongoing researches were excluded. The remaining articles were analyzed by two independent reviewers who eventually included only articles which responded to the research question.

The following items were extracted from the articles: authors, year, study design, population, intervention, duration and outcome. During analysis and synthesis, a critical reading was performed to match the objective of the review. The present study collected and summarized randomized clinical trials in a chart with interpretation of the main outcomes.

RESULTS

The initial search resulted in 30 articles. Figure 1 shows the selection and eligibility of the final sample of nine articles. In 2016 and 2017, two and four articles respectively have been published and in 2015, 2018 and 2020, only one article was published each year.

All the articles were published in English: four about breast cancer, two, solid tumors, one, lung cancer, one, gynecological and one with different types of tumor submitted to moderate or highly emetogenic chemotherapy. The study population consisted mostly of women due to the type of neoplasms found as breast cancer and gynecological tumors.

Chart 1[11-19] (authors, year, design, population, type of intervention, duration of the intervention and main outcomes) summarizes the studies included.

In total, the nine articles investigated 1,022 individuals mostly with breast, gynecological cancers and solid tumors. Doses varied from 10 mg to 2,000 mg administered as medicinal plant powder (500 mg to 2,000 mg) or standardized dry extract (10 mg to 500 mg). The

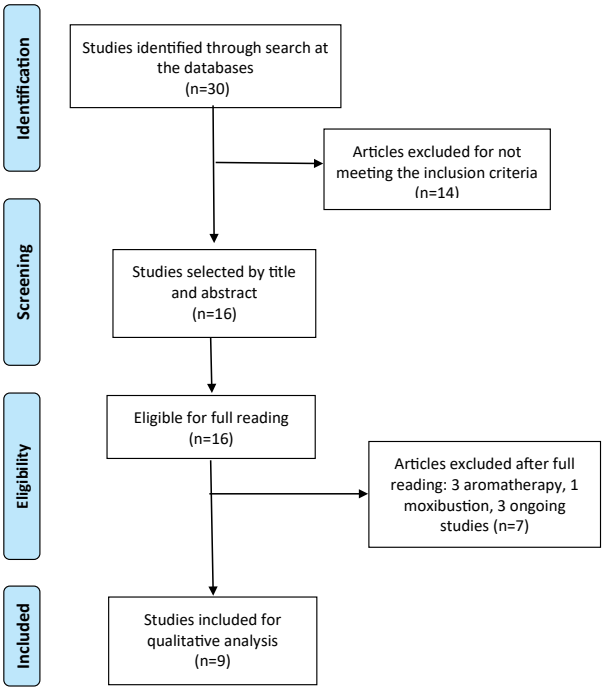

Figure 1. Flowchart of search according to PRISMA

duration of the interventions ranged from one to five days before the chemotherapy up to three to 12 days post chemotherapy, standing out five days of intervention post chemotherapy cycle.

Oral ginger potentially reduces CINV of patients with cancer, but conflicting results are found yet depending on the type of cancer and chemotherapy regimen utilized. However, some studies affirm there were no associated adverse effects.

DISCUSSION

The information collected were not sufficient to identify the ideal posology or presentation able to help the management of CINV. Doses below 500 mg/day of powder or standard dry extract ginger failed to reduce the severity and frequency of CINV in different types of tumor and chemotherapy regimens. Interventions above 500 mg/day and lower than 2 g/day of powder ginger were able to reduce the severity and frequency of CINV. Due to the heterogeneity of the studies, these results are not reliable.

Ginger has been studied in patients with breast cancer during chemotherapy. Four studies with this population were identified in the present review. Thamlikitkul et al.[16] concluded that 500 mg of powder ginger twice a day was safe, but its use was not effective to reduce the severity of nausea in women receiving adriamycin-cyclophosphamide even if a similar dose successfully controlled acute nausea[20].

Apparently, the studies demonstrated that the effect of ginger depends on the type of cancer and chemotherapy regimen. Ansari et al.[17] noticed that patients with breast cancer receiving ginger during the doxorubicin-cyclophosphamide cycle had less vomits but this effect was not significant for other chemotherapy regimens. These findings were also observed by Sanaati et al.[18] with positive results for frequency of vomits when ginger and chamomile were taken but emphasized ginger (1g/day) in reducing the frequency of nausea.

The efficacy of ginger (1g/day) in the first three days of chemotherapy reducing the severity of nausea in women with breast cancer who received anthracycline was demonstrated by Arslan and Ozdemir[19]. However, scientific literature is scarce for gynecological tumors, but Silva et al.[21] are developing a study with Brazilian patients with cervical cancer treated with cisplatin associated with radiotherapy who used ginger for CINV.

The inclusion of powder ginger in the antiemetic therapy of gynecological cancer in carboplatin and paclitaxel chemotherapy regimen was effective to manage acute nausea[11], an outcome also noticed when ginger tea in conjunction with standard antiemetic regimen in women with gynecological cancer receiving cisplatin-based regimen was utilized[22].

An experimental study with animals with cisplatin-induced vomits and nausea by Tian et al.[23] addressed the offer of gingerol at low, medium and high doses and noticed a beneficial and dose-dependent effect on symptoms improvement, but only the isolate active principle was offered, not the phytotherapic.

A randomized double-blinded controlled study with patients with different types of non-solid, solid, lung tumor among others receiving cisplatin in combination with other chemotherapics showed that the use of ginger was unable to reduce nausea and vomits when included (1g/day of powder ginger) in the standard antiemetic treatment[24]. Likewise, the clinical trials of Li et al.[12] and Bossi et al.[13], who utilized root ginger as standard dry extract did not find benefits when taken concomitantly with cisplatin.

The main chemical components of some ginger essential oils are gingerols and shogaols. The most likely mechanism of action for the benefic effects found by Tian et al.[23] is the suppression of the levels of substances P and neurokinin-1 (NK1) receptors in the area postrema of the ileum. In addition, the antiemetic action of 6-, 8- and 10 gingerol and 6-shogaol occurs through the antagonisms in the receptor 5HT3 of the central nervous system which, when activated, reduces nausea and vomits[25,26].

It is acknowledged that nausea and vomits worsen the quality-of-life of patients in chemotherapy, therefore, the

Chart 1. General characteristics of the clinical trials included in the review

Author/year	Study design	Population (n)	Intervention	Duration	Outcome (p)
Uthaipaisanwong et al., 2020[11]	Randomized, double-blinded, crossover, placebo-controlled trial	Female patients with gynecological cancer receiving combined carboplatin-paclitaxel regimen (n=47)	Intervention groups (n=23): 2 g per day of ginger tablets; control group (n=24): cornstarch tablets	1st to 5th day after each cycle of carboplatin-paclitaxel	During acute nausea, the intervention group reduced significantly the mean score compared to control ($p = 0.03$) with no severe effects ($p > 0.05$)
Li et al., 2018[12]	Randomized, double blinded, placebo-controlled clinical trial	Patients with lung cancer receiving cisplatin-based regimens (n=146)	Intervention group (n=73): 500 mg/day ginger DE with 5% gingerols, 2 capsules/day, 250 mg every 12 hours; control group (n=73): 250 mg of cornstarch	5 days from the first day of CT until the last cycle	No significant difference was observed between the two groups in reducing incidence and severity of nausea and vomits ($p > 0.05$)
Bossi et al., 2017[13]	Randomized. double-blinded, placebo-controlled multicenter study	Patients with solid tumors and CT-naive planned to receive cisplatin-based 2 cycles of highly emetogenic CT (n=244)	Intervention group (n=121): 160 mg/day of standard DE in 16 mg of gingerols and 1.12 shogaol; control group (n=123): 110 mg of vegetable oil	42 to 56 days according to different CT schedules	The incidence of delayed, intercycle and anticipatory nausea did not differ between the two arms in the first cycle and second cycle, but there was benefit of ginger over placebo in emesis and nausea score for females ($p = 0.048$) and head-and-neck patients ($p = 0.038$).
Konmun et al., 2017[14]	Randomized, double-blinded, placebo-controlled multicenter study	Men and women, ECOG between 0 and 2, diagnosis of solid tumors surgically resected with proposal of adjuvant, curative, potentially moderate to high emetic CT (n=81)	Intervention group (n=40): 6-gingerol 10 mg tablets with ginger extract, 5 mg (1.4% weight/ginger extract weight), twice a day; control group (n=41): 1 capsule with microcrystalline cellulose and thickening	Intake started 3 days before CT and continued for 12 weeks post CT	Intervention group presented overall complete response rate significantly higher than control (77 vs. 32%; $p < 0.001$). The difference of mean scores of appetite was significant ($p= 0.001$) and more perceptible in time. Quality-of-life was significantly higher (86.21) in intervention group in 64 days than control (72.36) ($p < 0.001$) and patients receiving 6-gingerol reported significantly less grade 3 fatigue (2 vs. 20%; $p = 0.020$)
Marx et al., 2017[15]	Randomized, double-blinded, placebo-controlled trial	Patients with breast, colon cancer, lymphoma and other types of tumors submitted to moderate or highly emetogenic CT (n=246)	Intervention group (n=123): 4 tablets/day, 5-gingerol standardized ginger DS, 15 mg of active ingredient per capsule; control group (n=123): placebo	1 capsule 4 times a day with each meal for 5 days per CT cycle, commencing on the day of CT	CINV quality-of-life ($p = 0.043$), global quality-of-life $p = 0.015$) and reduction of fatigue $p = 0.006$) were better in intervention than control

to be continued

Chart 1. continuation

Author/year	Study design	Population (n)	Intervention	Duration	Outcome (p)
Thamlikitkul et al., 2017[16]	Randomized, crossover, double-blinded placebo-controlled study	Women with breast cancer receiving the first cycle of adriamycin-cyclophosphamide-regimen with vomit or moderate to severe nausea (n=34)	Intervention group (n=19): 500 mg/day ginger powder; control group (n=15): inactive ingredients in ginger capsule	5 days, commencing in the first day of the second cycle of CT and in the third cycle they changed to another regimen (from ginger to placebo or vice-versa)	No significant differences between ginger in terms of incidence and severity of vomits ($p = 0.5$)
Ansari et al., 2016[17]	Randomized, double-blinded placebo-controlled study	Women diagnosed with non-metastatic breast cancer received at least 3 cycles of doxorubicin-based CT (n=119)	Intervention group (n=57): 2 250 mg ginger powder capsules (500 mg every 12 hours or 1 g a day); control group (n=62): cornstarch capsules and same intake prescriptions	2 capsules every 12 hours for 2 days since CT	Ginger reduced vomit severity from 1.4 (±1.04) to 0.71 (±0.86). Vomit reduced in intervention group receiving doxorubicin and cyclophosphamide than those receiving placebo ($p < 0.05$)
Sanaati et al., 2016[18]	Randomized double-blinded clinical trial	Women with breast cancer in CT (n=45)	Intervention group (n=15): 500 mg of ginger powder twice a day and DMA; group chamomile (n=15): 500 mg of extract of *Matricaria chamomilla* and DMA; control group (n=15): standard antiemetic	5 days before and after CT	Ginger and chamomile were ineffectual for nausea intensity ($p = 0.238$), but both were effective for vomit frequency ($p < 0.0001$) and ginger affected the frequency of nausea ($p = 0.006$)
Arslan e Ozdemir, 2015[19]	Randomized placebo-controlled clinical trial	Women with stage II or III breast cancer who received previous surgical treatment and were in adjuvant anthracycline-based CT (n=60)	Intervention group (n=30): 500 mg of powder ginger, twice a day; control group (n=30): no intervention in addition to hospital standard care	30 minutes before CT on day 1 and for 5 days after CT	Severity of nausea on days 2-5 and number of episodes of vomit/nausea reduced on days 2, 3 and 5 in patients of intervention vs control group ($p < 0.05$), in addition, severity of acute and late nausea of intervention group reduced significantly ($p < 0.001$)

Captions: DMA = dexamethasone, metoclopramide and aprepitant; CT = chemotherapy; DE = dry extract; ECOG = performance status scale; CINV = chemotherapy-induced nausea and vomit.

management with medicinal plants is relevant in clinical practice[6]. Bossi et al.[13] found benefit in the activities of daily life of women and individuals with head and neck cancer when ginger is utilized as these are the most vulnerable groups to develop nausea and vomits.

Three articles[13-15] included in the present review investigated the association of the supplementation with ginger and improvement of fatigue: Bossi et al.[13] did not find difference in the questionnaire Brief Fatigue Inventory (BFI) when ginger is utilized, Konmun et al.[14] and Marx et al.[15] revealed improvement of fatigue when ginger dry extract was taken. A clinical trial with 162 patients in chemotherapy treatment and randomized to receive placebo *vs.* 1 g or 2 g of standard 5-gingerol ginger dry extract daily concluded that the group treated with ginger complained less of fatigue[27].

Standard dry extract up to 300mg/day was effective to improve the quality-of-life, appetite and fatigue, most likely due to ginger's anti-inflammatory effects. However, none of the studies which assessed fatigue and appetite reached the same results for inflammatory markers. The studies with powder ginger and standard dry extract suggest further investigations related to the half-life of elimination of these drugs as it is probably impacting the management of CINV. These studies did not describe the most indicated fractioning, however, most of them offered twice a day.

The difficulty to compare the duration of the intervention, heterogeneity of posology and form of presentation of the ginger in the studies investigated is one of the limitations of the review. Different antiemetic regimens, types of cancer, chemotherapy protocols and dissimilar intervention protocols (dose, time and presentation) are the most relevant clinical heterogeneities.

CONCLUSION

Oral ginger – 1g/day of dry ginger – has been proven to be a safe strategy to manage CINV in patients with cancer and can be utilized as complementary therapy together with standard antiemetic regimens. Further randomized clinical trials with homogeneity of doses, schedule of administration and pharmaceutical presentation of ginger are necessary to support the recommendation of its use for different types of cancer and chemotherapy protocols and determine the efficacy of this intervention with meta-analyzes to evaluate separately the prescription of ginger adjusted to each type of cancer.

CONTRIBUTIONS

All the authors contributed substantially to the study design, analysis, interpretation of the data, wording and/or critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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