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The use of bioactive compounds in the modulation of adverse effects of antineoplastic treatment

O uso de compostos bioativos na modulação dos efeitos adversos do tratamento antineoplásico

Erika Klingelfus de Almeida Silva*, Estela Iraci Rabito, Christiane Queiroz

Federal University of Parana, Curitiba, PR, Brazil.
*erikaklingelfus@ufpr.br

ABSTRACT

Adverse effects caused by antineoplastic treatment can negatively affect the nutritional status of cancer patients. Nutritional therapy through the use of bioactive compounds may help to control the adverse effects of anticancer therapy. This study aims to identify which bioactive compounds can act as adjuvants in anticancer treatment. It is an integrative review elaborated in six stages, and it is written in accordance with PRISMA. Sixteen randomized clinical trials, obtained from the period 2003 to 2020, were included. The symptoms observed were mucositis (1 study, intervention with the use of calendula) and nausea and vomiting (15 studies with intervention with ginger). Nine studies had positive outcomes in terms of symptom relief, while in seven no statistically significant differences were found. The effectiveness of the interventions was attributed to the bioactive compounds present in marigold and ginger, especially gingerol and shogaol. There are some limitations that restricted the observations about the results obtained, such as: the lack of standardization of the content of bioactive compounds, limited number of studies and low methodological quality of some clinical trials. Due to the variability of results obtained in the studies, and low quality of evidences, the effectiveness of the use of bioactive compounds in modulating adverse symptoms caused by antineoplastic therapy is still uncertain. However, the results with the utilization of ginger seem promising, and further studies are required.
Keywords: Adverse effects. Antineoplastic treatments. Bioactive compounds.

RESUMO

Os efeitos adversos causados pelo tratamento antineoplásico afetam negativamente o estado nutricional dos pacientes oncológicos. A terapia nutricional por meio do uso de compostos bioativos pode auxiliar no controle dos efeitos adversos da terapia antineoplásica. Este estudo tem como objetivo identificar quais compostos bioativos podem atuar como adjuvantes no tratamento antineoplásico. Trata-se de uma revisão integrativa elaborada em seis etapas e redigida segundo PRISMA. Foram incluídos 16 ensaios clínicos randomizados encontrados no período de 2003 a 2020. Os sintomas encontrados foram mucosite (1 estudo, intervenção com uso de calêndula), enquanto náusea e vômito (15 estudos com intervenção com gengibre). Nove estudos tiveram desfechos positivos quanto ao alívio dos sintomas, enquanto em sete não foram encontradas diferenças estatisticamente significativas. A eficácia das intervenções foi atribuída aos compostos bioativos presentes na calêndula e no gengibre, sobretudo o gingerol e shogaol. Há algumas limitações que restringiram as observações acerca dos resultados obtidos, como: a falta de padronização de teor de compostos bioativos, número limitado de estudos e baixa qualidade metodológica de alguns ensaios clínicos. Devido a variabilidade de resultados encontrados nos estudos e a baixa qualidade das evidências, a eficácia do uso de compostos bioativos na modulação dos sintomas adversos causados pela terapia antineoplásica ainda é incerta. No entanto, os resultados com uso de gengibre parecem promissores, sendo necessário mais estudos.
Palavras-chave: Compostos bioativos. Efeitos adversos. Tratamento antineoplásico.

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INTRODUCTION

In Brazil, the estimated incidence of cancer is 625 thousand new cases for the years 2020 to 2022, corresponding to the second cause of death in the country. It is considered a public health issue. There are three main treatment modalities for the disease: surgery, radiotherapy and chemotherapy. In the majority of cases there is a joint use of these modalities (Instituto Nacional de Câncer, 2020).

The presence of malnutrition in cancer patients, regarding increased metabolic demand and/or as a result of a treatment, is a significant cause of morbidity and mortality, related to the severity of the disease and the adverse effects of treatment. For instance, chemotherapeutic agents are capable of compromising the patient's nutritional status, considering they have potential to cause symptoms such as nausea, vomiting, mucositis, diarrhea, among others that affect energy-protein intake, worsening quality of life (Instituto Nacional de Câncer, 2015; Rodrigues et al., 2019; Veloso, Caldas & Soares, 2019).

Nutritional therapy has an important role as it can improve life quality, survival time and generate more satisfactory clinical responses to treatment, when taking into account the objectives of preventing and treating malnutrition, modulating the organic response and containing adverse effects (Veloso, Caldas & Soares, 2019).

In the midst of the dietary strategies there are the bioactive compounds, which originate from the secondary metabolism of plants and can bring health benefits when in sufficient concentration. Many bioactive compounds have antioxidant, anti-inflammatory, antimicrobial and anticancer effects, so that it is possible to apply them in an alternative nutritional intervention (Horst, Cruz & Lajolo, 2016). These compounds will act as adjuvants to the main treatment, their addition is through food without the need to cancel some standard therapy (radiotherapy, chemotherapy). Among the advantages is the wide range of known bioactive compounds, their presence in various foods and low or no toxicity acting beneficially in the patient's body (Correia et al., 2020).

Therefore, this study seeks to clarify the use of bioactive compounds in cancer patients who are undergoing treatment, and present side effects that compromise their life quality, by understanding the differences in scientific literature for a better technical opinion on the effectiveness and recommendation of phytochemicals.

Moreover, this study aims to understand which bioactive compounds can be used as adjuvants in the treatment of adverse effects caused by anticancer drugs.

MATERIAL AND METHODS

This is an integrative review that makes use of the method described by Mendes, Silvera and Galvão (2008). The guiding question was: Which bioactive compounds can be used as adjuvants in the treatment of adverse effects caused by antineoplastic drugs? The established inclusion criteria were randomized clinical trials, with no defined publication date and in all languages found. Experimental and observational studies, studies with the objective of cancer prevention, as well as studies in which intervention is for the management of symptoms unrelated to nutrition, were excluded. The number of articles found and the databases used along with the descriptors and keywords are shown in table 1. The choice of descriptors bioactive compounds, phytonutrients, phytochemicals, dietary phytochemicals, and other variations of this term for intervention research also included bioactive compounds ginger and calendula, since they had already been included in the pre-review necessary for the construction of the guiding question.

The acronym PICO (Ministério da Saúde, 2012) was adapted from the systematic review model applied according to the research:

P (population): cancer patients.

I (intervention): use of bioactive compounds.

C (control): placebo, other diets without the addition of the bioactive compound.

O (outcome): relief of side effects related to food and nutrition caused by anticancer treatment.

Table 1.
Database and descriptors.

Database	Descriptors/ key-words	Number of articles
BVS	("Bioactive compound" OR "Plant Bioactive Compounds" OR "Phytonutrient" OR "Phytochemical" OR "Dietary Phytochemicals" OR "Ginger" OR "Calendula Oficinallis") AND ("Antineoplastic Agents" OR "Antineoplastic Drugs" OR "Antineoplastics" OR "Cancer Chemotherapy Agents" OR "Anticancer Agents") AND ("Drug-Related Side Effects and Adverse Reactions" OR "Adverse Reactions" OR "Adverse Drug Reaction" OR "Adverse effects" OR "Side effects")	0
PubMed		238
CINAHL		56
FSTA		17
Web of Science		12
Scopus		446
Manual inclusion		3

Source: The authors (2021).

EndNote reference manager was used® Web to export the material, in addition to exclude duplicate articles.

The risk of bias assessment was carried out according to the guidelines of the Cochrane manual (Higgins et al., 2019) and through the REVMAN Software (The Cochrane Collaboration, 2020). The extracted data were classified according to their relative importance for symptom management (Schünemann, 2013).

RESULTS AND DISCUSSION

The search resulted in 772 articles, the diagram with the process of screening, selection and eligibility of articles is represented in figure 1, and it was arranged by PRISMA method (Moher, 2009).

Sixteen studies were selected, all of them prospective and randomized, and thirteen double-blind in the period from 2003 to 2020. Regarding the symptoms evaluated, fifteen analyzed nausea and vomiting, considered the most prevalent symptoms, and one assessed mucositis.

The chemotherapy treatment was used exclusively among the study participants, it was used exclusively as the main treatment in articles, and in one, it combined with radiotherapy. types of cancer were diagnosed, seven of the studies included participants with different types of cancer, one specified in solid tumor without distinction of location, four participants with breast cancer, two studies with gynecological cancer, one study with lung cancer, one study with bone cancer and one study with head and neck cancer. Clinical trials had participants of different age groups ranging from 15.83 to 58.8 years of age. The number of study participants ranged from 32 to 744. Concerning the characteristics of the interventions, it was observed that both in the intervention group and in the placebo group, the administration was oral in all studies, and the intervention period ranged from 3 days to 56 days.

Intervention with ginger capsules was present in fifteen studies, in which the dosage ranged from 10 mg to 2 g, and the frequency used in most studies (n=9) was two times a day. A study made use of mouthwash with a formulation based on calendula at a dosage of 5 ml every 12 hours. The placebo group formulation was always composed of inactive ingredients in combination with the standard multi-dosage antiemetic drug regimen. In all studies, the capsules of the placebo group were

identical to the intervention capsules, with nothing but the content modified. The primary outcomes of the studies refer to symptom relief, and the assessment tool used to analyse the outcomes showed variations. In twelve studies, assessment tools already validated by some associations were used, while four studies chose to record the outcomes through the patient's diary or through the monitoring of the nursing team.

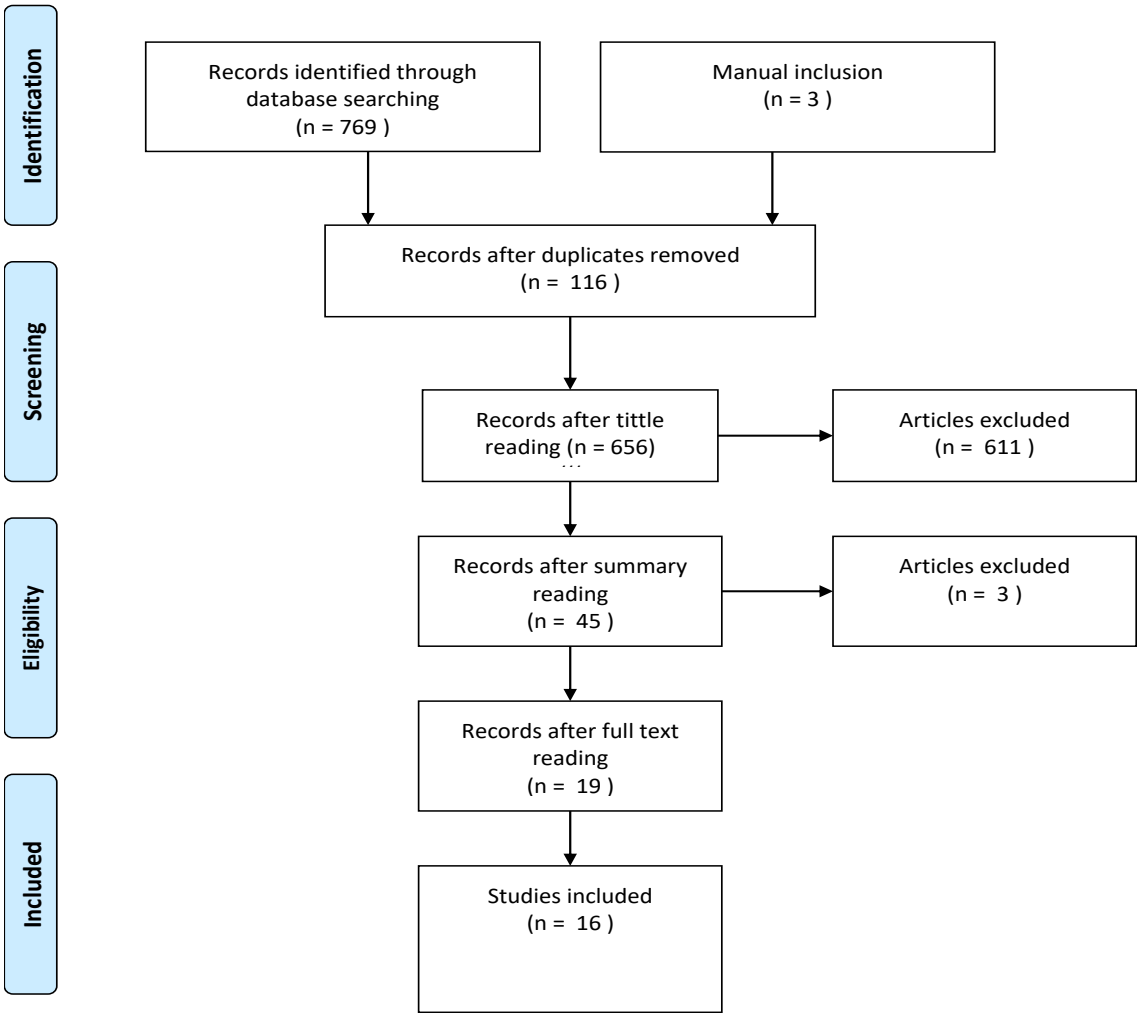

Figure 1. Article selection diagram.
Source: Prisma (2009). Adapted by the authors.

Nine studies showed a statistically significant difference in favor of the intervention group, indicating improvement in the evaluated symptom, while in seven intervention studies did not demonstrate relevant efficacy. The secondary outcomes of the studies carry the prevalence or not of side effects, both in the intervention group and in the placebo group. Six articles report adverse effects in the intervention group, diarrhea, constipation and heartburn were some of the most prevalent symptoms in the studies. In the comparator group, five studies reported adverse effects in participants who were receiving placebo, such as diarrhea, constipation, heartburn, among others.

More information about the studies is specified in Table 1.

Table 1.
Study information.

Author/Year	No intervention	Intervention formulation	Dose	No placebo	Placebo formulation	Dose	Time course	Frequency	Symptom relief	Intervention side effects	Buyer side effects
Uthaipaisanwong, Oranratanaphan & Musigavong (2020)	23	500 mg powdered ginger capsules	2 g	24	500 mg corn starch capsules	2 g	5 days	4 times a day	Significant reduction in nausea (P = 0.03)	Diarrhea (n=13), heartburn (n=4), constipation (n=7)	Diarrhea (n=17), heartburn (n=6), constipation (n=2)
Li et al. (2018)	73	250 mg powdered ginger capsules	0.5 and 1.0 g	73	250 mg cornstarch capsules	0.5 and 1.0 g	5 days	2 times a day	There were no significant differences	Not reported.	Not reported.
Bossi et al. (2017)	121	40 mg capsules of ginger extract	1 g	123	110 mg soft gelatin gel capsules containing vegetable oil	440 mg	46 to 56 days	2 times a day	There were no significant differences	Not reported.	Not reported.
Marx et al. (2017)	24	300 mg capsules of ginger extract	1.2 g	27	Inert filling capsules	1.2 g	7 days	4 times a day	There were no significant differences	Constipation (n=2), reflux (n=4)	Not reported.
Konmun et al. (2017)	42	Ginger extract capsules with 5 mg of 6-gingerol	10 mg	46	Capsules with diluents/binder and thixotropic thickening	10 mg	12 weeks	2 times a day	Reduction of nausea and vomiting (P < 0.001)	Not reported.	Not reported.
Thamlikitkul et al. (2017)	19	500 mg ginger capsules	1 g	15	Inactive Ginger Capsule Ingredients	Uninformed	5 days	2 times a day	There were no significant differences	Not reported.	Not reported.
Ansari et al. (2016)	57	250 mg capsules of ginger powder	1g	62	Starch 250 mg capsules	1g	3 days	2 times a day	Reduction in the severity of vomiting (P<0.05)	Not reported.	Not reported.
Arslan and Ozdemir. (2015)	30	500 mg powdered ginger capsules	500 mg	30	No intervention.	Uninformed	3 days	2 times a day	Reduction in severity of nausea and vomiting episodes (P < 0.05)	Not reported.	Not reported.
Babae et al. (2013)	20	20 g of marigold extract per 1000 ml (2%)	5 ml	20	Carboxymethylcellulose, glycerin, methylparaben, profilparaben, 95% ethanol and distilled water	5 ml	6 weeks	2 times a day	Reduction of mucositis at week 2 (P = 0.019), 3 (P < 0.0001) and 6 (P = 0.031)	Not reported.	Not reported.
Pnahi et al. (2012)	37	Ginger Root Powder 500mg Capsules	1.5 g	41	Standard antiemetic regimen (granisetron and dexamethasone)	Uninformed	4 days	3 times a day	Reduction of nausea 6 to 24 hours (P=0.04)	Heartburn, headache and vertigo	Not reported.

Ryan et al. (2012)	427	250mg Capsules of Ginger Root Extract	0.5g, 1.0g, 1.5g	149	Extra virgin olive oil capsules with excipients	0.5g, 1.0g, 1.5g	6 days	2 times a day	Reduction of nausea (P<0.02)	Gastrointestinal symptoms, heartburn, bruising, flushing and skin rash (n=9)	Not specified (n=15)
Pillai et al. (2010)	31	167 mg or 400 mg capsules	1g and 2g	0	167mg capsules or 400mg starch powder	1g and 2g	3 days	3 times a day	Reduction in nausea (P=0.003) and moderate to severe vomiting (P=0.002)	Not reported.	Not reported.
Zick et al. (2009)	105	250 mg capsules of dry ginger root extract standardized to 15 mg (5%) total gingerols	1g and 2g	57	Lactose Powder Capsules in Red Animal Gelatin Capsules	250 mg	3 days	2 times a day	There were no significant differences	Laboratory abnormalities (n=9), fatigue (n=1), miscellaneous (n=4)	Laboratory abnormalities (n=8), fatigue (n=5), miscellaneous (n=8)
Levine et al. (2008)	19	250 mg capsules of ginger powder, 17 g of whey protein	500 mg	9	No intervention.	Uninformed	3 days	2 times a day	Reduction of nausea in the high protein group (P<0.01)	Not reported.	Not reported.
Manusirivithaya et al. (2004)	22	250mg Capsules of Ginger Root Extract	1g	21	250 mg cornstarch capsules	1 g	5 days	4 times a day	There were no significant differences	Diarrhea (n=6), constipation (n=3), restlessness (n=2), headache (n=1), dizziness (n=6), heartburn (n=3), palpitation (n=1), others (n=8)	Diarrhea (n=2), constipation (n=6), restlessness (n=8), headache (n=3), dizziness (n=5), heartburn (n=3), palpitation (n=1), others (n=14)
Sontakke, Thawani & Nai (2003)	50	500 mg powdered ginger capsules	2g	50	Lactulose and metaclopramide or ondansetron	30 mg of metoclopramide and 8 mg of ondansetron	21 days	2 times a day	No significant difference for ginger	Not reported.	Oral ulcer (n=3) diarrhea (n=2)

Source: The authors (2021).

Notes: Compiled from key data from studies.

The risk of bias analysis is represented in Figure 2, in which a high prevalence of high risk of bias is observed, especially in the criteria: blinding in the outcome assessment, incomplete outcome data and other biases, which may represent low reliability in the results of these studies. Methodological quality of a study is associated with a lower risk of bias, which confers greater reliability on the results.

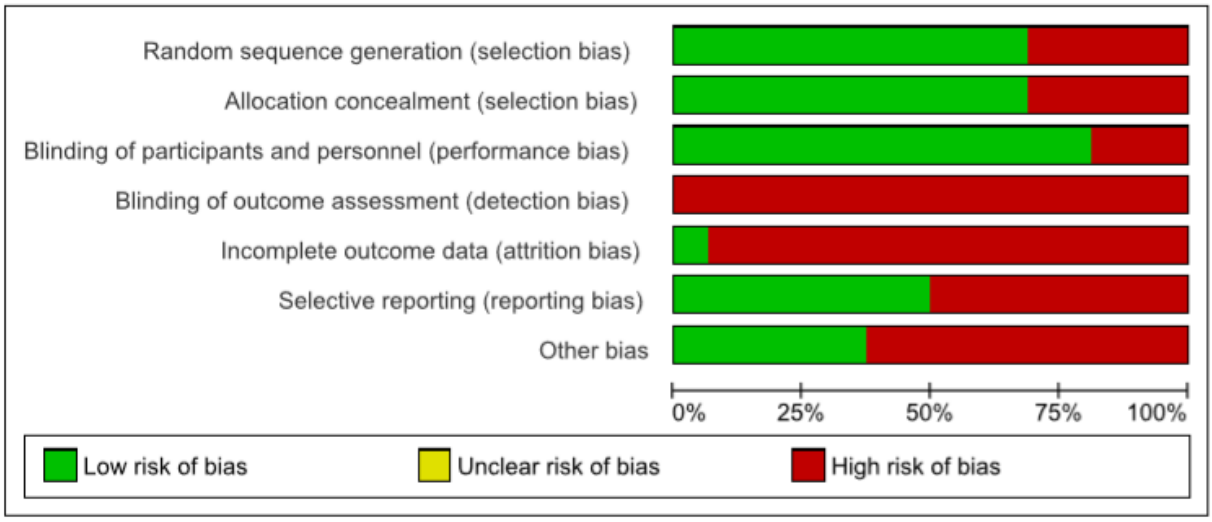

*Figure 2***.** Bias analysis chart of studies (Software Review Manager, 2020).
Source: Review Manager (2020), adapted by the authors.

The analyzed studies reported diversified results regarding the effectiveness of the use of bioactive compounds, for example gingerol, shogaol, zingerone and others, in modulating adverse effects caused by anticancer treatments.

Among the works that analyzed the effectiveness of ginger for the relief of symptoms such as nausea and vomiting, the intervention was favorable in eight studies, and in seven there was no difference between intervention and control groups.

Nausea and vomiting are the most frequent side effects during treatment that impact patient's well-being, varying according to the chemotherapy protocol. They are produced as a consequence of chemotherapy medication causing systemic cytotoxicity, mainly in the mucous membranes of the gastrointestinal system, increasing the concentration of serotonin, that through central and peripheral neural processes, activates the chemoreceptor trigger zone in the brain through 5-HT3 and NK-1 receptors, triggering nausea and vomiting (Saxena et al., 2016).

The interventions by Konmum et al. (2017) using extract with 5 mg of 6-gingerol, Pillai et al. (2010), and Arslan and Ozdemir (2015) using powdered ginger capsules, were included in the studies that had a positive effect on the improvement of nausea and vomiting. Four studies managed to alleviate the symptom of nausea, they are by Ryan et al. (2012) making use of ginger extract containing 8.5 mg of gingerol, zingerone and shogaol, and Uthaipaisanwong, Oranratanaphan & Musigavong (2020), Levine et al. (2008) and Panahi et al. (2012) with powdered ginger capsules. Ansari et al. (2016) obtained attenuation in the severity of vomiting through intervention with 250 mg capsules of powdered ginger.

The studies by Ryan et al. (2012) and Konmun et al. (2017), who used ginger extract with gingerol standardization at lower doses, obtained better results for nausea or vomiting control when compared to the studies by Manusirivithaya et al. (2004), Bossi et al. (2009), Zick et al. (2009) and Marx et al. (2017) who also used ginger extract, but with higher doses of gingerol.

There is the hypothesis raised by Ryan et al. (2012) that higher doses can saturate receptors and therefore, be ineffective. It was also attributed to ginger that its effectiveness is due to its anti-

inflammatory and antispasmodic activities, and indicates that a previous treatment helps in the intestinal preparation of 5HT3 receptors in the anti-nausea response.

Gingerol is the main bioactive compound present in ginger (Zingiber officinale), the antiemetic effect is attributed by its mechanisms of action. It is important to point out that ginger contains several phytochemicals in its composition, in addition to gingerol. These compounds have different chemical structures, for example sesquiterpenes, monoterpenes and the class of non-volatile pungent (Haniadka et al., 2012). Although the mechanism of action of gingerol in combating nausea and emesis is not yet exact, there is an investigation that these compounds, especially gingerol and shogaol, act as an antagonist to the 5-hydroxytryptamine (5-HT3) and neurokinin-1 (NK1) through the 5-HT3 receptor ion channel, leading to antiemetic effects due to interruption of stimulation of the vomiting center in the brain (Haniadka et al., 2012; Saxena et al., 2012; Saxena et al., 2016). Antiemesis drugs also act as 5-HT3 and NK-1 antagonists, so that the use of ginger associated with these drugs can bring benefits to the patient (Saxena et al., 2016).

One of the drugs used as antiemetics is aprepitant, which Zick et al. (2009) linked it to a possible interaction with ginger, raising the hypothesis that ginger may interfere with drug absorption and reduce anti-nausea effects. Arslan and Ozdemir (2015) mentioned that ginger has a similar effect to the drugs used in the antiemetic protocol, and there is the hypothesis of Ryan et al. (2012) saturation of 5HT3 receptors, which may occur by competitive inhibition between the drug and the secondary metabolites of ginger by the receptor site. That is, there is an assumption that bioactive compounds have an antiemetic function similar to that of drugs, however the drug and the metabolite would compete for the same receptor site, which could cause competitive inhibition or even saturation of this receptor.

It was noted that more recent studies showed positive results in greater numbers when compared to studies that did not obtain a statistical difference, this could interfere since the most current research protocols are already more adequate.

A large number of biases were observed in the selected studies, circumstances that can impact the reliability of the results, as well as the quality of the evidence (Boutron et al., 2020).

For Babae et al. (2013) who observed relief from the severity of mucositis in patients undergoing radiotherapy, the calendula solution was able to reduce the severity of mucosal lesions, but was not able to completely prevent it. This author linked his results to the anti-inflammatory, antibacterial and antioxidant properties of the Calendula officinal plant.

Calendula is a plant considered a source of phytochemicals, by reason of the presence of terpenoids, flavonoids, phenolic acids, carotenoids, etc. The use of Calendula officinalis extract in the treatment of adverse effects caused by chemoradiation therapy in cancer patients is being studied, but the mechanism of action has not yet been clarified. (Cruceriu, Balacescu & Rakosy, 2018). Studies indicate that the presence of bioactive compounds namely calendulin, calendin, calendic acid, lutein, glycosides, triterpenes, saponins and flavonoids (Heitor, 2013), is responsible for the chemical properties with antimicrobial, anti-inflammatory, bactericidal, antitumor, diuretic, analgesic and wound healing antiseptic (Heitor, 2013; Cruceriu, Balacescu & Rakosy, 2018).

Studies revealed cytotoxic capacity in marigold extracts against cancerous strains, highlighting the extract with ethyl acetate in healing capacity, evidencing a possible benefit in lesions caused by mucositis (Cruceriu, Balacescu & Rakosy, 2018).

Mucositis is an inflammation of the oral mucosa as a result of incident radiation in radiotherapy treatment, radiation causes various cellular damage. Studies have evaluated if those flavonoids and polyphenols exert a radioprotective function on normal cells, in addition to the radiosensitizing effects that various phytochemical can exert, acting as adjuvants to radiotherapy and increasing its effectiveness. Therefore, calendula has the potential to be used in the management of cancer, especially in radiotherapy-induced side effects (Nambiar, Rajamani & Singh, 2011; Cruceriu, Balacescu & Rakosy, 2018).

There are some points that limited the observations and conclusions about the use of bioactive compounds in clinical applicability, for instance the lack of standardization of the content of bioactive

compounds presented in food, especially in studies that used powdered ginger capsules, so it was not possible to say which dosage of gingerol or shogaol is required to take effect. As for calendula, the limited number of studies found is also a difficulty in evaluating its effectiveness in the treatment of mucositis, more clinical trials are required to obtain an outcome. The inclusion of the keywords calendula and ginger together with the keywords for the definition of bioactive compounds may have favored the finding of a greater number of studies with these compounds for this review. However, this tendency was minimized by the use of five keywords that describe bioactive compounds in a generic way through the search. Another difficulty is related to the chemotherapy protocol and the interaction between drug and bioactive compound, sometimes not allowing a clear observation of the effects.

For further studies, it is suggested to specify the content of bioactive compounds, administration schedules and with fewer systematic errors, so that there is a consensus on the efficacy and recommendation of application in clinical practice.

CONCLUSION

The study indicates that bioactive compounds present in ginger and calendula are promising as adjuvants to anticancer treatments in modulating adverse effects.

Considering the variability of results found in the studies, it was not possible to form a decisive opinion on the use of ginger and its compounds as a resource for the modulation of symptoms, such as nausea and vomiting caused by antineoplastic therapy. Regarding the use of calendula, it is also not possible to state that its use is relevant, considering the limited number of clinical trials found.

Future studies are required to clarify the role of bioactive compounds as adjuvants in cancer treatment.

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