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Effect of Chamomile on the Complications of Cancer: A Systematic Review

Maryam Maleki, Doctoral Candidate[1], Abbas Mardani, Doctoral Candidate[2], Mahdi Manoochehri, MSc student[2], Mansoureh Ashghali Farahani, PhD[2], Mojtaba Vaismoradi, PhD[3,4], and Manela Glarcher, PhD[5]

Abstract

Background and objectives: Despite significant advances in the diagnosis and treatment of cancer, many people across the world still suffer from this chronic disease and its complications. Chamomile as an herbal medicine has gained an increasing attention for relieving cancer complications. This study aimed to integrate and synthesize current international evidence regarding the effect of chamomile on cancer complications. **Methods:** A systematic review was undertaken. Five online databases including Web of Science, PubMed [including MEDLINE], Cochrane Library, Scopus, and Embase were searched and articles published from inception to January 2023 were retrieved. All clinical trials and similar interventional studies on human subjects examining the effects of chamomile on cancer complications were included in the review and research synthesis. Relevant data were extracted from eligible studies after quality appraisals using proper methodological tools. The review results were presented narratively given that meta-analysis was impossible. **Results:** A total of 2240 studies were retrieved during the search process, but 18 articles were selected. The total sample size was 1099 patients with cancer of which 622 participants were female. Fifteen studies used an RCT design. Various forms of chamomile were used such as mouthwash, topical material, tea, capsule, syrup and aromatherapy massage. Chamomile effectively reduced oral mucositis, skin complications, depression, and vomiting and also improved appetite and quality of life among cancer patients. **Conclusion:** The use of chamomile as a non-pharmacologic and safe method can be helpful for mitigating cancer complications in patients with cancer. Therefore, it can be incorporated into routine care along with other therapeutic measures to reduce patients' suffering related to cancer.

Systematic review registration number (PROSPERO): CRD42022307887

Keywords

chamomile, cancer, complication, non-pharmacologic methods, systematic review

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Introduction

Cancer is a major cause of death worldwide.[1] It is also considered the second leading cause of death in the United States. According to statistics 1 898 160 new cancer cases and 608 570 cancer deaths occurred in 2021 only in the USA.[2]

Despite significant advances in cancer diagnosis and treatment, many people around the world still suffer from cancer and its complications, that impose high costs on individuals, their families, and the healthcare system.[3] Physical and psychological complications of cancer are observed in the different stages of cancer.[4] Antineoplastic chemotherapy and radiation therapy are the most widely used interventions

[1]Pediatric and Neonatal Intensive Care Nursing Education Department, School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran
[2]Nursing and Midwifery Care Research Center, School of Nursing and Midwifery, Iran University of Medical Sciences, Tehran, Iran
[3]Faculty of Nursing and Health Sciences, Nord University, 8049 Bodø, Norway
[4]Faculty of Science and Health, Charles Sturt University, Orange, NSW 2800, Australia
[5]Institute of Nursing Science and Practice, Paracelsus Medical University, Strubergasse 21, 5020 Salzburg, Austria

Corresponding Author:
Abbas Mardani, Nursing and Midwifery Care Research Center, School of Nursing and Midwifery, Iran University of Medical Sciences, Tehran 1449614535, Iran.
Email: mardani.a@iums.ac.ir

for the treatment of cancer.[5] Although these treatments aim at improving the quality of life of cancer patients, they are associated with many side effects leading to acute symptoms such as mucositis, dermatitis, stomatitis, nausea, vomiting, xerostomia, and skin scaling.[6,7] It has been estimated that about 40% of patients are treated with standard chemotherapy develop mucositis.[8] Nausea and vomiting due to chemotherapy are among the most severe side effects of the treatment and of the major concerns of patients with cancer, with a prevalence of 54% to 96%.[9] In addition, dermatitis due to radiotherapy is a common complication of radiation therapy in patients with cancer, which occurs in 95% of cases, causing pain, itching, burning and discomfort, and reduces their quality of life.[10,11] Furthermore, cancer has a wide impact on patients' mental health and the prevalence of anxiety and depression is high among people with cancer.[6]

Medicinal plants have long been used for the treatment of different types of cancer complications and due to the side effects of chemical medications, the tendency toward their use has increased gradually.[12] According to the World Health Organization (WHO), almost 65% of the world's inhabitants trust traditional medicine for their primary healthcare.[13] One of the basic and low-risk measures for relieving suffering and pain in patients is the use of herbal medicine.[14]

Chamomile as an herbal medicine has increasingly gained the attention of healthcare providers over the past decade. Two different plant species with similar effects are known as chamomile including German chamomile (*Matricaria recutita*) and Roman chamomile (*Chamaemelum nobile*).[1,15] Both contain similar ingredients, including sesquiterpenes, sesquiterpene lactones, flavonoids and volatile oils.[15,16]

Chamomile usually is used orally and topically and it is a well-known medicinal plant from the Asteraceae family.[17] Chamomile essential oil has over 120 chemical constituents, permitting multiple therapeutic effects.[18] Nowadays, it is widely distributed all around the world, and also it has been used traditionally in several countries to cure a number of diseases, including gastrointestinal disorders,[19,20] liver disorders,[21] neuropsychiatric problems,[22] common cold and respiratory problems.[16] In addition, this plant is widely used against pain and infection[23] and to cure skin and mouth diseases.[24] Moreover, chamomile exhibited antiparasitic, insecticidal,[25] antidiabetic,[21] anticancer,[26] anti-depressant, anti-anxiety,[27,28] and anti-inflammatory activities.[24]

The effectiveness of various herbal medicines including chamomile on cancer complications such as oral mucositis has been shown.[29-32] However, no systematic review has been conducted to specifically examine the effect of chamomile on different complications experienced by patients with cancer. Therefore, this systematic review aimed to integrate and synthesize relevant scientific evidence about the effectiveness of chamomile on cancer complications.

Material and Methods

Protocol and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement has been applied as guidance to develop and report this systematic review (Supplemental File 1). The review protocol has been registered on the PROSPERO website with the registration number CRD42022307887 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022307887.

The PICOS (Population, Intervention, Comparison, Outcomes, Study design) for the current review was as follows:

P: patients with all types of cancer;
I: administration of chamomile in any form;
C: all kinds of comparison or control;
O: all adverse effects of cancer and its treatments;
S: All kinds of interventional designs.

Search Process

The authors specified suitable keywords via conducting a primary search on Google Scholar and applied their knowledge in complementary and alternative medicine. Five databases including Web of Science, PubMed [including MEDLINE], Cochrane Library, Embase, and Scopus were used for search to retrieve articles published in the English language from inception to January 2023. The search was performed using the following search strategies: ((chamomile OR chamomiles OR chamomilla OR recutita OR camomile OR chamaemelum OR anthemis OR matricaria OR matricarias OR "chamaemelum nobile") AND (cancer OR carcin* OR oncology OR tumor OR neoplas* OR "integrative oncology")). Also, a complementary search was performed on the Google Scholar to ensure of the full identification of relevant studies. Moreover, grey literature search and back tracking of the reference lists of finally included articles and previous systematic reviews enhanced the search coverage.

Selection of Studies

Inclusion criteria. This systematic review included clinical trials and similar interventional studies on human subjects in English language that described the use of chamomile in patients with cancer for the purpose of prevention or treatment of complications experienced by cancer patients.

Exclusion criteria. The following studies were excluded from the review: studies with the use of a combination of chamomile and other herbs that failed to determine the isolated effect of each substance; studies with ambiguous or an unknown number of patients; preclinical studies; review

articles; books; conference proceedings; non-research articles such as commentaries and editorials.

Screening

Two authors (AM and MM) independently performed the search and screening of the titles according to the predetermined inclusion and exclusion criteria all retrieved articles. Next, they assessed the abstracts of selected studies. They shared the search results via EndNote software and held frequent discussions to determine which articles fulfilled the inclusion criteria to be included in the review. Following the first screening, they read the full text of articles twice and assessed them based on the inclusion criteria for inclusion in the review and research synthesis. Disagreements were settled through discussions and where required, by seeking the opinion of the third review author.

Risk of Bias Assessment

Two authors (MM and AM) assessed independently the risk of bias in eligible studies. The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)[33] and the Cochrane Collaboration's tool for judging the risk of bias for randomized controlled trials (RCTs)[34] were used to evaluate the risk of bias in nonrandomized studies and RCTs, respectively. Appraisal of RCT studies was conducted in terms of random sequence generation, blinding of participants and personnel, allocation concealment, incomplete outcome data, blinding of outcome assessment, and selective reporting. The risk of bias for these domains were classified as low, high, or unclear. Furthermore, 7 domains in non-randomized studies were used including confounding and bias in the selection of participants, in the classification of interventions, due to deviation from intended interventions, due to missing data, in the selection of the reported result, and in the measurement of outcomes. These domains were categorized in terms of risk of bias as low, moderate, serious, critical, and no information. Disagreements about the quality appraisals' results were resolved through discussions between the review authors until consensus was achieved.

Data Collection Process and Synthesis of Results

The authors developed a table for data extraction consisting of the general characteristics of the study including author, year, country, research design, participants' characteristics, intervention, outcome measurement, and result. Since the interventions of included studies varied in terms of duration, the dosage of chamomile, and data collection tools, meta-analysis could not be performed. Therefore, a narrative review was performed on the studies' results and for research synthesis.

Results

Search Outcome and Selection of Studies

The flow diagram of the study based on the PRISMA has been shown in Figure 1. A total of 2240 articles were retrieved during the search process using the pre-defined keywords. Of these, 28 studies were selected for full-text reading after removing irrelevant and duplicate titles. Finally, 18 articles were entered into the review and research synthesis. The reasons for excluding 10 other studies were presented in Supplemental File 2.

Risk of Bias Assessment

The risk of bias in 15 RCTs has been reported in Supplemental File 3, Figure 1. In terms of random sequence generation, 7 studies were appraised to have a low risk of bias, 7 articles did not present enough information, and 1 study had a high risk of bias. In addition, 7 studies were evaluated to have a low risk of bias and also 8 studies were unclear in the view of allocation concealment. Furthermore, most studies were at low risk of bias regarding the blinding of participants and personnel, and blinding of outcome assessment. Moreover, 13 studies were judged to have a low risk of bias, and 2 studies were at high risk of bias in terms of bias in the blinding of incomplete outcome data. Finally, 11 studies were evaluated to have a low risk of bias, and 4 studies were unclear in terms of bias in the selective outcome reporting.

The risk of bias evaluation of 3 non-randomized studies has been presented in supplemental File 2, Figure 2. All studies had a low risk in terms of bias due to confounding and missing data. In terms of the selection of participants, 1 article was evaluated to have a low risk of bias, 1 article did not present enough information, and 1 study had a moderate risk of bias. In addition, 2 studies were rated as having a low risk with regard to bias in the deviations from intended interventions, measurement of the outcome, and bias in the selection of the reported result, and 1 study did not provide sufficient information. Moreover, 2 studies were judged to have a low risk of bias and also 1 study had a moderate risk of bias in the view of classification of interventions.

General Characteristics of the Selected Studies

A summary of selected articles (n = 18) has been presented in Table 1. All studies were published in English from 1991 to 2022. Seven studies were from Brazil,[35-41] 6 from Iran,[42-47] 2 from United Kingdom,[48,49] 1 from Egypt,[50] 1 from Finland,[51] and 1 from United States,[52] Regarding methodology, 15 studies were RCTs[35-37,39,41,43-52] 3 were non-RCT.[38,40,42]

The total sample size was 1099 patients with cancer of which 622 patients were female (56.6%). Five studies were

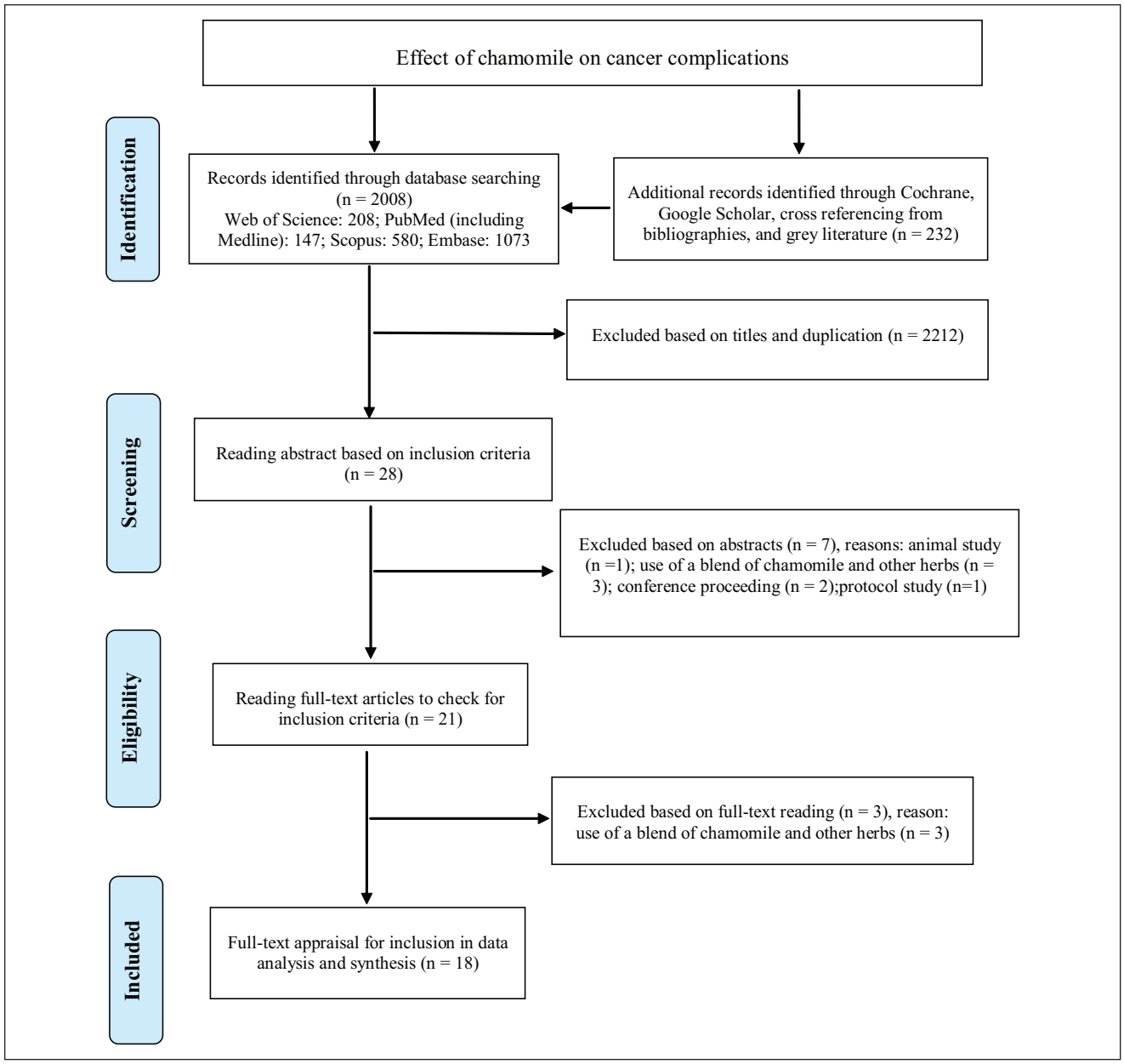

Figure 1. The preferred reporting items for systematic reviews and meta-analyses (PRISMA).

conducted on patients with head and neck cancer,[37,38,40,42,50] 4 on patients with leukemia,[35,41,43,45] 4 on patients with multiple types of cancer,[44,47-49] 1 on patients with gastric and colorectal cancer,[36] 3 on patients with breast cancer,[39,46,51], 1 on patients with an unspecified cancer type.[52]

Intervention and Safety

Chamomile mouthwash was used in 5 studies.[35,42,45,47,52] In addition, other forms of chamomile were used in the studies, including ice chips,[36] topical oral gel,[38,50] topical skin gel,[37] chamomile cream,[51] chamomile tea,[44] capsule,[46] syrup,[43] aromatherapy massage,[48,49] chitosan-coated chamomile microparticles formulation,[39] and compression packs moistened with chamomile infusion.[40,41] Two studies did not specify which type of chamomile they used,[47,52] 14 used German chamomile,[35-46,50,51], 2 used Roman chamomile.[48,49] No side effects from the use of chamomile were reported by the included studies.

The Effect of Chamomile on Cancer Complications

Oral Mucositis. Eight studies investigated the effect of chamomile on oral mucositis. A non-RCT study showed that mouthwash for 1 minute with 3 ml of chamomile mixed

Table 1. General Characteristics of the Selected Studies.

Author, year, country	Research design	Participants: number; age; gender; type of cancer; condition for chamomile use	Intervention	Type of chamomile	Compounds of extractant, chamomile/extract ratio	Outcome measurement	Result
Bahramnezhad et al[42] 2015, Iran	Non-Randomized clinical trial (RCT)	n = 104; mean age = 48.8 y; 28.9% female; head and neck cancer; radiotherapy	Group 1: mouthwash for 1 min with 3 ml of chamomile mixed in half-glass water; Group 2: mouthwash for 1 min with 20 ml of honey mixed with one glass of water; Group 3: mouthwash for water; intervention duration: three times a day for 2 wk	German chamomile	Water; 3 cc/30 cc	Oral mucositis: world health organization's (WHO) standard instrument; Measurement time: on days 1, 7, and 14	Decreasing incidence and severity of oral mucositis
Braga et al[35] 2015, Brazil	RCT	n = 40; mean age = 36.4 y; 37.5% female; leukemia; hematopoietic stem cell transplantation	Group 1: mouthwash with 10 ml of 0.5% liquid extract of chamomile for 1 min; Group 2: mouthwash with 10 ml of 1% liquid extract of chamomile for 1 min; Group 3: mouthwash with 10 ml of 2% liquid extract of chamomile for 1 min; Group 4: standard care; intervention duration: twice a day from the first day of conditioning to when the oral mucosa reestablishes or the granulocyte count exceeds 500 mm^3 for 3 consecutive days in patients without mucositis	German chamomile	Total ashes: 7.45 max 13% m/m; Ashes insoluble in HCL: 0.84 max. 4% m/m; level of essential oils: 0.4 min. 0.4% m/m; level of apigenin-7-glucoside: 1.01 min 0.3% m/m	Oral mucositis: WHO standard instrument; Measurement time: daily during the intervention	1% dosage of chamomile reducing incidence, intensity, and duration of oral mucositis
Daneshfard et al[43] 2020, Iran	RCT	n = 40; mean age = 6.1 y; 37.5% female; acute lymphoblastic leukemia; chemotherapy	Group 1: 2.5 ml of chamomile extract syrup (125 mg) for 30 d; Group 2: 2.5 ml of placebo syrup; intervention duration: daily from the first 24 h of remission chemotherapy to 30 d	German chamomile	Ethanol 70%; 1/5	Quality of life: TNO-AZL Preschool Children Quality of Life questionnaire; white blood cell (WBC) count and absolute neutrophil count (ANC); Measurement time: WBC and ANC repetitively during and after the hospitalization, and quality of life before and after the intervention	Increasing ANC; lack of impact on overall quality of life; significant improvements in appetite
Dos Reis et al[36] 2016, Brazil	RCT	n = 38; mean age = 54.9 y; 47.3% female; gastric and colorectal cancer; chemotherapy	Group 1: 5 min before the chemotherapy infusion, swish chamomile ice chips (made with chamomile infusion at 2.5%) in the oral cavity for at least 30 min; Group 2: ice chips without chamomile in a similar way; intervention duration: 5 consecutive days in the first course of chemotherapy	German chamomile	Water; 2.5% (10 gr/400 cc)	Oral mucositis: WHO standard instrument; Measurement time: on days 8, 15, and 22 after the first chemotherapy infusion	Decreasing incidence and severity of oral mucositis; Decreasing presence of ulceration and mouth pain

(continued)

Table 1. (continued)

Author, year, country	Research design	Participants: number; age; gender; type of cancer; condition for chamomile use	Intervention	Type of chamomile	Compounds of extractant, chamomile/extract ratio	Outcome measurement	Result
Elhadad et al[50] 2022, Egypt	RCT	n = 45; mean age = 48 y; 53.3% female; head and neck cancer; chemotherapy with 5-fluorouracil (5-FU)	Group 1: conventional symptomatic treatment including antifungal agents, topical anesthetics, and anti-inflammatory agents; Group 2: chamomile topical oral gel 3%; Group 3: chamomile topical gel in combination with the conventional symptomatic treatment; intervention duration: three times per day, 1 d before the scheduled cycle of chemotherapy for 3 wk	German chamomile	1. The powdered dried flower heads + ethyl alcohol (70%); 2. Mucoadhesive hydrogels + distilled water + Hydroxypropyl methylcellulose + glycol propyl (for enhancing the consistency of the solution); 3. Hydroxypropyl methylcellulose + distilled water + paraben glycol + chamomile-extract 4. step 2 solution + step 3 solution + NaOH; Finally 3% Matricaria chamomilla with a gel consistency supplied	Oral mucositis: WHO standard instrument; Pain: Numeric Rating Scale; Measurement time: 1, 2, and 3 wk for at least two cycles of chemotherapy	Decreeing severity of oral mucositis and pain in chamomile 3% gel group
Ferreira et al[37] 2020, Brazil	RCT	n = 48; mean age = 57.5 y; 31.2% female; head and neck cancer; radiation therapy	Group 1: chamomile gel 8.35% topically on the skin at the irradiated area; Group 2: urea cream on the skin at the irradiated area; intervention duration: three times per day, during the whole period of the radiation treatment	German chamomile	Not specified; 3.5%	Skin toxicity: Radiation Therapy Oncology Group (RTOG) criteria; time to development of erythema; measurement time: every radiation therapy session from the first to the last session (15 sessions)	Delay the onset of dermatitis grade 2 and lower itching, burning, and hyperpigmentation in chamomile gel group
Fidler et al[52] 1996, United States	RCT	n = 164; mean age = 63.9 y; 43.2% female; unspecified cancer type; chemotherapy with 5-fluorouracil (5-FU)	Group 1: mouthwash with 100 mL of water + 30 drops of a concentrated chamomile; Group 2: placebo in a similar way; intervention duration: 3 times per day for 14 d starting on the first day of 5-FU therapy	Not specified	Water; 30 drops/100 cc	Oral mucositis: attending physicians' assessment and patient-completed form; measurement time: daily for 3 wk after the first day of 5-FU therapy	No significant differences between chamomile and placebo groups
Garbuio et al,[39] 2022, Brazil	RCT	n = 44; mean age = 56.22 y; 100% female; breast cancer; radiotherapy	Group 1: 0.20% chitosan-coated Chamomile microparticles formulation Group 2: standard treatment; intervention duration: once a day after the session from the first day of radiotherapy to the end of the treatment	German chamomile	Not specified	Skin-related QoL: Radiation Therapy Oncology Group (RTOG) scale; pain, itching, and burning symptoms: visual analog scale; measurement time: before the beginning of the treatment, then weekly, and 15 d after the end of the treatment	No significant difference between the groups in the incidence or time to develop any grade of radiodermatitis; reducing the incidence, the time to appearance grade 2 or higher radiodermatitis; reducing pain, and pruritus; a superior skin recovery
Ghamchini et al[44] 2019, Iran	RCT	n = 110; age range = 20-69 y; 44.5% female; multiple types of cancer; chemotherapy	Group 1: using chamomile tea; Group 2 (control): not specified; intervention duration: once a day for 2 wk	German chamomile	Not specified	Anxiety and depression: Beck anxiety inventory; measurement time: not specified	Decreasing depression levels; No effect on anxiety levels

(continued)

Table 1. (continued)

Author, year, country	Research design	Participants: number; age; gender; type of cancer; condition for chamomile use	Intervention	Type of chamomile	Compounds of extractant, chamomile/extract ratio	Outcome measurement	Result
Holmes et al[38] 2013, Brazil	Non-RCT	n = 22; mean range = 65.9 y; 31.8% female; head and neck cancer; radiotherapy	Group 1 and 2: treating with 3% chamomile gel; Group 2: treating with 1% chlorhexidine gluconate gel; intervention duration: for group 1 during radiotherapy and for group 2 and 3 from the beginning of mucositis until the end of treatment, or until 1 wk after relapse of symptoms	German chamomile	Not specified; 3%	Oral mucositis: WHO standard instrument; Measurement time: weekly	No effect of chamomile on oral mucositis prevention; Decreasing the severity of oral mucositis
Maiche et al[51] 1991, Finland	RCT	n = 48; mean range = 56 y; 100% female; breast cancer; radiotherapy	Each participant served as her own control. The areas above and below the scar were randomly treated with chamomile cream or almond ointment; intervention duration: twice daily:30 min before irradiation and before bedtime during the radiotherapy course	German chamomile	Not specified	Dermatitis: researcher-made scale; measurement time: after every radiotherapy session, after 2 wk, and after 3 mo from the discontinuation of radiotherapy	A lesser number and a later appearance of dermatitis for areas treated with chamomile cream, but the difference between the results were not statistically significant
Menêses et al[40] 2022, Brazil	Intervention study without control group	n = 43; mean range = 60.9 y; 90.7% male; head and neck cancer; radiotherapy	Intervention group: treating with a compress with 2.5% chamomile infusion intervention duration: from the first day of occurrence of dry desquamation until the end of radiotherapy; 3 times a day for 20 min to the region	German chamomile	Water; 10gr/400 cc	Dermatitis: Acute Radiation Dermatitis Graduation (GRAL) Scale; dry desquamation regression; occurrence of moist desquamation in the irradiated region (yes or no); measurement time: daily from the initiation of the intervention up to the end of radiotherapy	The mitigation of dry desquamation and the prevention of moist desquamation
Pourdeghatkar et al 2017,[45] Iran	RCT	n = 62; mean range = 9.8 y; 43.5% female; acute lymphoblastic leukemia; chemotherapy	Group 1: receiving 20 cc topical mouthwash for a minute (powdered pill (sucralfate, allopurinol) combined with sodium bicarbonate 7.5% and half-saline serum); Group 2: receiving chamomile mouthwash for a minute; intervention duration: a day before chemotherapy for 14 d afterward	German chamomile	Water; 30 drops/20 cc	Oral mucositis: WHO standard instrument; measurement time: the day before chemotherapy and on days 7 and 14	Decreasing the incidence and severity of oral mucositis in chamomile group

(continued)

Table 1. (continued)

Author, year, country	Research design	Participants: number; age; gender; type of cancer; condition for chamomile use	Intervention	Type of chamomile	Compounds of extractant, chamomile/extract ratio	Outcome measurement	Result
Reis et al[41] 2011, Brasil	Experimental and dose-response curve study	n = 25; age: 20-30 y old; 52% female; acute myeloid leukemia; degree-2 phlebitis	Group 1: treating with the compress moistened with 1.25% chamomile infusion; Group 2: treating with the compress moistened with 2.5% chamomile infusion; Group 3: treating with the compress moistened with 5% chamomile infusion; Group 4: treating with the compress moistened with 10% chamomile infusion; Group 5: control; intervention duration: after removing the peripheral venous device until the entire disappearance of the erythema; 3 times per day for 20 min (changing every 5 min)	German chamomile	Water; group (1): 5 g/400 cc; group (2): 10 g/400 cc group (3): 15 g/400cc group (4): 20 g/400 cc	Degree-2 phlebitis (erythema as the parameter of the inflammatory regression): staging proposed by the Infusion Nursing Society; measurement time: 3 times per day (at 8, 13, and 19 h)	The time of regression of phlebitis was shorter for the group with 2.5% concentration compared to other groups
Sanaati et al[46] 2016, Iran	RCT	n = 45; age range = 20-60 y; 100% female; breast cancer; chemotherapy	Group 1: 500 mg capsules of powdered ginger root and routine antiemetic regimen; Group 2: 500 mg capsules of chamomile and routine antiemetic regimen; Group 3: routine antiemetic regimen; intervention duration: 2 times a day for 5 d before and 5 d after chemotherapy	German chamomile	Not specified	Nausea and vomiting: visual analog scale; measurement time: every night during the study	Decreasing the frequency of vomiting in the chamomile group
Shabanloei et al[47] 2009, Iran	RCT	n = 83; mean range = 33.4 y; 43.3% female; multiple types of cancer; chemotherapy	Group 1: mouthwashes with allopurinol solution; Group 2: mouthwashes with chamomile solution; Group 3: mouthwash with normal saline; intervention duration: four times a day for 16 d after starting chemotherapy	Not specified	Distilled water; 8gr/50 cc	Oral mucositis: WHO standard instrument; intensity of pain: self-reporting tool; measurement time: Not specified	Decreasing severity and pain of oral mucositis in the chamomile group
Wilkinson,[49] 1995, United Kingdom	RCT	n = 51; mean range = 53 y; 94% female; multiple types of cancer; palliative care	Group 1: whole body massage with carrier oil and 1% Roman Chamomile essential oil; Group 2: whole body massage with a carrier oil intervention duration: weekly intervention over 3 consecutive weeks	Roman chamomile	Sweet almond (carrier oil); 1%	Quality of life: Rotterdam Symptom Checklist: before the first massage and 1 wk after the last massage; anxiety: state anxiety inventory: before and after each massage; trait anxiety inventory: 1 wk after the last intervention session	Decreasing anxiety and improving quality of life in the aromatherapy massage group
Wilkinson et al[48] 1999, United Kingdom	RCT	n = 87; mean range = 53.5 y; 90% female; multiple types of cancer; palliative care	Group 1: aromatherapy massages of the whole body; Group 2: the whole-body massage intervention duration: weekly intervention over 3 consecutive weeks	Roman chamomile	Sweet almond (carrier oil); not specified	Quality of life: Rotterdam Symptom Checklist; anxiety: state and trait anxiety inventory; measurement time: before the intervention and the week after the last intervention session	Decreasing anxiety and improving quality of life in the aromatherapy massage group

in half-glass water 3 times a day for 2 weeks decreased the incidence and severity of oral mucositis in patients with head and neck cancer.[42] In addition, the study by Braga et al[35] indicated that mouthwash with 10 ml of 1% liquid extract of chamomile for 1 minute twice a day decreased the incidence, intensity, and duration of oral mucositis in patients with leukemia undergoing hematopoietic stem cell transplantation. Furthermore, it was shown that swishing chamomile ice chips 2.5% in the oral cavity for at least 30 minutes before the chemotherapy infusion decreased the incidence and severity of oral mucositis and presence of ulceration and mouth pain.[36] The study of Elhadad et al[50] also reported that chamomile topical oral gel 3% 3 times per day, 1 day before chemotherapy for 3 weeks decreased the severity of oral mucositis and pain in patients with head and neck cancer. In the study by Pourdeghatkar et al,[45] the incidence and severity of oral mucositis decreased in patients with acute lymphoblastic leukemia receiving 30 drops of chamomile solutions in 20 cc of water for a minute from a day before chemotherapy to 14 days afterward. In addition, it was found that mouthwashes with chamomile solution 4 times a day for 16 days after starting chemotherapy decreased the severity and pain of oral mucositis in patients with cancer.[47] However, one study demonstrated that mouthwash with 100 ml of water + 30 drops of concentrated chamomile 3 times per day for 14 days starting on the first day of 5-FU therapy had no effect on oral mucositis in patients with cancer.[52] Moreover, the results of a clinical trial study showed that 3% chamomile gel during radiotherapy had no effect on oral mucositis prevention but decreased the severity of oral mucositis in patients with head and neck cancer.[38]

In general, evidence from 7 studies[35,36,38,42,45,47,50] showed that chamomile use with the mentioned concentrations and durations can reduce oral mucositis in cancer patients. Only one study[52] reported no effect of chamomile on oral mucositis.

Skin Complications. Five studies examined the effect of chamomile on skin complications. Results of an intervention study showed that treatment with a compression pack containing 2.5% chamomile infusion 3 times a day for 20 minutes on the radiotherapy region mitigated dry desquamation and prevented moist desquamation in patients with head and neck cancer.[40] In addition, applying chamomile gel 8.5% topically on the skin at the irradiated area delayed the onset of dermatitis grade 2 and decreased itching, burning, and hyperpigmentation in patients with head and neck cancer undergoing radiation therapy.[37] A RCT also found the reduced number and delayed appearance of dermatitis in areas treated with chamomile cream during the radiotherapy in patients with breast cancer. However, the results were not statistically significant.[51] Furthermore, Reis et al, in an experimental and dose-response study applied chamomile compression pack on degree-2 phlebitis 3 times per day for 20 minutes in patients with acute myeloid leukemia and reported that the time of regression of phlebitis was shorter for the group receiving 2.5% concentration compared to other groups.[41] Recently, Garbuio et al,[39] in a RCT study on patients with breast cancer reported that the use of 0.20% chitosan-coated Chamomile microparticles formulation once a day after the session of radiotherapy decreased the incidence, time to appearance grade 2 or $>$ 2 radiodermatitis, pain, and pruritus. In addition, a superior skin recovery was observed in the Chamomile group. However, the groups had no significant difference in the time to develop or the incidence of any grade of radiodermatitis.

Overall, the results showed that topical use of chamomile reduced skin complications such as dermatitis and grade 2 phlebitis in cancer patients, though the results of one of the studies were not statistically significant.

Psychological Complications. Three studies investigated the effect of chamomile on anxiety[44,48,49], 1 study on depression.[44] In 2 RCTs, aromatherapy massage of the whole body using chamomile essential oil weekly over 3 consecutive weeks decreased anxiety levels in patients with cancer.[48,49] The findings of another RCT study by Ghamchini et al[44] showed that chamomile tea once a day for 2 weeks had no effect on the anxiety level in patients with cancer, but it decreased depression.

Quality of Life (QoL). In 3 studies, the effect of chamomile on QoL was evaluated. In 2 studies, QoL improved following aromatherapy massage of the whole body using chamomile weekly over 3 consecutive weeks in cancer patients.[48,49] However, 1study showed that 2.5 ml of chamomile extract syrup (125 mg) daily for 30 days had no effect on QoL in patients with acute lymphoblastic leukemia.[43]

Other Complications. In a RCT study by Daneshfard et al[43] the use of 2.5 ml of chamomile extract syrup daily for 30 days increased absolute neutrophil count (ANC) and improved appetite in patients with acute lymphoblastic leukemia undergoing chemotherapy. The findings of 1 study showed that 500 mg capsules of chamomile combined with a routine antiemetic regimen 2 times a day for 5 days before and 5 days after chemotherapy decreased the frequency of vomiting in patients with breast cancer.[46]

Discussion

This systematic review integrated and synthesized current evidence regarding the effect of chamomile in the reduction of cancer complications. It was found that the use of chamomile had a positive effect on the reduction of cancer complications by patients.

The included studies mostly showed that the use of chamomile effectively reduced oral mucositis in cancer patients. Similarly, a systematic review by Santos et al[53] reported that chamomile reduced oral mucositis, as well as other oral complications in patients with head and neck cancer. Another systematic review concluded that topical chamomile was effective in the treatment and prevention of oral mucositis in 4 of the 6 included studies.[54] Moreover, a systematic review was conducted to investigate medicinal plants applying the treatment of mucositis due to oncotherapy. Chamomile had the ability to reduce severity and lesion incidence and improved pain symptomatology.[7] Furthermore, the results of a systematic review by Silva et al demonstrated that different forms of chamomile was effective in the treatment of oral mucositis in cancer patients due to its anti-inflammatory action.[55]

Another problem experienced by cancer patients is anxiety and depression related to the disease and the treatment process.[56] Based on our review results, 1 study demonstrated that the use of aromatherapy massages of the whole body using chamomile essential oil decreased anxiety in patients with cancer. In addition, our review results showed that chamomile tea had no effect on the anxiety level in patients with cancer, but it decreased their depression. Similarly, the result of a systematic review supported that chamomile was one of the most effective herbal medicines for reducing the level of anxiety and depression.[28] Ghiasi et al[57] in a systematic review investigated the effect of aromatherapy on anxiety during the first stage of labor. Two of 16 included studies used chamomile and it was reported that women receiving aromatherapy had lower anxiety levels. The results of a RCT showed that chamomile-lavender aromatherapy decreased the anxiety of nurses compared to the control group.[58] In another study, it was reported that the inhalation of chamomile essential oil reduced patients' anxiety before endoscopy.[59] Furthermore, it was found in a study that inhalation aromatherapy using chamomile essential oils reduced depression and anxiety levels in community-dwelling older adults.[27] Results of another RCT illustrated that those women who drank chamomile tea realized improvements in their symptoms-related postpartum depression.[60] A cross-sectional study demonstrated that chamomile was one of the most widely used complementary alternative medicine therapies that 62.8% of depressed patients used due to its anti-depressant effects.[61] The effect of chamomile on anxiety and depression can be attributed to the stimulation of the limbic system, releasing several neurotransmitters and neurobiological changes. A balance of neurotransmitters is vital to prevent depression and anxiety. After the use of chamomile, essential oils can be absorbed into the blood and then their effects are exerted.[62] Therefore, the anti-depressant and anti-anxiety properties of chamomile are related to the improvement of the basic behavioral conditions in stressful situations.[63]

According to our review findings, aromatherapy massages of the whole-body using chamomile increased QoL in patients with cancer, but studies in this area are limited. However, chamomile extract syrup had no effect on QoL in patients with acute lymphoblastic leukemia. The effect of chamomile on QoL in other patients has been documented. For instance, aromatherapy massage applying a blend of chamomile essential oil and 4 other herbal medicines improved QoL in diabetic patients.[64] A RCT found that foot massage using chamomile increased QoL in hemodialysis patients.[65]

In our review, the findings of one study supported the effect of chamomile on the reduction of the frequency of vomiting in patients with breast cancer. In addition, a RCT study showed that chamomile extract syrup improved appetite in patients with acute lymphoblastic leukemia undergoing chemotherapy. Similarly, a RCT indicated that the use of topical chamomile had a significant impact on the reduction of nausea and vomiting and lack of appetite in pregnant women after cesarean section.[66] These effects can be attributed to anti-neoplastic, chemopreventive, and antioxidant activity of the chamomile.[67]

According to our review findings, chamomile gel on the skin delayed the onset of dermatitis and decreased itching, burning, and hyperpigmentation. This finding can be attributed to chamomile's anti-inflammatory, anti-spasmodic, and antibacterial properties due to compounds such as bisaboloids, levomenol, flavonoids, and chamazulene.[68]

No side effects related to chamomile use in patients with cancer were reported in the included studies in this systematic review. It indicates the safety of chamomile use in this group of patients. However, due to the existence of high heterogeneity in terms of chamomile concentration, dose and duration of use, and compounds of extractant and their various amount and concentration, it is difficult to make clear recommendations about what kind of chamomile extract and with what properties should be applied to create an optimal response. Future studies should focus more on these aspects of chamomile use in cancer patients.

Limitations

To our knowledge, this systematic review is the first one on the effect of chamomile on cancer complications beyond oral mucositis. As the review limitations, we included only studies published in English in this review. Furthermore, a meta-analysis was not possible due to heterogeneity in chamomile doses, data gathering procedures, and administration methods. In addition, there were few studies about the effect of chamomile on some outcomes such as dermatitis, nausea, vomiting, and ANC. Further research is needed to improve evidence-based practice on the use of chamomile in patient care. Therefore, decisions about how to use

chamomile in patients with cancer should be made with caution.

Conclusion

Chamomile can reduce cancer complications including oral mucositis, anxiety and depression level, dermatitis, vomiting, and also can improve patients' QoL. The use of chamomile as a non-pharmacologic and safe method can be helpful for mitigating cancer complications in cancer patients. Therefore, it is suggested to be incorporated into routine care along with other therapeutic measures. Further experimental studies are needed to identify the standardized form, dose, duration, concentration, and route of the administration of chamomile and investigate its effect on cancer complications.

Author contributions

The authors contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript as follows; M.M. (first author) & AM: Conceptualization; A.M., M.M. (third author), M.A.F. & M.V.: Data curation, Formal analysis, Investigation, Methodology; Project administration, Resources, Software; M.M. (first author), A.M., M.M. (third author), M.A.F., M.G.; M.V.: Writing—original draft, Writing-review and Editing. All authors have read and agreed to the published version of the manuscript.

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ORCID iDs

Abbas Mardani https://orcid.org/0000-0003-2861-6037
Mojtaba Vaismoradi https://orcid.org/0000-0002-5157-4886

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