Clinical Nutrition ESPEN 63 (2024) 20–30

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Meta-analysis

Pharmacological strategies and nutritional supplements for managing dysgeusia among chemotherapy patients: A systematic review

Beatrice Mazzoleni [a], Giulia Ferrari [b], Riccardo Caccialanza [c], Daniela Cattani [b], Francesca Savioni [b], Sergio Ferrante [b], Diego Lopane [b], Alessandra Dacomi [b], Chiara Coldani [b], Giuseppina Tomaiuolo [b], Giuliano Anastasi [d], Stefano Mancin [e, *]

[a] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
[b] IRCCS Humanitas Research Hospital, Rozzano Milan, Italy
[c] Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[d] Department of Trauma, AOU G. Martino University Hospital, Messina, Italy
[e] Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Rome, Italy

ARTICLE INFO

Article history:
Received 14 February 2024
Accepted 31 May 2024

Keywords:
Dysgeusia
Chemotherapy
Pharmacological strategies
Management
Nutritional supplement

SUMMARY

Background/objective: Among the side effects of chemotherapy, there is dysgeusia, which is an alteration or damage to the taste perception that negatively impacts the biopsychosocial sphere of the patient. Therefore, it is important to recognize and manage it appropriately. The objective of this study is to identify clinical pharmacological strategies to reduce dysgeusia in chemotherapy patients.

Methods: A systematic literature review was conducted following the PRISMA guidelines between February and May 2023, utilizing PubMed, Embase, Cochrane Library, CINAHL, and the British Nursing Database. Methodological quality and bias risk assessment were performed using the JBI framework, while evidence certainty was evaluated using the Oxford OCEBM methodology.

Results: Out of 1225 consulted records, 12 articles were included. The results underscore the efficacy of diverse pharmacological interventions in mitigating dysgeusia among chemotherapy patients. These include zinc supplementation with a daily dosage ranging between 50 and 220 mg ($p \leq 0.005$), lactoferrin at 250 mg thrice daily ($p < 0.001$), delta-9-tetrahydrocannabinol at 2 mg per day ($p < 0.05$), and cannabidiol at 150 mg per day ($p = 0.04$). All studies analysed showed a low risk of bias. The zinc and Delta-9-Tetrahydrocannabinoid treatment proved particularly promising, compared to the other treatments considered, where sample sizes were smaller and the placebo effect was not always clear.

Conclusion: Among the various pharmacological strategies identified, those that appear most promising concern the integration of zinc and Delta-9-Tetrahydrocannabinoid. Future studies should further explore the treatments identified in this review to expand the evidence base in this relatively underexplored field.

1. Introduction

Cancer, a complex and multifactorial disease, manifests in over 200 identified forms, emerging from aberrant cellular mechanisms leading to uncontrolled proliferation [1]. The increasing incidence of cancer is largely attributed to the ageing population, though this trend has been further compounded by the COVID-19 pandemic, which critically strained healthcare systems worldwide, resulting in delayed diagnoses and interruptions in routine cancer screenings [2]. The therapeutic landscape for cancer is multifaceted, comprising approaches such as radiotherapy, hormonal therapies, immunotherapy, targeted molecular therapies, and surgical interventions. Nevertheless, chemotherapy remains a pivotal strategy in oncological treatment, offering the potential for tumour reduction and improving survival rates [3]. The primary action of chemotherapy involves the use of chemical agents to disrupt the rapid division of cancer cells, a process that can lead to tumour size

* Corresponding author. Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Viale Montpellier, 1, 00128 Rome, Italy.
E-mail address: stefano.mancin.84@students.uniroma2.eu (S. Mancin).

https://doi.org/10.1016/j.clnesp.2024.05.026

reduction [4]. However, the indiscriminate nature of these agents often leads to collateral damage to healthy cells, manifesting a spectrum of adverse effects including alopecia, anaemia, nausea, vomiting, and fatigue. Among these, there is dysgeusia, a commonly overlooked and under-discussed side effect.

Dysgeusia, a disorder characterized by altered taste perception, often results in patients experiencing distorted or unpleasant taste sensations [5]. The phenomenon of dysgeusia is not merely a quantitative alteration in taste intensity (as seen in conditions like hypergeusia or hypogeusia) but rather a qualitative change, often distorting the patient's perception of flavours [6,7]. In the context of chemotherapy, more than 75% of patients report experiencing some form of taste alteration which can manifest as metallic, excessively intense, or otherwise altered flavours [8,9]. This condition not only impacts patients' dietary habits and preferences but also extends to broader health implications, including weight loss, increased fatigue, and potentially social isolation [3]. Despite the high prevalence of dysgeusia and its recognition in the Common Terminology Criteria for Adverse Events (CTCAE) since 2009, it often remains underreported in clinical practice [10]. However, the clinical implications of dysgeusia are substantial, affecting the nutritional status and appetite of patients, increasing the risk of malnutrition, and impacting the quality of life, thus adversely affecting the effectiveness of cancer treatments and overall patient outcomes [11]. Given these considerations, early assessment and intervention for dysgeusia are crucial. Investigating and implementing treatments for dysgeusia is essential to alleviate patient discomfort and improve their overall well-being [12]. However, the management of dysgeusia in clinical settings remains a significant challenge [13], necessitating continued research and development of effective strategies.

1.1. Systematic review objectives

The principal aim of this systematic review was to discern pharmacological strategies and nutritional supplements designed to alleviate dysgeusia in patients undergoing chemotherapy.

2. Methods

2.1. Study design

This systematic review (SR) was conducted, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [14] and following the PRISMA checklist (Supplementary File 1). The protocol of this SR was registered in the International Prospective Register of Systematic Reviews (PROSPERO) of the National Institute of Health Research available at https://www.crd.york.ac.uk/prospero/ with protocol registration number: CRD42023460479.

2.2. Eligibility criteria

In this research we established inclusion and exclusion criteria that align with the review's scope and methodology, ensuring the selection of relevant articles. line with the review's scope and methodology. The development of these criteria was a collaborative effort among the authors, structured following the PICO (Population, Intervention, Comparison, Outcome) framework [15], as recommended by the literature, for this review we use the form PIO, because there isn't a comparison.

Inclusion criteria included articles published in English or Italian from January 2010 to December 2023, focusing on chemotherapy patients with any type of cancer. All primary quantitative studies involving adult patients (age $\geq$18 years) undergoing any chemotherapy treatment and focused on pharmacological interventions such as drugs, dietary supplements and natural substances taken orally were included. No restrictions have been placed regarding the type or duration of chemotherapy treatment or the concomitant administration of artificial nutrition. Exclusion criteria involved studies before 2010, incomplete sources, non-primary studies, duplicate articles, and non-pharmacological interventions. Secondary studies were also excluded.

2.3. Search strategy

For the identification of potentially relevant records, we conducted a comprehensive and systematic literature search on the following databases: PubMed, Embase, Cochrane Library, CINAHL, and British Nursing Database. Additionally, we conducted a search in grey literature. The search for pertinent literature was conducted over three months, from February to May 2023. Our search strategy, based on the PICO model [15], was pivotal in sourcing information. The model focused on 'P' (patients with dysgeusia), 'I' (multidisciplinary interventions), and 'O' (reduction of dysgeusia). The 'C' component (comparison intervention) was not considered for this review. Specific search strings were formulated, employing targeted keywords and Medical Subject Headings (MeSH Terms). Key terms such as "dysgeusia", "chemotherapy", "multidisciplinary interventions", and "management", along with their variations, formed the basis of our query. These terms were interconnected using Boolean operators (AND, OR) to optimize the search. The construction of search strings was adapted to the specificities of each consulted database, ensuring efficient literature retrieval. This selection of keywords was aligned with our predefined eligibility criteria, ensuring a focused search (Supplementary File 2).

2.4. Selection process

The study selection process was structured into two phases: initial screening of titles and abstracts, followed by a full-text screening. To manage and organize this process, all studies identified as potentially relevant were imported into EndNote 20 software (https://endnote.com/) [16]. We utilized automated tools within EndNote and manual examination to eliminate duplicate records. This combined approach ensured thoroughness, accounting for any duplicates the software might have missed due to minor variances. The initial screening phase involved two authors, SM and GF, who independently reviewed all titles and abstracts retrieved from the database searches. This step was crucial in determining the preliminary relevance of the studies. In cases of disagreement or conflict in assessment, a third author, FS, was consulted to achieve a resolution. For studies that passed this initial screening, we proceeded to obtain and review the full-text articles. This evaluation was again independently conducted by the same two authors, SM and GF, using the predefined eligibility criteria. This stage was essential for a comprehensive understanding of the study's relevance and suitability for inclusion in our review. Disagreements were addressed through consensus meetings, with FS providing arbitration when necessary. FS's involvement in arbitration, especially given their non-involvement in initial reviews, added additional rigour to the selection process.

2.5. Data collection process

The data collection process was structured to ensure the accurate extraction of relevant information from the selected studies. To facilitate this, we utilized a specifically designed data-charting template. This template was developed in accordance with the recommendations of the latest edition of the Cochrane Handbook

for Systematic Reviews of Interventions [17]. The data extraction process employed a combination of Microsoft Excel and EndNote software. The use of Microsoft Excel allowed for a clear organization of the collected data, while EndNote facilitated reference management. To enhance the reliability and accuracy of our data collection, two reviewers, SM and GF, independently extracted data from each study. Consistent with the methodology this independent dual-reviewer approach minimized bias and ensured the integrity of the data collection process. In instances of disagreement or differing interpretations of the data, a third researcher, FS, was involved in a conclusive discussion session.

2.6. Data items

The data extracted from the included studies were organized into several key dimensions. This categorization facilitated both comprehensive reporting and a thorough analysis of the findings. The classification included bibliographic details (authors and the year of publication), study design (e.g. randomised controlled trial, longitudinal, cross-sectional, qualitative studies), country, sample characteristics, inclusion and exclusion criteria, study purpose, evaluation tool employed, main findings, limitations, level of evidence, direction of effect and risk of bias. Overall, this approach to data categorization enhanced the clarity and depth of our analysis, adhering to methodological standards.

2.7. Risk of bias and quality assessment

In our study, the evaluation of both the risk of bias and the methodological quality of the included articles was conducted in adherence to the methodological guidelines [18,19]. This assessment was independently undertaken by two reviewers, SM and GF, ensuring an objective appraisal. In instances of disagreement, conflicts were resolved with the involvement of a third author, FS, thus ensuring a consensus-driven evaluation. To assess the quality of the included studies, we employed the latest versions of the Joanna Briggs Institute Critical Appraisal Checklists [20]. This approach aligns with the methodological guidelines and provides a structured and comprehensive framework for evaluation. The appraisal process involved assigning a classification of 'Yes', 'No', 'Unclear', or 'Not Applicable' to each item on the checklist. The final quality scores for each study were derived from the cumulative count of 'Yes' responses. We employed a scoring system based on a previous study [21] to determine the risk of bias in individual studies. According to this approach, studies with scores higher than 70% were classified as high quality, those with scores between 50% and 70% as medium quality, and those with scores less than 50% as low quality. For transparency, detailed tables related to these critical appraisal checklists are provided in Supplementary File 3.

2.8. Effect measures

The synthesis and presentation of results were aligned with the methodological guidelines. This approach involved an extraction and analysis of quantitative elements from the included studies, ensuring a rigorous and consistent representation of findings. In the interest of maintaining the integrity of the original research, we chose not to standardize the presentation of statistical significance across the studies. Instead, we retained the original format in which each study reported its statistical findings, preserving the authenticity of the results.

2.9. Synthesis methods

In this systematic review, while acknowledging the benefits of a meta-analysis, we determined that a pooled quantitative synthesis was not feasible. This decision was grounded in the heterogeneity identified among the included studies, as detailed in the latest edition of the Cochrane Handbook for Systematic Reviews of Interventions [17]. The heterogeneity was primarily due to variations in interventions and differences in the methods used to quantify relationships between variables, resulting in a lack of methodological and statistical uniformity. Consequently, a formal narrative synthesis was conducted, adhering to the Synthesis Without Meta-analysis (SWiM) reporting guidelines [22]. This approach was selected for its ability to provide a transparent and robust synthesis of quantitative data, in line with the PRISMA methodology [16]. To elucidate the interactions between the variables of interest, we employed a "vote counting" method as recommended by the SWiM guidelines [22]. This method is particularly suitable for handling varied effect measures, as highlighted in the Cochrane Handbook for Systematic Reviews of Interventions [17]. Results were classified as "+" for a positive effect (interventions reduced dysgeusia), "−" for a negative effect (interventions increased dysgeusia), and "0" for a neutral or null effect. In cases where studies provided multiple data concerning the effects of the interventions, each was counted individually. The narrative synthesis is detailed in the Results section, featuring a blend of tables and textual descriptions organized into thematic segments corresponding to the study's objectives. For clarity, studies were ordered by reference and grouped based on their outcomes. To visually represent the direction of effects and provide additional study details, a Harvest plot was utilized [23] as suggested by the Cochrane Handbook for Systematic Reviews of Interventions [17]. In the plot, the reference showed the source of information, the height of the bars indicated the sample size, the bar shade illustrated the nature of the association (black for positive, grey for negative, and white for no effect) and labels denote typology of intervention.

Finally, the certainty of the evidence was assessed following the methodology proposed by the Oxford Centre for Evidence-Based Medicine (OCEBM) in 2011 [24]. This system stratifies studies into five levels of evidence based on their design and research quality. The highest-level studies, such as systematic reviews of randomized controlled trials, were attributed to the first level of evidence. Conversely, studies based on expert opinions or not supported by empirical data were classified at the last level. Intermediate studies, such as individual randomized controlled trials of lower quality, cohort studies, and research like case series or case−control studies, were respectively assigned to the second, third, and fourth levels. The evidence level of some studies was downgraded or upgraded based on factors such as methodological quality, result accuracy and data applicability.

3. Results

3.1. Study selection

In our comprehensive search across databases, we initially identified a total of 1225 records: 153 from PubMed, 754 from Embase, 30 from CINAHL, 56 from the Cochrane Library, and 232 from the British Nursing Database. The initial screening phase involved the removal of 113 duplicates, leaving 1112 records for more detailed examination. Subsequent manual screening of these records, based on titles and abstracts, led to the exclusion of 1073 articles that were not relevant to our study. This process narrowed

the field to 39 articles, which were then subject to full-text screening, advancing to the full-text screening phase. An additional check of references and citations within these articles revealed 6 more eligible records (reference lists = 4; citations = 2), bringing the total to 42 full-text articles for the final phase of screening. After a thorough examination of these full texts, we excluded 30 articles for various reasons (not focused on interventions to manage dysgeusia = 10; wrong population = 11; lack of details about interventions = 9). This meticulous screening process ultimately resulted in the inclusion of 12 records in our systematic review. To provide a clear visual representation of our screening process and its outcomes, we have included a PRISMA flow-diagram [16] in Fig. 1. This diagram details the number of records included and excluded at each phase of the screening process, as recommended by the JBI guidelines [18]. This approach not only ensures a comprehensive review of the literature but also enhances the transparency and replicability of our study.

3.2. Study characteristics

The studies included in this systematic review encompassed a diverse array of research designs, including 4 Randomized Controlled Trials (RCTs) [25–28], 5 quasi-experimental studies [29–33], 1 case–control study [34], 1 case report [35] and 1 cohort study [36]. Geographically, the majority of the studies originated from Asia [25,28], particularly Japan [30,34,36]. These studies predominantly explored areas such as zinc supplementation, oral hygiene modalities, and the role of vitamin D in dysgeusia management. In contrast, the American continent, led by research from the United States of America (USA) [26,27,29,31,32], Germany [35] and Danmark [33], investigated a range of interventional strategies. These included natural adjuncts like the "Miracle Fruit". Delving into the specifics, three studies highlighted the therapeutic role of zinc supplementation in managing dysgeusia. Shintani et al. [34] and Fuji et al. [30] from Japan provided insights into this area. The impact of vitamin D on dysgeusia mitigation was explored by Fink [35] from Japan. Additionally, the study by Brisbois et al. [27] delved into how Delta-9-tetrahydrocannabinol (THC) modulate gustatory and olfactory perception in oncology patients. The study by Wilken et al. [29] investigated the "Miracle Fruit" potential in alleviating taste distortions. A detailed summary of the main characteristics of these studies is reported in Table 1, offering a comprehensive overview and synthesis of the varied research contributions to this systematic review, while Fig. 2 reported the Harvest plot,

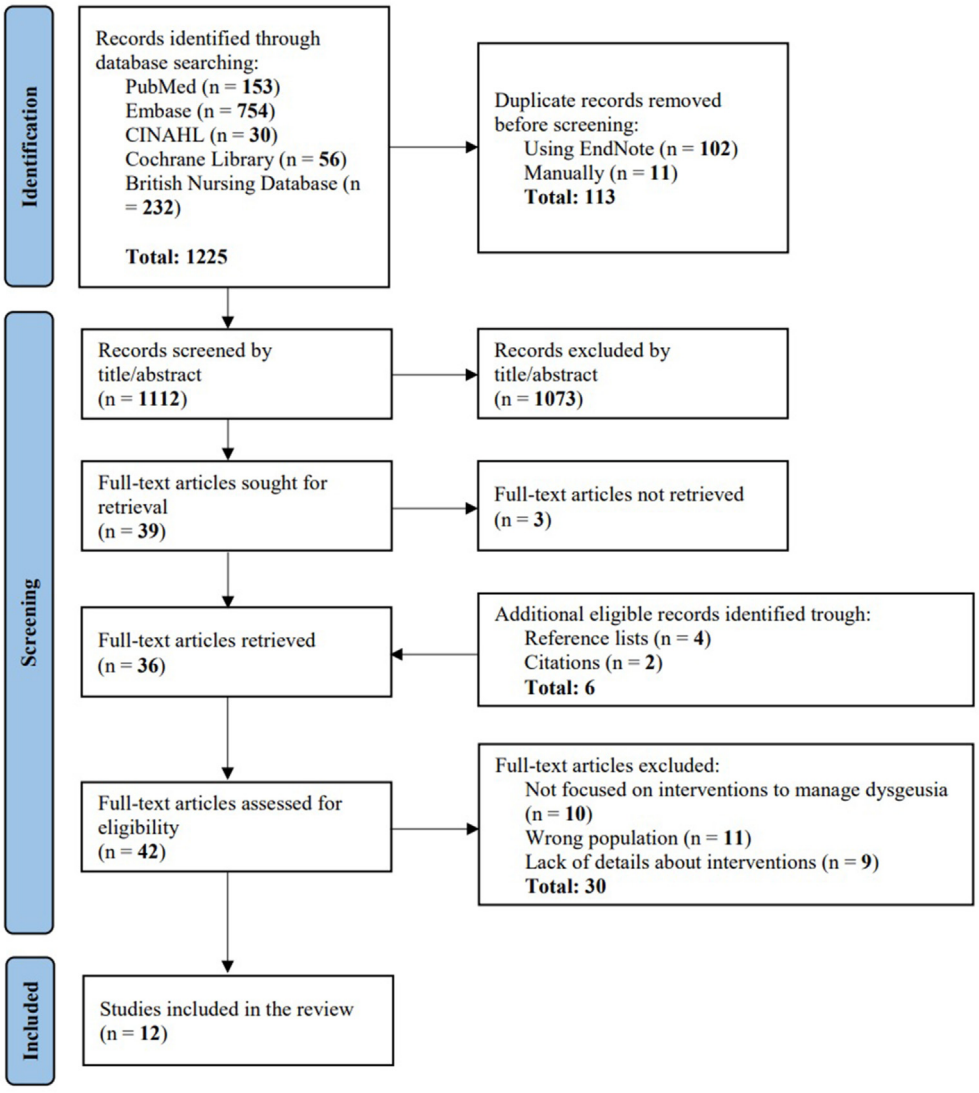

Fig. 1. PRISMA flow-chart.

Table 1
Characteristics of the studies included.

Authors Years	Study Design	Country	Sample (n)/CT − RT Treatment	Eligibility criteria	Intervention	Study Objective	Results	Reported Limitations	OCEBM Level	Effect	Quality/Bias
Dominiak et al., 2023	Quasi-experimental study	Denmark	(n = 32) CT IG = 22 CG = 10	Inclusion: age ≥18 years, cancer, CT-naïve, scheduled to receive 4 cycles of CT. Exclusion: inability to cooperate or understand the study, previous use of cannabis.	**CBD** IG= CBD 150 mg orally CG = placebo Treatment: 8 days for every cycle of CT.	Improve taste alterations	After 3 cycles of CT, CBD-treated patients increased the ability to distinguish between weak and strong sweetness ($p = 0.03$) and saltiness ($p = 0.04$), while controls lost it.	Small sample size	3	+	+++/Low
Shintani et al., 2023	Case control study	Japan	(n = 70) CT IG = 42 CG = 28	Inclusion: taste disorder, zinc deficiency, hypozincaemia-induced dysgeusia, informed consent. Exclusion: NR	**ZAH** IG = ZAH 50 mg/die CG= PPZ 34 mg/die Treatment: 24 weeks.	Explore the efficacy and safety of ZAH administration in patients with hypozincaemia-induced dysgeusia	Compared to baseline, ZAH group showed significant improvement in dysgeusia at 12 and 24 weeks; PPZ group showed significant improvement only at the 24 weeks ($p < 0.05$).	Single center, small sample, differences between groups, confounding factors	2	+	+++/Low
Lesser et al., 2022	Quasi-experimental study	United States	(n = 17) CT	Inclusion: cancer, undergoing CT, normal taste perception prior to CT, at least 1 month of planned CT. Exclusion: leukaemia, HIV, pregnancy, hospitalized for blood transplantation, life expectancy <3 months, gastrointestinal reflux, diabetes, allergic to milk or iron, oral infection.	**LFN** LFN 250 mg Treatment: three times daily for 30 days, followed by 30 days of pause.	Assess change in subjective taste and smell perception	Mean TSQ score improved at 30 days ($p = 0.018$). Mean TSQ score and taste improved at 60 days ($p < 0.0001$; $p = 0.001$).	Small sample size, confounding factors	3	+	++/Moderate
Ito et al., 2022	Cohort study	Japan	(n = 160) CT IG 1 = 52 IG 2 = 57, CG = 51	Inclusion: gastrointestinal cancer, undergoing CT, dysgeusia. Exclusion: previous administration of zinc, history of head and neck RT.	**Zinc** CG (no intervention) IG 1 = ZAH (50 −100 mg/die) IG 2 = PPZ 34.1 mg/die). Treatment: 12 weeks.	Examine the effect of zinc on CT-induced dysgeusia in patients with gastrointestinal cancer	Compared with the non-IG, PPZ group showed significant improvement in subjective total taste acuity ($p = 0.045$); ZAH group showed no statistical differences.	Possible selection bias, no placebo used.	3	+	+++/Low
Khan et al., 2019	RCT	Pakistan	(n = 68) CT/RT IG = 34 CG = 34	Inclusion: age >20 and ≤60 years, oral cancer, receiving concurrent CT-RT for the first time, both genders. Exclusion: history of CT or RT, oral/cranial nerve	**Zinc** IG = zinc sulphate 50 mg CG = placebo Treatment: three daily for almost three months, starting at the	Observe the efficacy of zinc sulphate on taste alterations in oral cancer patients	Zinc sulphate was not found to be beneficial in preventing chemoradiation induced taste alterations.	Brief follow-up, strict exclusion criteria, serum zinc levels not assessed, only oral cancer included.	2	0	++/Moderate

				lesions, glossectomy, nose/ear infections, metabolic/endocrine disorders, concurrent administration of other drugs, no consent/ cooperation.	beginning of CT and RT.					
Fujii et al., 2018	Quasi-experimental study	Japan	(n = 80) CT IG = 40 CG = 40	Inclusion: patients in treatment in outpatient CT clinic, with cancer and dysgeusiaExclusion: NR	**Polaprezinc** IG = polaprezinc 150 mg CG = polaprezinc 150 mg Treatment: IG twice a day during CT; CG twice a day from follow-up.	Examine the effect of oral administration of polaprezinc on dysgeusia	Polaprezinc-treated patients reported: higher ($p = 0.0007$) and shorter ($p = 0.019$) recovery from dysgeusia compared to follow-up group. Polaprezinc was less effective in elderly and pancreatic cancer patients, while more effective in colorectal cancer patients.	Single center retrospective study. Blood zinc concentration not addressed.	3	+	+++/Low
Wang et al., 2018	Quasi-experimental study	United States	(n = 12) CT	Inclusion: cancer, undergoing CT, normal taste perception prior to CT. Exclusion: difficulty in producing abundant saliva, HIV, pregnancy or breastfeeding, allergic to milk or iron, oral infections/lesions.	**LFN** IG = LFN tablets 250 mg Treatment: three times daily for 30 days, followed by 30 days of pause.	Assess taste and smell alteration	Compared to baseline, non-significant change of taste/smell/total scores were observed at 30 days, while all score significantly reduced at 60 days ($p < 0.001$). LFN supplement reduced taste alterations.	NR	3	+	++/Moderate
Najafizade et al., 2013	RCT	Iran	(n = 35) CT/RT IG = 20 CG = 15	Inclusion: head and neck cancers, scheduled for RT, with or without CT.Exclusion: oral lesions, metabolic/ endocrine disorders.	**Zinc** IG = zinc sulphate 50 mg CG = placebo Treatment: three times daily, starting at the beginning of RT and one month after completion.	Preventive effects of zinc sulphate on radiation-induced taste alterations.	All taste thresholds significantly increased in the placebo group ($p = 0.001$), while only salty taste thresholds ($p = 0.046$) increased in the IG at the end of treatment. Zinc supplement can prevent taste alterations.	Small sample size, included only head/ neck cancer, brief follow-up.	2	+	+++/Low
Lyckholm et al., 2012	RCT	United States	(n = 41) CT/RT IG = 20 CG = 21	Inclusion: age ≥18 years, cancer, receiving/ received CT, experience of taste/smell alterations.Exclusion: NR	**Zinc** IG = zinc sulphate 220 mg CG = placebo (lactose monohydrate) Treatment: twice daily for 3 months.	Determine the efficacy of zinc sulphate on taste/smell alterations	No statistically significant difference in smell and taste loss/ distortion between groups.	Non-objective measurement, small sample, confounding factors (i.e. comorbidities)	2	0	+++/Low

(*continued on next page*)

Table 1 (*continued*)

Authors Years	Study Design	Country	Sample (n)/CT − RT Treatment	Eligibility criteria	Intervention	Study Objective	Results	Reported Limitations	OCEBM Level	Effect	Quality/Bias
Wilken et al., 2012	Quasi-experimental study	United States	(n = 8) CT IG = 4 CG = 4	Inclusion: age ≥18 years, cancer, undergoing three or more cycles of CT, experience of taste alterations. Exclusion: NR	**Miraculine** IG = Miracle Fruit™ 6 servings per day + Placebo (dried cranberries) CG= Placebo + Miracle Fruit™ 6 servings per day Treatment: 2 weeks +2 weeks before the meal	Assess for improvement in taste changes	Taking the supplement (6 servings per day) improved taste for all and increased food intake for some participants.	Small sample, no quantitative data	4	+	++/Moderate
Fink, 2011	Case report	Germany	(n = 2) CT	Inclusion: vitamin D deficiency, CT-related problems (i.e. dysgeusia, stomatitis, dermatitis).Exclusion: NR	**Vitamin D** 2000 U vitamin D3/die Treatment: 1st patient 2 weeks and 2nd patient 1 week	Report the effect of vitamin D on CT-related problems	Improvement in dysgeusia during and after CT.	NR	4	+	++/Moderate
Brisbois et al., 2011	RCT	Canada	(n = 21) CT IG = 11 CG = 10	Inclusion: age ≥18 years, advanced cancer of any site (except brain), score ≥2 on Taste and Smell Survey. Exclusion: enteral or parenteral nutrition, allergies to THC, substance abuse, oral mechanical obstructionRT to head/neck, nausea, diseases affecting chemosensory function (i.e. infection of mouth), cardiac diseases, liver impairment, previous use of marijuana.	**THC** IG = THC (2.5 mg, Marinol®) CG = placebo Treatment: once daily (first 3 days) and twice daily (on fourth day) for 18 days.	Improve taste and smell perception, appetite, caloric intake, QoL	THC-treated patients reported: improved ($p = 0.026$) and enhanced ($p < 0.001$) chemosensory perception and food 'tasted better' ($p = 0.04$), increased premeal appetite ($p = 0.05$) and proportion of calories consumed as protein ($p = 0.008$), increased quality of sleep ($p = 0.025$) and relaxation ($p = 0.045$) compared to placebo.	NR	1	+	+++/Low

Legend: THC = Delta-9-Tetrahydrocannabinoid; CT = chemotherapy; RT = radiotherapy; CBD = cannabidiol; NR = Not Reported; IG = Intervention Group; CG = Control Group; QoL = quality of life; ZAH = Zinc acetate hydrate; LFN = Lactoferrin; TSQ = Test and Smell questionnaire. Quality/Bias was assessed according to the JBI guidelines and using the JBI quality appraisal checklist. The level of bias risk was considered: high <50% "yes" scores; moderate = 50%–70% "yes" scores; low >70% "yes" scores according with Pimsen et al. (2022) Level of evidence is in accordance with grading OCEBM (Howick et al., 2011). Direction of effect was assessed according to Cochrane guidelines. Positive effect was denoted by a plus sign (+); Negative effect was denoted by a minus sign (−); Neutral effect was denoted as 0.

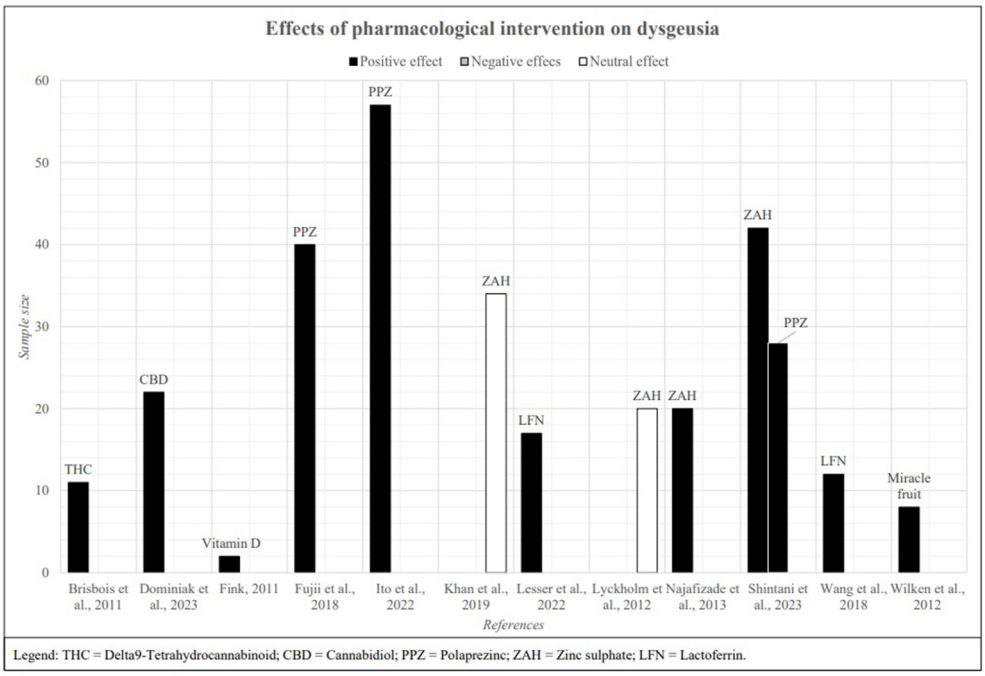

Fig. 2. Effect of Pharmacological Intervention on Dysgeusia.

illustrating the positive, negative, or neutral effects of the various interventions on dysgeusia in chemotherapy patients.

3.3. Risk of bias and certainly evaluation in studies

The methodological quality of the studies included in our systematic review was generally high. Most studies scored above 70%, a threshold considered indicative of excellent quality according to the JBI assessment score [23]. Specifically, all but 4 studies were categorized as high quality, as reported in Table 1 and detailed in Supplementary File 3. Additionally, when evaluated using the Oxford Centre for Evidence-Based Medicine (OCEBM) grading system [24], the distribution of study quality varied. One study was rated at level 1, representing the highest quality and accounting for 10% of the total. Four studies fell into level 2, comprising 40%, while five studies were classified as level 3, making up 30%. Level 4 included two studies, also constituting 20%, and the remaining five studies. This distribution of study quality, as outlined in Table 1, reinforces the validity of the studies for discussion and analysis in our systematic review. The diversity in levels reflects a comprehensive range of evidence, ensuring a robust and well-rounded evaluation of the research topic.

3.4. Pharmacological intervention

Our systematic review encompassed a range of pharmacological interventions, including drugs, taken orally, with a specific focus on managing dysgeusia. The included studies, as summarized in Table 1, explored interventions such as zinc and delta-9-tetraidrocannabinoide.

3.4.1. Zinc

Several studies assessed the efficacy of zinc in managing dysgeusia. One [30] reported significant improvements in post-chemotherapy dysgeusia patients treated with oral polaprezinc supplementation. In this study, a 150 mg oral dose of zinc sulfate showed promising outcomes. After six weeks of treatment, taste alterations notably diminished and at three months none of the patients exhibited signs of dysgeusia. Another [34] found that zinc acetate was effective in treating dysgeusia caused by hypozincaemia. The authors demonstrated that the group of patients treated with “zinc acetate hydrate-ZAH” in 50 mg capsules per day had taste benefits at the twenty-fourth week of administration compared to the control group ($p < 0.005$). However, there were no significant differences in taste perception in the short term. Similarly, an RCT [26] addresses zinc's potential benefits for taste and smell alterations in chemotherapy patients. The intervention group ($n = 20$) was administered 220 mg of zinc per day, while the control group ($n = 21$) received a placebo. They were evaluated one month after administration through a questionnaire. The study found no significant differences between the zinc and placebo groups regarding the improvement of taste and smell alterations, but it revealed a strong correlation between taste and smell changes ($p < 0.0001$). In another study [36] Patients were divided into a non-intervention ($n = 51$) and two intervention groups, with ZAH ($n = 52$, 50–100 mg/die) and “polaprezinc-PPZ” ($n = 57$, 34.1 mg/die). Patients were treated for 12 weeks. Compared with the non-intervention group, the PPZ group showed significant improvement in subjective total taste acuity ($p = 0.045$); the ZAH group showed no statistical differences. In another [25], the two groups received zinc sulphate (150 mg/day total dosage) in three administrations of 50 mg/day or placebo for almost three months, starting at the beginning of chemotherapy and radiotherapy. Zinc sulphate was not found to be beneficial in preventing chemoradiation-induced taste alterations. In the last [28] The two groups received zinc sulphate capsules (50 mg) or placebo three times daily (150 mg/day total dosage), starting at the beginning of radiotherapy and one month after completion. All taste thresholds significantly increased in the placebo group ($p = 0.001$), while only salty taste thresholds ($p = 0.046$) increased in the intervention group at the end of treatment. Zinc supplements can prevent taste alterations.

3.4.2. Delta-9-tetraidrocannabinoide

A study [27] conducted a pilot study to evaluate the effectiveness of THC (delta-9-tetraidrocannabinoidol) in improving taste and smell perception, appetite, caloric intake, and quality of life in cancer patients with chemosensory alterations. Results indicated that the group of patients (n = 24) who received THC (2.5 mg, Marinol) experienced an improvement in chemosensory taste and smell perception ($p < 0.001$) and appetite ($p = 0.008$) compared to the control group (n = 22). Additionally, the THC-treated group reported improvements in other aspects such as sleep quality ($p = 0.025$) and relaxation ($p = 0.045$). However, there were no significant differences in quality of life and caloric intake between the two groups. In another study [33] the intervention group received 150 mg of cannabidiol (CBD) orally for 8 days for every cycle of chemotherapy. After 3 cycles of chemotherapy, CBD-treated patients increased the ability to distinguish between weak and strong sweetness ($p = 0.03$) and saltiness ($p = 0.04$), while controls lost it.

3.5. Nutritional supplements

A series of interventions involving oral dietary supplements were analysed, with a specific focus on the management of dysgeusia. The included studies, as summarized in Table 1, explored various interventions such as vitamin D, lactoferrin, and Miracle Fruit.

3.5.1. Vitamin D and lactoferrin

In a case series [35] there is a discussion on the relationship between vitamin D deficiency and dysgeusia. The author discussed two real-life experiences where vitamin D supplementation led to improvements in patients' taste disturbances. The first patient, suffering from breast cancer and undergoing chemotherapy, exhibited a vitamin D level lower than the standard range, experiencing dysgeusia. The doctors prescribed a daily supplement of 2000 U of vitamin D3 (cholecalciferol). After one month, the taste disturbance had almost completely regressed. The second case involved a patient with pancreatic cancer experiencing dysgeusia and having a vitamin D deficiency. As the previous case, doctors prescribed the same vitamin D3 supplement. Dysgeusia resulted improved after just one week of supplementation. In a quasi-speriemental study [32] patients received lactoferrin (LFN) 250 mg three times daily for 30 days, followed by 30 days of pause. The mean TSQ (Test and Smell questionnaire) score improved at 30 days ($p = 0.018$). Mean TSQ score and taste improved at 60 days ($p < 0.0001$; $p = 0.001$). It shows that there is a change in subjective taste and smell perception after LFN supplementation. In another study [31] patients received LFN tablets (250 mg) three times daily for 30 days, followed by 30 days of pause. Compared to baseline, non-significant changes in taste/smell/total scores were observed at 30 days, while all scores significantly reduced at 60 days ($p < 0.001$). LFN supplement reduced taste alterations.

3.5.2. Miracle Fruit

Another study [29], investigated the efficacy of *Synsepalum dulcificum*, known as the “Miracle Fruit,” in alleviating dysgeusia. Notably, this treatment had never been cited before. The author assessed the effectiveness of the “Miracle Fruit” through daily diaries kept by patients, documenting increased appetite, reduced taste alteration, and improved nutritional status in patients undergoing chemotherapy. Patients consuming this fruit (n = 4) experienced enhanced taste perception and reported improvements in appetite, food intake, and quality of life compared to the control group (n = 4).

4. Discussion

This systematic literature review aimed to identify pharmacological interventions effective in reducing dysgeusia among chemotherapy patients. The results indicate a mix of promising interventions and others that warrant further research due to limited evidence. Interventions with demonstrated benefits in reducing dysgeusia, supported by high OCEBM grading scores, include zinc supplementation and Delta-9-Tetrahydrocannabinoid (level 2). Analysing the various pharmacological treatments and nutritional supplements reveals different mechanisms of action in addressing dysgeusia. Specifically, zinc acts as a cofactor for enzymes involved in taste signal transduction, thus helping to restore damaged taste receptors. On the other hand, vitamin D and lactoferrin play anti-inflammatory and immunomodulatory roles, reducing inflammation and promoting the healing of compromised taste receptors. Delta-9-tetrahydrocannabinol, the active ingredient in cannabis, interacts with cannabinoid receptors, modulating taste signal transmission and influencing taste perception. Lastly, miraculin found in Miracle Fruit acts as a taste modulator, binding to taste receptors and temporarily altering taste perception, inducing a perception of sweetness in acidic foods.

The efficacy of this approach underscores the value of a well-rounded, multidisciplinary strategy. Furthermore, it must be considered how the effectiveness of these treatments must take into account a multidisciplinary strategy, where education plays a crucial role, involving practical advice and consultancy from medical and nursing staff to help patients manage taste alterations [8, 37]. Establishing trust and open communication between patients and healthcare professionals is essential in this context. Continuous training for healthcare professionals is essential for effective patient communication. Nurses and doctors are instrumental in providing information, involvement, and support, fostering a collaborative environment that reinforces the knowledge shared with patients and solidifies the collective goal of well-being. Among these strategies, zinc supplementation also appears promising, but further research is needed to confirm its efficacy. For instance, the “Miracle Fruit” currently have limited supporting data. Given dysgeusia's substantial impact on patient's quality of life, employing objective assessment tools like the CiTAS scale is critical. These tools offer guidance for clinical approaches, ensuring patients receive comprehensive and effective treatment strategies tailored to their needs.

Despite the limited number of studies directly addressing dysgeusia in chemotherapy patients, the articles considered in this review have provided valuable insights into the research question and are pertinent to the theme under discussion. This highlights dysgeusia as a relatively underexplored and understudied area in current literature, emphasizing the need for further research in this domain.

4.1. Limitations

A potential limitation of this systematic review is the heterogeneity observed across the studies. Variations in sample populations and the different disciplines investigated contribute to this heterogeneity. Additionally, the differing assessment methodologies and data collection methods used in these studies further compound this issue, potentially affecting the uniformity and comparability of the findings. This diversity, while offering a broad perspective, also presents challenges in drawing generalized conclusions from the reviewed literature. Furthermore, it should be noted that the final number of articles available for some of the interventions studied is limited to only one. Given this limitation, it is crucial to approach the reported results with extreme caution.

4.2. Main evidence and implications for clinical practice and research

This systematic literature review delved into various interventions aimed at managing dysgeusia in chemotherapy patients, encompassing both pharmacological and nutritional supplement approaches. From our findings, the most promising interventions, selected based on rigorous study design criteria such as RCTs with low bias risk (JBI assessment ≥70%) and high certainty of evidence (OCEBM level 1–2), were pharmacological interventions involving zinc and Delta-9-Tetrahydrocannabinoid.

In terms of zinc administration, a single RCT [28] revealed a significant increase in taste thresholds ($p = 0.001$), with salty taste thresholds also rising ($p = 0.046$) in the intervention group by the treatment's conclusion. However, it's crucial to note the relatively small sample size in this study ($n = 35$; $IG = 20$; $CG = 15$), and a comparable RCT [26] failed to observe statistically significant differences in taste loss between the intervention and control groups.

Regarding Delta-9-Tetrahydrocannabinoid administration, only one RCT [27], with a relatively small sample size ($n = 21$; $IG = 11$, $CG = 10$), demonstrated that THC-treated patients reported improved ($p = 0.026$) and enhanced ($p < 0.001$) chemosensory perception. They also noted that food 'tasted better' ($p = 0.04$), premeal appetite increased ($p = 0.05$), and there was a higher proportion of calories consumed as protein ($p = 0.008$) compared to the placebo group.

Our review offers a comprehensive overview of the primary pharmacological interventions and orally administered nutritional supplements utilized in managing dysgeusia among chemotherapy patients. However, recognizing the limitations inherent in the examined treatments, it is essential to conduct further investigation through high-quality studies, including RCTs with larger sample sizes, to validate the efficacy of these interventions.

5. Conclusion

Dysgeusia represents a significant yet relatively underexplored and understudied issue in medical cancer research. This systematic review has highlighted potential management strategies for dysgeusia by identifying pharmacological oral interventions and nutritional supplements. However, only a few studies have shown promise, including pharmacological interventions such as zinc and Delta-9-Tetrahydrocannabinoid. There is a clear need for further experimental studies to evaluate the efficacy of the treatments identified in this review through high-quality research designs and larger population samples. This would facilitate the development and implementation of effective treatment strategies to prevent and manage dysgeusia, thereby improving the quality of life for chemotherapy patients.

CRediT author statement

BM: Conceptualization, Methodology, Writing Original Draft, Review& Editing, Supervision; **GF:** Conceptualization, Methodology, Writing Original Draft, Review & Editing, Investigation, Visualization; **RC**: Review & Editing, Visualization; **DC**: Review & Editing, Visualization; **FS**: Conceptualization, Methodology, Writing Original Draft, Review& Editing, Supervision; **SF**: Review & Editing, Visualization; **DL:** Review & Editing, Visualization; **AD:** Review & Editing, Visualization; **CC**: Review & Editing, Visualization; **GT**: Review & Editing, Visualization; **GA**: Review & Editing, Data analysis, Visualization; **SM**: Methodology, Data analysis, Writing Original Draft, Review & Editing, Investigation, Visualization, Supervision.

BM & GF provided an equal contribution as the first author in drafting the manuscript; GA & SM provided an equal contribution to the coordination of the research group. All authors read and approved the final manuscript.

Sources of funding

The authors declare that there are no sources of funding

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.05.026.

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