AMANDA GOMES DE MENÊSES

EFEITOS DA SUPLEMENTAÇÃO ORAL NO MANEJO DA MUCOSITE EM PACIENTES COM CÂNCER: REVISÃO SISTEMÁTICA E METANÁLISE DE ENSAIOS CLÍNICOS RANDOMIZADOS

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Dissertação apresentada como requisito parcial para a obtenção do Título de Mestre em Ciências da Saúde pelo Programa de Pós-Graduação em Ciências da Saúde da Universidade de Brasília.

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“Consagre ao Senhor tudo o que você faz,
e seus planos serão bem-sucedidos”.
Provérbios 16:3

RESUMO

A mucosite oral é uma toxicidade comum em pacientes submetidos ao tratamento oncológico. O manejo da mucosite oral é realizado pela redução dos sintomas, prevenção de complicações, controle da dor e manutenção da higiene bucal. Este estudo teve por objetivo avaliar evidências acerca dos efeitos da suplementação oral no manejo da mucosite em pacientes com câncer submetidos à quimioterapia e/ou radioterapia. Foi desenvolvida uma revisão sistemática seguindo o guia para relato de itens de revisão sistemática e metanálise (PRISMA). A busca foi realizada nas bases Cinahl, Cochrane, Lilacs, PubMed, Scopus e Web of Science. A busca na literatura cinzenta foi realizada no Google Scholar, Open Grey, e ProQuest Dissertações e Teses. Somente ensaios clínicos randomizados que avaliaram a suplementação oral comparada a outra intervenção ou nenhuma intervenção, para prevenção e/ou tratamento de mucosite oral em pacientes com câncer submetidos a quimioterapia e/ou radioterapia foram incluídos. Os estudos foram selecionados em duas fases, com dois revisores de forma independente. A ferramenta Cochrane Collaboration´s Review Manager® 5 (RevMan 5.3) foi utilizada para realizar a metanálise. Onze ensaios clínicos randomizados foram incluídos nessa revisão. As suplementações orais encontradas foram Elental, Glutamina e Zinco. Os estudos foram agrupados de acordo com a intervenção (Zinco ou Glutamina) para a realização da metanálise. Na metanálise do grupo que utilizou Zinco foi obtido (RR 0,76; 95% IC: 0,56 – 1,02; I^2 = 65%; n = 604) e no grupo da glutamina (RR 1,00; 95% IC = 0,81 – 1,24; I^2 = 0%; n = 327). Não existe forte evidência para a suplementação oral no manejo da mucosite oral em pacientes com câncer submetidos à quimioterapia e/ou radioterapia. Entretanto, o uso do Zinco pode ser uma estratégia promissora para o manejo da mucosite oral.

Palavras chaves: Mucosite oral; Suplementação oral; Revisão sistemática; Metanálise.

ABSTRACT

Oral mucositis is a common toxic side effect in patients ongoing cancer treatment. The management of oral mucositis is based on the reduction of the symptoms, in the prevention of complications, pain control and maintenance of oral hygiene. The study aims to evaluate the evidence of the effects of oral supplementation in the management of mucositis in cancer patients undergoing chemotherapy and/or radiation therapy. A Systematic review was developed following the Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA). The search was performed at Cinahl, Cochrane, Lilacs, PubMed, Scopus, and Web of Science. Additional gray literature search was performed on Google Scholar, Open Grey, and ProQuest Dissertation & Theses. Only randomized clinical trials studies that evaluated oral supplementation compared to other interventions or no interventions for prevention and/or treatment of oral mucositis in cancer patients undergoing chemotherapy and/or radiation therapy were included. The study selection was conducted in two phases, with two reviewers independently. The Cochrane Collaboration´s Review Manager® 5 (RevMan 5.3) was used to execute the meta-analysis. Eleven randomized clinical trials were included in this review. The oral supplementation used were Elental, Glutamine, and Zinc. The studies were grouped in two meta-analysis according to the interventions (Zinc or Glutamine). In the meta-analysis the zinc group presented (RR 0.76, 95% CI: 0.56 – 1.02. I^2=65% n=604) and the glutamine group presented (RR 1.00, 95% CI= 0.81 – 1.24. I^2=0% n=327). There was not strong evidence for oral supplementation in the management of oral mucositis in cancer patients undergoing chemotherapy and/or radiation therapy. However, Zinc might be a promise strategy for the management of oral mucositis.

Keywords: Oral mucositis; Oral supplementation; Systematic review; Meta-analysis.

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LISTA DE ABREVIATURAS E SIGLAS

AML	Acute Myeloid Leukaemia
CI	Confidence Interval
CH	Chemotherapy
CHRT	Chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events version 3.0
ECOG	Eastern Cooperative Oncology Group
ED	Elemental Diet
GLN	Glutamine
GY	Gray
HD	Hodgkin's Disease
HNC	Head and Neck Cancer
NCI-CTC	National Cancer Institute-Common Toxic Criteria
ND	Not Determined
NCI	National Cancer Institute
NIH	National Institutes of Health
NHL	Non-Hodgkin's Lymphoma
NPC	Nasopharyngeal Carcinoma
OC	Oral Cancers
OM	Oral Mucositis
OMAS	Oral Mucositis Assessment Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QT	Quimioterapia
RR	Risk Ratio
RT	Radioterapia/ Radiotherapy
RTOG	Radiation Therapy Oncology Group
WHO	World Health Organization

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1 INTRODUÇÃO

O câncer é um problema de saúde pública, principalmente nos países em desenvolvimento. A incidência do câncer cresce em todo o mundo e, no Brasil, a estimativa para o biênio 2018-2019 aponta a ocorrência de 600 mil casos novos de câncer em cada ano (1).

O tratamento do câncer inclui quimioterapia (QT) e radioterapia (RT), modalidades terapêuticas que, embora eficazes no controle e cura da doença, estão associadas a toxicidades de curto e longo prazo (2).

Antigamente, as toxicidades decorrentes do tratamento oncológico eram consideradas significativas apenas se prejudicassem a capacidade do paciente de continuar o tratamento. Atualmente, o manejo terapêutico envolve também proporcionar ao paciente qualidade de vida, redução da dor e do desconforto, por meio de medidas e intervenções eficazes (3).

A mucosa possui alta taxa de renovação celular, tornando-a vulnerável aos efeitos da QT e/ou RT, que predispõem o desenvolvimento da mucosite oral (OM, do inglês *oral mucositis*). O grau de severidade da OM implica em importante comprometimento bucal, que pode variar desde a dificuldade na manutenção da higiene bucal até a necessidade de internação hospitalar e suspensão do tratamento oncológico, impactando na qualidade de vida desses pacientes (4, 5).

A OM já foi considerada uma consequência inevitável do tratamento oncológico (6). Atualmente, as evidências são amplas no manejo desse efeito adverso, entre elas destacam-se as suplementações orais, pelo seu baixo custo, facilidade de acesso e de administração. Cabe ao enfermeiro que atua em setores de oncologia, juntamente com a equipe multidisciplinar, escolher cuidados e intervenções efetivas e seguras para prevenir e tratar a OM, sendo este um desafio na prática clínica oncológica.

Considerando o exposto, esse trabalho foi desenvolvido para avaliar as evidências científicas acerca dos efeitos da suplementação oral no manejo da OM nos pacientes com câncer.

2 REVISÃO DE LITERATURA

2.1 MUCOSITE ORAL

A mucosite é uma reação inflamatória e ulcerativa na mucosa que pode ocorrer na cavidade oral, faríngea, laríngea, regiões esofágicas e em regiões de mucosa gastrointestinal em pacientes que são submetidos à QT, RT e quimioradioterapia. A OM acomete a mucosa oral e/ou faríngea e é caracterizada por eritema, dor, edema e ulceração (7).

O desenvolvimento da OM envolve um complexo e multifatorial processo biológico constituído por cinco fases, a saber:

Fase 1 - iniciação: ocorre por lesão ao DNA causada pela RT e/ou QT, o que afeta a capacidade de proliferação das células epiteliais basais que ocorrem simultaneamente com a geração de espécies reativas de oxigênio, como superóxido;

Fase 2 - resposta à lesão primária: as células da submucosa são afetadas, ocorrendo ativação de fatores de transcrição em resposta aos fatores oxidativos, seguida de superregulação gênica, que resulta na produção de citocinas pró-inflamatórias como TNF-α, lL-1, IL-6 e óxido nítrico, gerando apoptose e lesão tecidual;

Fase 3 - sinalização e amplificação: induzidas pelo dano primário essas substâncias fornecem um *feedback* positivo, o que altera a resposta tecidual,induzindo maior produção de citocinas pró-inflamatórias, o que impulsiona o processo destrutivo;

Fase 4 - ulceração: é resultante da citotoxicidade nas células primordiais na camada basal, caracterizando-se por alterações atróficas que levam à ulceração;

Fase 5 - cicatrização: se inicia por sinalização da matrix extracelular da submucosa, estimulando a migração, diferenciação e proliferação do epitélio da mucosa oral. Neste período há também o restabelecimento da vascularização (4, 8, 9), conforme figura 1.

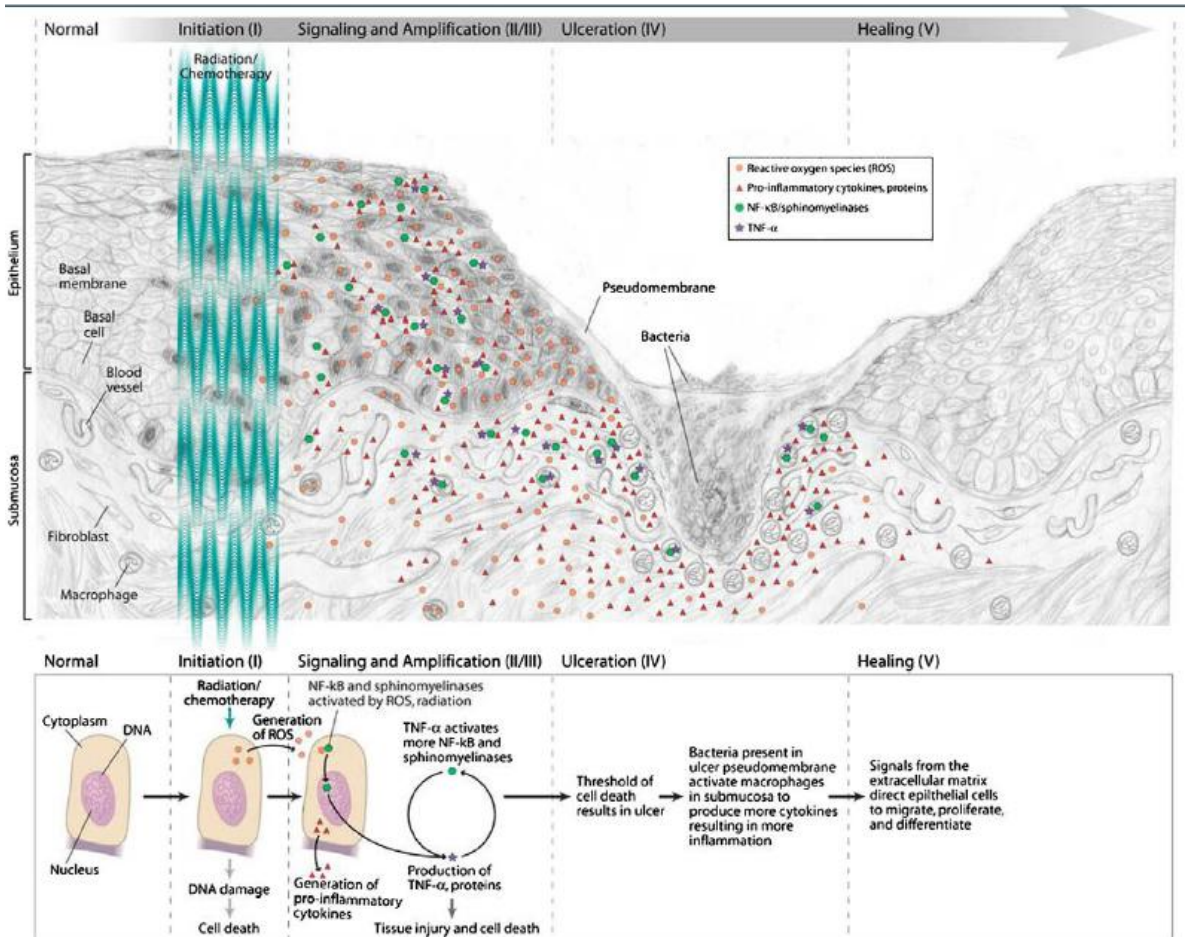

Figura 1 – Processo da fisiopatologia da mucosite (9).

A ulceração é a fase mais sintomática e complexa, geralmente caracterizada pela presença de lesões profundas que são rapidamente colonizadas pela microbiota da cavidade oral. A ulceração gera dor e desconforto, pela presença de terminações nervosas locais e infecções secundárias que coincidem com o pico de neutropenia do paciente, afetando negativamente a recuperação da integridade da mucosa. Os impactos do desenvolvimento da OM não se limitam apenas aos sinais e sintomas clínicos. A severidade da reação pode levar à interrupção do tratamento oncológico, aumento das hospitalizações para antibioticoterapia intravenosa e alimentação por nutrição parenteral expondo o paciente à maior risco de infecção (4, 9, 10).

Determinados fatores podem elevar o risco do desenvolvimento da OM. Alguns fatores são intrínsecos ao paciente, como idade, massa corporal, suceptibilidade genética, co-morbidades associadas, estado nutricional comprometido e higiene oral prejudicada (9, 11, 12). Fatores extrínsecos estão

relacionados com a modalidade de tratamento oncológico, a saber: quimioterapia, radioterapia ou quimioradioterapia.

2.1.1 Mucosite Oral induzida por quimioterapia

Na QT, os fatores estão relacionados à dose, duração e tipo do quimioterápico. A Cisplatina, o metotrexato e a ciclofosfamida são quimioterápicos que possuem alto risco para o desenvolvimento da OM. Pacientes que desenvolvem mucosite no primeiro ciclo quimioterápico, possuem risco elevado para desenvolver mucosite de maior intensidade nos ciclos subsequentes (8, 9, 11).

A OM induzida por QT ocorre em cerca de 40% dos pacientes que recebem QT de baixa dose em ciclos intermitentes, e pode atingir até 80% dos pacientes submetidos a altas doses quimioterápicas com infusões em bolus ou contínuas (7, 13). Em pacientes que realizam QT com o objetivo de supressão medular existe maior risco de desenvolvimento da OM, que pode ocorrer entre 60 a 100% (14).

Em pacientes submetidos à QT, a OM é geralmente uma condição aguda. A primeira manifestação clínica é caracterizada pela presença de áreas eritematosas na cavidade oral, que são visíveis cerca de 3 a 5 dias após a infusão quimioterápica. Após 7 a 10 dias, a presença de ulceração é notada, podendo evoluir gradualmente em tamanho e quantidade, formando grandes zonas de ulceração, caracterizadas por áreas necróticas e margens com infiltração inflamatória. O seu desaparecimento ocorre dentro de três semanas após a suspensão quimioterápica (11, 14).

2.1.2 Mucosite oral induzida por radioterapia

Fatores extrínsecos relacionados ao desenvolvimento da OM em pacientes submetidos à RT, são: localização do tumor irradiado, volume da mucosa exposta à radiação, dose total, dose fracionada e mudanças na microbiota bucal decorrentes da exposição à dose acumulada de 10 Gy (9, 11, 15).

OM ocorre em 100% dos pacientes com câncer de cabeça e pescoço submetidos à RT e em pacientes que realizam quimioradioterapia concomitantes (13, 14).

A OM induzida por RT é de natureza crônica. Os primeiros sinais de eritema aparecem na segunda semana de RT, com doses padrão de fracionamento de 2 Gy

por dia. A ulceração, geralmente, ocorre em torno de duas a sete semanas de radioterapia, quando o paciente está exposto a uma dose acumulada igual ou superior a 30 Gy. A ulceração pode permanecer por até quatro semanas após a conclusão do tratamento, diferentemente da OM induzida por QT que possui curta duração (9, 13).

2.2 MANEJO DA MUCOSITE ORAL

As lesões da OM cicatrizam após algumas semanas depois da interrupção do tratamento oncológico. São práticas desejáveis para o manejo da OM no paciente oncológico: reduzir a duração da OM, retardar o aparecimento da fase de ulceração, prevenir complicações, controlar a dor e assegurar a manutenção da higiene bucal (3, 16).

A higiene bucal pode reduzir a presença de microbiota oral, dor, sangramento e prevenir infecções. Porém, apenas a realização da higiene oral como estratégia de manejo não é suficiente para a prevenção do desenvolvimento da OM, sendo necessário associar a higiene oral com intervenções eficazes para reduzir a ocorrência e a severidade da OM (6, 17).

Diversas intervenções tópicas e sistêmicas são utilizadas na prática clínica para prevenção e tratamento da OM, como laserterapia, crioterapia, anti-inflamatórios, antimicrobianos, imunoglobulinas, anestésicos, corticoesteróides, aminoácidos não essenciais, vitaminas e outros agentes (16, 18, 19).

A suplementação oral possui efeito sistêmico por ser administrada por via oral e inclui micronutrientes, vitaminas, minerais e aminoácidos não essenciais (20). Atualmente, vem sendo utilizada na prática clínica para o manejo da OM. Entretanto, não há consenso quanto a melhor suplementação oral e sua eficácia na prevenção e tratamento da OM (16).

As Diretrizes Clínicas da *Multinational Association of Supportive Care in Cancer* e *International Society of Oral Oncology* (MASCC/ISOO) recomendam o uso de palifermina, amifostina e crioterapia para prevenção da OM (7, 21). Para o tratamento é recomendado que seja realizado alívio dos sintomas e redução da carga microbiana oral, mas não é estabelecido uma intervenção de escolha (7, 16).

A heterogeneidade de intervenções existentes e as diversas opções de dose e vias de administração dificultam a padronização de uma intervenção.

2.2 ESCALAS DE AVALIAÇÃO PARA MUCOSITE ORAL

Diversas escalas de avaliação são utilizadas para caracterizar o grau de severidade da OM. A escala de avaliação da *World Health Organization* (WHO) é amplamente utilizada. A severidade da OM é graduada de 0 a 4. Os critérios de avaliação incluem a capacidade do indivíduo de tolerar alimentos líquidos e sólidos, associado com critérios de avaliação do eritema e da ulceração (8, 22).

Entre as escalas mais utilizadas está a escala do *National Cancer Institute* (NCI) da *National Institutes of Health* (NIH) denominada *Common Terminology Criteria for Adverse Events* (CTCAE), possui quatro versões e atualmente suas graduações incluem a funcionalidade, como capacidade do paciente de se alimentar e necessidade de hidratação venosa (8, 22).

A escala de avaliação do Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group (ECOG), utiliza nas suas graduações as alterações anatômicas associadas à OM, o tamanho e as características da ulceração (22).

Outra escala utilizada para avaliação da OM é denominada *Oral Mucositis Assessment Scale* (OMAS) que inclui nos seus critérios de avaliação o tamanho da ulceração, e gradua a OM de 0 a 3. É uma escala previamente validada em um estudo multicêntrico (8, 22, 23).

As escalas de avaliação para OM fornecem medidas que permitem padronizar a avaliação e acompanhar a severidade do desenvolvimento da OM. As escalas de avaliação também possibilitam a tomada de decisão quanto a intervenções utilizadas no manejo da OM (22).

3 OBJETIVOS

3.1 OBJETIVO GERAL

Avaliar a evidência científica dos efeitos da suplementação oral na prevenção e/ou tratamento da mucosite oral em pacientes com câncer submetidos à QT e/ou RT.

3.2 OBJETIVOS ESPECÍFICOS

Identificar e avaliar a eficácia das diferentes suplementações orais para a prevenção e/ou tratamento da mucosite oral em pacientes com câncer submetidos à QT e/ou RT;

Avaliar a qualidade das evidências dos estudos incluídos na revisão;

Sintetizar e comparar os resultados coletados dos estudos e as especificidades das suplementações orais.

4 ARTIGO

Essa revisão sistemática, apresentada em formato de artigo, foi submetida para publicação na revista *Nutrition and Cancer*, ISSN 1532-7914 versão online, fator de impacto 2,447, classificada como periódico B1 no Qualis-Capes Medicina II, no dia primeiro de março de 2018, sob registro de envio número N&C-03-18-3313.

TITLE: Effects of oral supplementation to manage oral mucositis in cancer patients: a meta-analysis of randomized clinical trials

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Short running head: Oral supplementation for oral mucositis

Conflict of interest: none

4.1 ABSTRACT

Purpose: To evaluate the evidence of the effects of oral supplementation in the management of oral mucositis in cancer patients undergoing chemotherapy and/or radiation therapy.

Method: Systematic review. The search was performed at Cinahl, Cochrane, Lilacs, PubMed, Scopus, and Web of Science. Additional gray literature search was performed on Google Scholar, Open Grey, and ProQuest Dissertation & Theses. Only randomized clinical trials studies that evaluated oral supplementation compared to other interventions or no interventions for prevention and/or treatment of oral mucositis in cancer patients undergoing chemotherapy and/or radiation therapy were included.

Results: Eleven randomized clinical trials were included in this review. The oral supplementation used were Elental, Glutamine, and Zinc. The studies were grouped in two meta-analysis according to the interventions (Zinc or Glutamine). In the meta-analysis the zinc group presented (RR 0.76, 95% CI: 0.56 – 1.02. I^2=65% n=604) and the glutamine group presented (RR 1.00, 95% CI= 0.81 – 1.24. I^2=0% n=327)

Conclusions: There was not strong evidence for oral supplementation in the management of oral mucositis in cancer patients undergoing chemotherapy and/or radiation therapy. However, Zinc might be a promise strategy for the management of oral mucositis.

Keywords: Oral mucositis; Oral supplementation; Systematic review; Meta-analysis.

4.2 INTRODUCTION

Oral mucositis (OM) is a common toxic side effect in patients ongoing cancer treatment that negatively impacts the treatment outcomes and patients' survival (7, 24). The prevalence is aggravated by cancer type and treatment modality. It is expected that about 40% of patients treated by conventional chemotherapy and 100% of head and neck cancer patients treated by radiation therapy develop OM (13).

OM is characterized by erythema, areas of desquamation, in some cases ulceration and/or bleeding, generate progressively oral pain, odynophagia and reduce oral intake. Factors that increase OM occurrence are ineffective oral hygiene, nutritional status, alterations in salivary immunoglobulins, and the association of chemotherapy and radiation therapy (24, 25).

OM usually appears in the second week of radiation therapy with fractionated doses of 2 Grays (Gy), and three to five days after bolus or continuous infusions of chemotherapy. This side effect causes a loss in the protective function of the mucosal barrier leading to destruction and breakage of mucosa, increasing the risk of a local infection due to the colonization of resident microflora, bacteremia, and sepsis (3, 13). Severe mucositis may be responsible to premature interruption of radiation therapy and the reduction of chemotherapy dose (7).

The management of OM is based on the reduction of the symptoms, in the prevention of complications, pain control and maintenance of oral hygiene, since these are the most effective strategies to prevent and minimize its progression. Several systemic and topical agents have been used in OM management, such as anti–inflammatory, antimicrobials, granulocyte macrophage colony stimulating factor, corticosteroids, anesthetics, analgesics, non-essential amino acid, vitamins, honey, and other agents. Nevertheless, there is a lack of evidence-based standard approach for the prevention and the treatment of OM (16, 21, 26). Palifermin is an agent approved for the prevention and treatment of OM (27), and palifermin, amifostine, and cryotherapy have been recommended to prevent OM by the Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) (7).

Despite all available strategies and agents, OM still remains a difficult condition to be managed by the health multidisciplinary team. Oral supplementation

has been investigated to manage OM (19, 28), but there is no systematic review that evaluates the efficacy of all oral supplementation.

Therefore, the aim of this study was to conduct a systematic review to evaluate the evidence of the effects of oral supplementation in the prevention and/or treatment of OM in cancer patients undergoing chemotherapy and/or radiation therapy.

4.3 METHODS

4.3.1 Protocol and registration

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA Checklist (29). The systematic review protocol was registered at the International Prospective Register of Systematic Reviews (30) database under registration number CRD42017078646.

4.3.2 Terminology definition

In this systematic review, we only considered supplementations administered orally. Since we were planning to investigate only the systemic effect of oral supplementations, we did not consider supplementations that were administrated as oral suspension or mouthwash because of its local effect due to swish of the solution.

4.3.3 Eligibility criteria

Only randomized clinical trials that evaluated oral supplementation compared to other interventions or no interventions for prevention and/or treatment of OM in cancer patients undergoing chemotherapy (CH) and/or radiation therapy (RT) were included in this review. There were no restrictions in studies' year of publication.

Studies were excluded for the following reasons:

1 - Studies evaluating oral mucositis secondary to blood marrow transplantation, or another treatment that does not involve CH or RT;

2 - Studies evaluating other types of mucosa different from oral mucosa (intestinal/bowel mucosa);

3 - Studies assessing only intervention that is not oral supplementation, such as topical mouthwashes, cryotherapy, and parenteral interventions;
4 - Reviews, letters, conference abstracts, personal opinions, book chapters, case reports or cases series;
5 - Non-randomized clinical trials;
6 - Language restriction (non-roman languages);
7 - Full paper copy not available;
8 - Studies with the same sample.

4.3.4 Information sources and search strategy

Studies were identified using a search strategy, which was performed in August 24th, 2017, and adapted for each of the following electronic databases: Cinahl, Cochrane, Lilacs, PubMed, Scopus, and Web of Science (Appendix 1). An additional gray literature search was performed on Google Scholar, Open Grey, and ProQuest Dissertation & Theses. The searches were rerun in February 2018 just before the final analysis and the results were screened for eligible studies, however no articles were added.

After obtaining all references, duplicates were removed by appropriate reference manager software (EndNoteBasic®, Thomson Reuters, USA). The hand screening was performed on the reference lists from the selected articles for potential relevant studies that could have been missed during the electronic database search.

4.3.5 Study selection

The screening and data extraction phase was performed on Rayyan - a web and mobile app for systematic reviews (31). The study selection was conducted in two phases. In phase 1, two reviewers (A.G.M. and A.G.C.N) independently screened titles and abstracts of all identified electronic database citations that appeared to meet the inclusion criteria. Any studies that appeared not to fulfill the inclusion criteria were discarded. In phase 2, the same selection criteria were applied to the full-text articles to confirm their eligibility. The same two reviewers independently participated in phase 2. Any disagreement in either phase was resolved by discussion and mutual agreement between the two reviewers. A third

author (I.P.T.) was involved when required to make a final decision in case of conflicts. The reference list of all included articles was reviewed by one examiner. Final selection was always based on the full-text of the publication, and the excluded studies and the reasons for their exclusion are listed in Appendix 2.

4.3.6 Data collection process and items

One reviewer (A.G.M.) collected the data from the each included study. The second reviewer (A.G.C.N) crosschecked the collected information to confirm its accuracy. Any disagreement between them was resolved by discussion and mutual agreement between the three reviewers (A.G.M., A.G.C.N and I.P.T.). The included studies were divided by subgroups, and the following information were recorded: study characteristics (author(s), year and country of publication, objectives), population characteristics (age, cancer type, cancer treatment), intervention characteristics (groups, treatment period, oral mucositis assessment criteria), and main results.

4.3.7 Risk of bias in individual studies

Risk of bias of selected studies was assessed by using the Cochrane Collaboration Risk of Bias Tool (32), including judgments about the sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. The risk of bias was assessed as low, high or unclear. Two investigators scored each item and assessed independently the risk of bias of each included study (A.G.M. and A.G.C.N.). Disagreements between the 2 reviewers were resolved by a third investigator (I.P.T).

4.3.8 Summary measures

The primary outcome was prevention of OM or reduction of the severity of OM (grade of OM). The secondary outcome was reduction of pain intensity, scores of erythema, ulceration, eating, drinking ability, and healing.

4.3.9 Synthesis of results

Statistical grouping of data using meta-analysis was performed whenever studies were considered combinable and homogeneous in relation to interventions and outcomes. The Cochrane Collaboration´s Review Manager® 5 (RevMan 5.3) was used to execute the results. Heterogeneity within studies was evaluated by inconsistency indexes I^2 statistical test, and a value from 0 to 40% was considered of not important heterogeneity, between 30 to 60% moderate heterogeneity, whereas 50 to 90% was considered to represent substantial heterogeneity, and the results were presented with 95% confidence intervals (95% CI) (32).

4.3.10 Risk of bias across studies

The quality of evidence and grading of recommendations strength was assessed using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) instrument (33, 34). The criteria for this assessment were study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The quality of evidence was characterized as high, moderate, low, or very low (33, 34). The GRADE was assessed using tools from the website http://gradepro.org.

4.4 RESULTS

4.4.1 Study Selection

In phase 1 of study selection, 2,111 citations were identified across six electronic databases. After the duplicated articles were removed, 1,408 citations remained. One record was selected from gray literature. A thorough screening of the titles and abstracts was completed and 1,374 records were excluded. Hand screening from the reference lists of the identified studies yielded one additional study. Thus, 36 articles remained for a full-text reading for eligibility (phase 2). This process led to the exclusion of 25 studies (Appendix 2). In total, 11 articles (35-45) were selected for data extraction and qualitative synthesis. Figure 1 (Flow diagram) details this process of study selection.

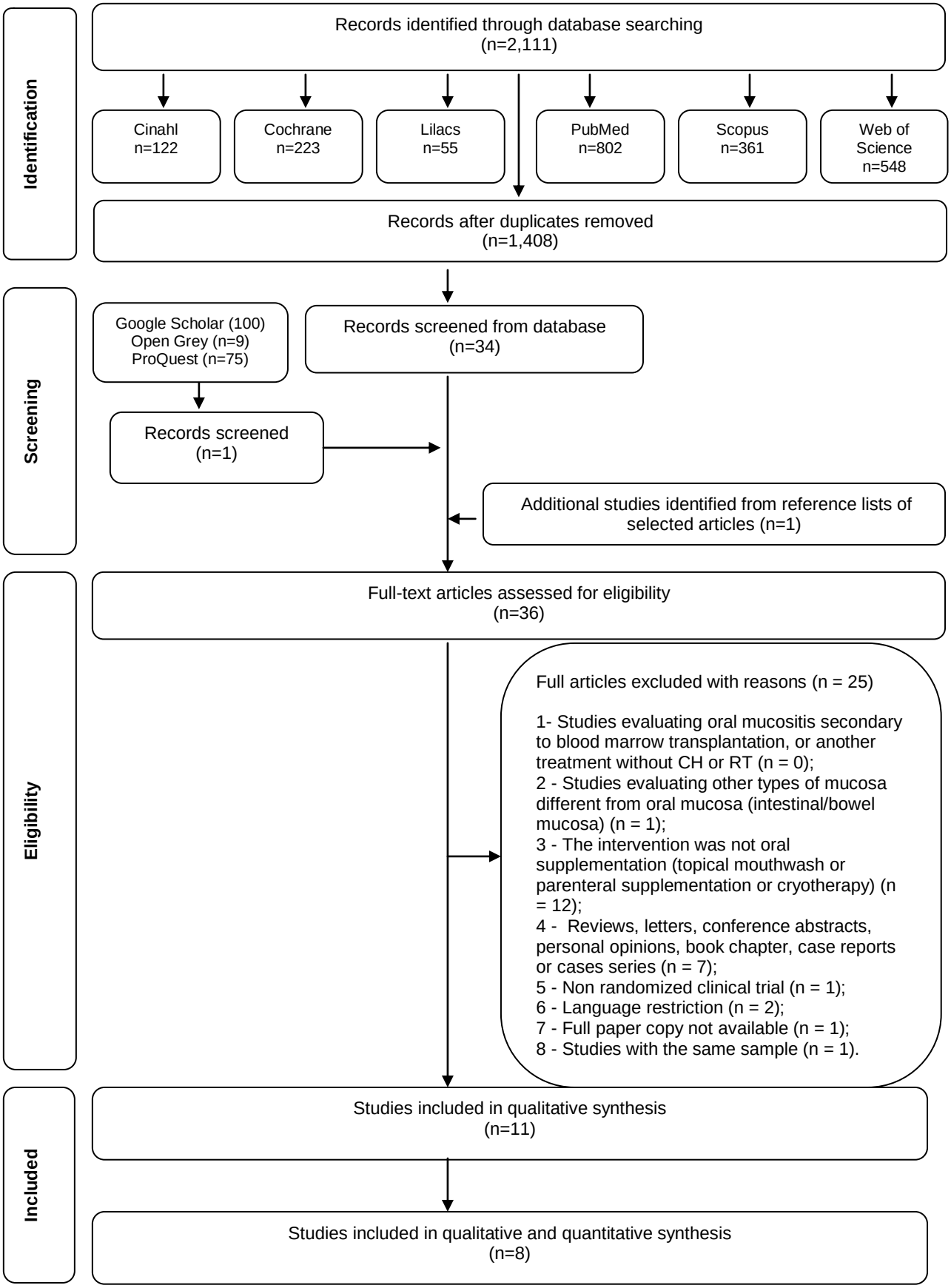

Figure 1 - Flow diagram of literature search and selection criteria adapted from PRISMA (29).

4.4.2 Study characteristics

Table 1 summarizes the descriptive characteristics of included articles. All studies were randomized clinical trials, published in English language, from 2004 to 2017. The studies were divided by subgroups according to the following interventions: Elental (42), Glutamine (39, 44, 45), and Zinc (35-38, 40, 41, 43).

The oral supplementation used as control were placebo (35, 36, 40, 41, 43, 45), Malto-dextrin (39), Soybean oil (38) and no treatment (37, 42, 44). Seven studies included patients undergoing chemoradiotherapy as treatment modality (36-41, 45). Seven evaluated sample with patients undergoing radiation therapy (36-41, 43), and three studies assessed patients undergoing chemotherapy (35, 42, 44).

Two studies (42, 44) included only esophageal cancer patients in the sample. Eight studies (36-41, 43, 45) included head and neck cancer patients and only one study (35) included multiple types of cancer.

About secondary outcomes, five studies (35, 39, 42, 43, 45) evaluated severity of pain. No study assessed scores of erythema, ulceration, eating and drinking ability and healing.

Table 1 - Summary of descriptive characteristics of included articles.

Subgroup	Study characteristics	Population characteristics				Intervention characteristics			
	Author Year Country	Age in years Mean (range)	Cancer Type	Cancer treatment	Intervention (N. of patients)	Control (N. of control patients)	Treatment Period	Oral Mucositis Assessment Criteria	Main results
Elental	Okada et al 2017 (42) Japan	C - 65.3 K - 67.1	Esophageal	CH	Elental (one pack per day) (10)	No treatment (10)	14 days	CTCAE	The maximum grade of oral mucositis evaluated with clinical examination declined in the Elental group compared with the control group, but without statistical significance. The proportion of patients with CTCAE grade ≥2 was consistently lower in the Elental group than in the control group (p = 0.078).
Glutamine	Lopez-Vaquero et al 2017 (39) Spain	C - 59 (39-78) K - 61.5 (32-81)	HNC	CHRT (55%) RT (45%)	L-Glutamine - 10 g, 3 times daily (25)	10 g of maltodextrin (25)	ND	CTCAE	The incidence of clinical mucositis was 87.5% in the placebo group and 76% in the Gln group (81.6% of global incidence). The comparison of clinical and functional mucositis had a higher value in placebo group, although without statistical difference. A direct significant statistical correlation was found between the values of the clinical and functional mucositis (p = 0.01), with a coefficient of 0.71 and 0.597 at the 3rd and 6th week, respectively.
	Tanaka et al 2015 (44) Japan	C – 75 (58-83) K glutamine - 73.5 (68-78) K no treatment - 68 (49-82)	Esophageal	CH	6930 mg glutamine + one pack of elental 300 mL/day (Gln plus ED) (10)	8910 mg glutamine daily (Gln) (10) No treatment (control) (10)	ND	CTCAE	The incidence of oral mucositis was significantly lower in the Gln plus ED group (10%) than in the control group. During the first cycle of CH, the incidence of oral mucositis was significantly lower in the Gln plus ED group than in the control group (p = 0.040). No significant difference between the control and Gln groups was observed during this study. The results of the multivariate analysis demonstrated that in addition to Gln plus ED (p = 0.02), cancer stage (p = 0.01) was an independent factor affecting mucositis grade during CH.
	Tsujimoto et al 2015 (45) Japan	C - 60.5 ± 10.8 K - 63.2 ± 5.4	HNC	CHRT	L-Glutamine – 10 g, 3 times daily (20)	Placebo (20)	During CHRT course	CTCAE	Gln significantly decreased the mean maximal grade (p = 0.005). The mean time to mucositis onset was 2.3±0.8 and 2.1±0.8 weeks (p=0.663), while the mean mucositis duration was 4.8±0.9 and 5.0±0.8 weeks in groups Gln and Placebo group, respectively (p=0.617). The mean time to severe mucositis onset (≥G3) was 4.2±1.1 and

									4.2±1.0 weeks (p = 0.829), while the mean severe mucositis (≥G3) duration was 2.2±1.4 and 2.8±1.1 weeks in groups Gln and placebo, respectively. The mean mucositis grade was significantly lower in group of Glne than in group of placebo at weeks 5 and 6 (p = 0.027, p = 0.002, respectively).
Zinc	Arbabi-Kalati et al 2012 (35) Iran	C- 51.5 (18-70) K- 47.2 (18-79)	Lung Nasopharynx Hematologics cells Esophagus Stomach Prostate Breast	CH	Zinc Sulfate - 200 mg, 3 times daily (25)	Placebo capsules (25)	Until the end of chemotherapy	WHO	In the 8th, 12th, 16th, and 20th weeks of CH there were statistically differences in mucositis intensity between both groups (p < 0.005). The recovery period was 7 weeks and 3 days for the zinc treatment group and 8 weeks for the placebo group, which was not statistically significant (p = 0.13). Patient pain intensity from the third visit (CH week 6) until the tenth meeting (CH week 20) exhibited statistically differences between both groups, indicating that pain intensity in the drug group was less than in the placebo group (p < 0.005)
	Ertekin et al 2004 (36) Turkey	C- 53 (36-69) K- 59 (18-71)	HNC	CHRT C(3) K(3) RT C(12) K(9)	Zinc – 50 mg, 3 times daily at 8 hour intervals (15)	Placebo capsules (12)	During RT since the first day and for 6 weeks after treatment	RTOG	In the zinc sulfate group, grade 1 mucositis was found in 8 patients and grade 2 in 5 patients. Mucositis Grade 3 and 4 did not develop in any of the zinc sulfate group of patients. In the placebo group grade 2 mucositis was found in 4 patients and grade 3 in 8 patients. There was a statistically significant difference in the start of mucositis (p<0.05), in the severity of mucositis (p<0.05) and in the RT dose at which mucositis developed (p<0.01).
	Gorgu et al 2013 (37) Turkey	C- 56 (42-74) K- 58 (41-73)	HNC	CHRT C(10) K(10) RT C(6) K(14)	Zinc – 25 mg, 4 tablets daily (16)	No treatment (24)	ND	RTOG	When compared two groups for the development of mucositis, there was no relationship between zinc replacement and mucositis (p = 0.159). Patients with low post-treatment serum zinc levels, grade 1 and 2 mucositis was noted in 8 and 6 patients, respectively; in those with normal post-treatment serum zinc levels grade 1 mucositis was noted in 5 patients, grade 2 in 5 patients, and grade 3 in 1 patient. The incidence of mucositis was lower in the patients with normal serum zinc levels before and after RT, though that was not statistically significant (p = 0.476).
	Lin et al 2006 (38) Taiwan	C- 50 K- 51	HNC	CHRT C(20) K(20) RT C(29) K(28)	Zinc – 25 mg, 3 capsules daily (49)	Soybean oil (48)	Approximately 2 months	RTOG	Grade 2 mucositis (p = 0.017) appeared earlier in the placebo group than in the experimental group receiving Pro-Z. A similarly significant difference in the development of Grade 3 mucositis (p = 0.0003) was observed between the two groups. When the severities of inflammation were assessed and

									evaluated, mucositis (p = 0.003) seemed to be milder in the experimental group than in the control group.
	Mosalaei et al 2010 (40) Iran	C - 58.1 K - 56.5	HNC	CHRT(46) RT (12)	Zinc sulphate – 220 mg, 3 times daily, at 8 hour intervals (29)	Placebo (29)	From day 1 until the end of treatment	RTOG	At the end of the 2nd week, 31% of the zinc group developed oral mucositis; this number in the control group was 37%. This difference was not statistically significant and oral mucositis initiated simultaneously in both groups. In weeks 4, 5 and 6, the severity of oral mucositis was lower in the zinc group, which was statistically significant (p = 0.02, 0.007 and 0.012 for weeks 4, 5 and 6).
	Moslemi et al 2014 (41) Iran	C - 49 (18-78) K - 52 (29-78)	HNC	CHRT(32) RT(5)	Zinc sulphate – 30 mg, 3 times daily at 8 hours intervals (20)	Placebo (17)	Started 10 days before beginning of treatment and continued to 8 weeks after the end of treatment	OMAS	Control group showed highest severity in mucositis (p<0/0001). The mucositis score in the zinc group was lower at the weekends(p<0.0001) compared to placebo group. For 2 weeks after end of the treatment, difference between results of zinc and placebo groups were statistically significant (p<0.05). In weeks 2-7 and 8, the severity of oral and pharyngeal mucositis was lower in the zinc group, (p<0.003).
	Sangthawan et al 2013 (43) Thailand	C – 62 K - 60	HNC	RT	Zinc sulfate - 10 cc per meal, 3 times daily (72)	Placebo (72)	From the first day of RT until the completion of radiation	NCI-CTC	Six patients and ten patients in zinc sulfate and placebo group respectively, developed grade 3 oral mucositis, which was not significantly different (p = 0.054). Twenty-two patients and nineteen patients in the zinc sulfate and placebo group respectively, developed grade 3 pharyngitis, which was not significantly different (p = 0.84). The mean differences of oral pain scores were lower in the zinc sulfate group, however, no significant differences were detected (p=0.77).

C = case group; **K** = control group

Abbreviation:

AML = acute myeloid leukaemia; **CH** = chemotherapy; **CHRT** = chemoradiotherapy; **CTCAE** = Common Terminology Criteria for Adverse Events version 3.0; **ED** = elemental diet; **GLN** = glutamine; **HD** = Hodgkin's disease; **HNC** = head and neck cancer; **N**. = Number; **NCI-CTC** = National Cancer Intitute-Common Toxic Criteria; **ND** = Not determined; **NHL** = Non-Hodgkin's lymphoma; **NPC** = nasopharyngeal carcinoma; **OC** = oral cancers; **OMAS** = Oral Mucositis Assessment Scale; **RT** = radiotherapy; **RTOG** = Radiation Therapy Oncology Group; **WHO** = World Health Organization.

4.4.3 Risk of bias within studies

The risk of bias was performed individually in all included studies (Figure 2). Five studies (35, 37, 41, 42, 44) exhibited an unclear risk of selection bias due to the poor description about how the randomization strategy was performed.

Three studies (37, 42, 44) were graded as having high risk of bias due to no blinding or incomplete blinding of participants, and the outcome is likely influenced by lack of blinding. The domain “incomplete outcome data” showed predominantly low risk of bias in the evaluation of all the studies.

One of the studies (43) was graded as having a low risk of bias in the six domains assessed. Five studies were classified as unclear risk of bias because they contained three or more compromised domains (36, 37, 41, 42, 44), and six studies (35, 38-40, 43, 45) were classified as low risk of bias because they contained two or less domains with low risk of bias.

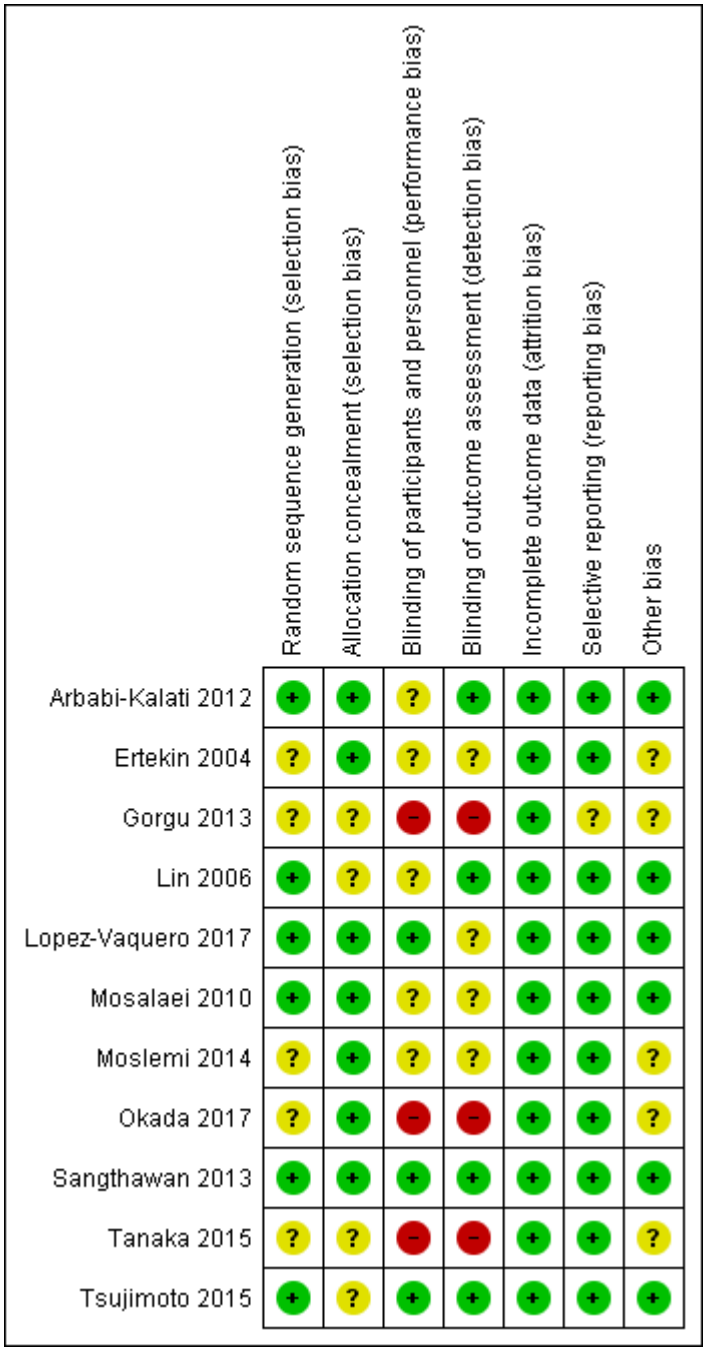

Figure 2 - Risk of bias (+ low risk, ? unclear, and - high risk).

4.4.4 Results of individual studies

The studies evaluated three different oral supplementations reported in 11 studies. They showed heterogeneity regarding intervention dose and period of administration for prevention and/or treatment of OM in cancer patients. Characteristics and results of the studies are in Table1.

4.4.5 Synthesis of results

The studies were grouped in two meta-analysis according to the interventions (zinc or glutamine). The meta-analysis of zinc synthesized the results according to occurrence of OM by week. The result of this random-effect meta-analysis did not demonstrate efficiency with the use of zinc oral supplementation to prevent OM (RR 0.76, 95% CI: 0.56 – 1.02. I^2 = 65% total sample=604) (Figure 3).

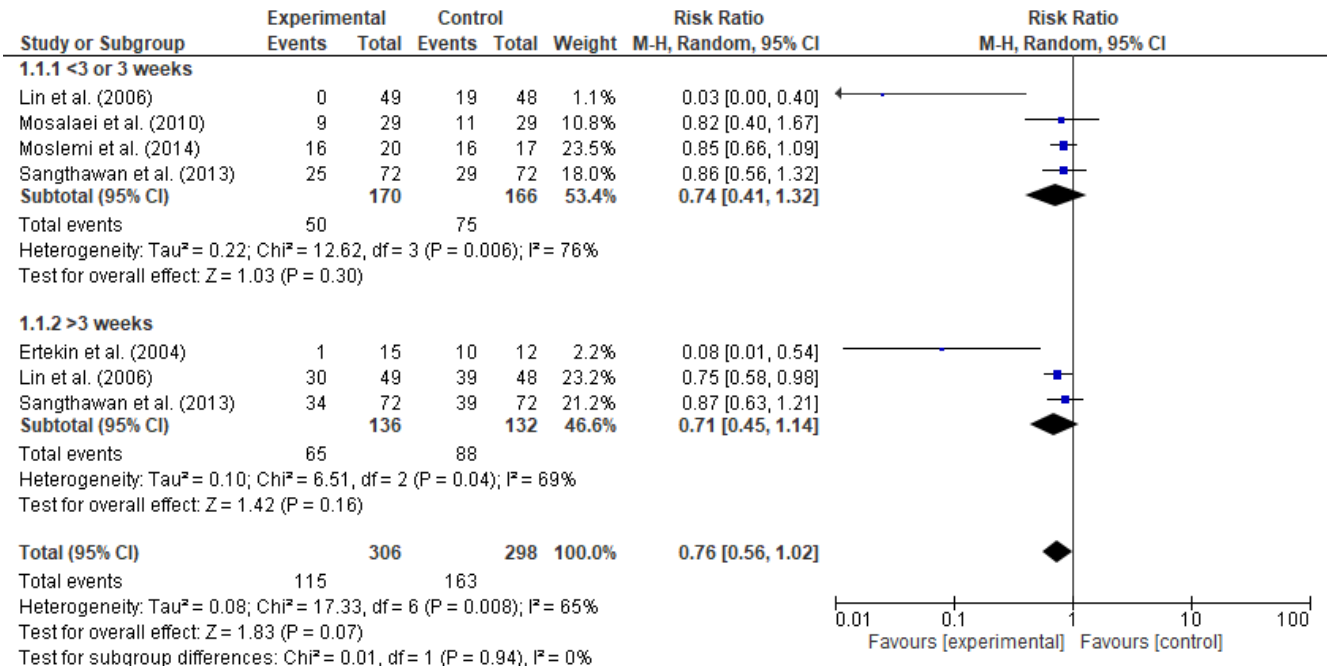

Figure 3 - Forest plot of zinc vs. controls according to occurrence of oral mucositis by week.

The second meta-analysis evaluated glutamine vs. controls according to the grade of OM. The results demonstrated that there is no significant difference

between the use of glutamine oral supplementation and controls to severity of OM (RR 1.00, 95% CI: 0.81 – 1.24. I^2 = 0% total sample=327) (Figure 4).

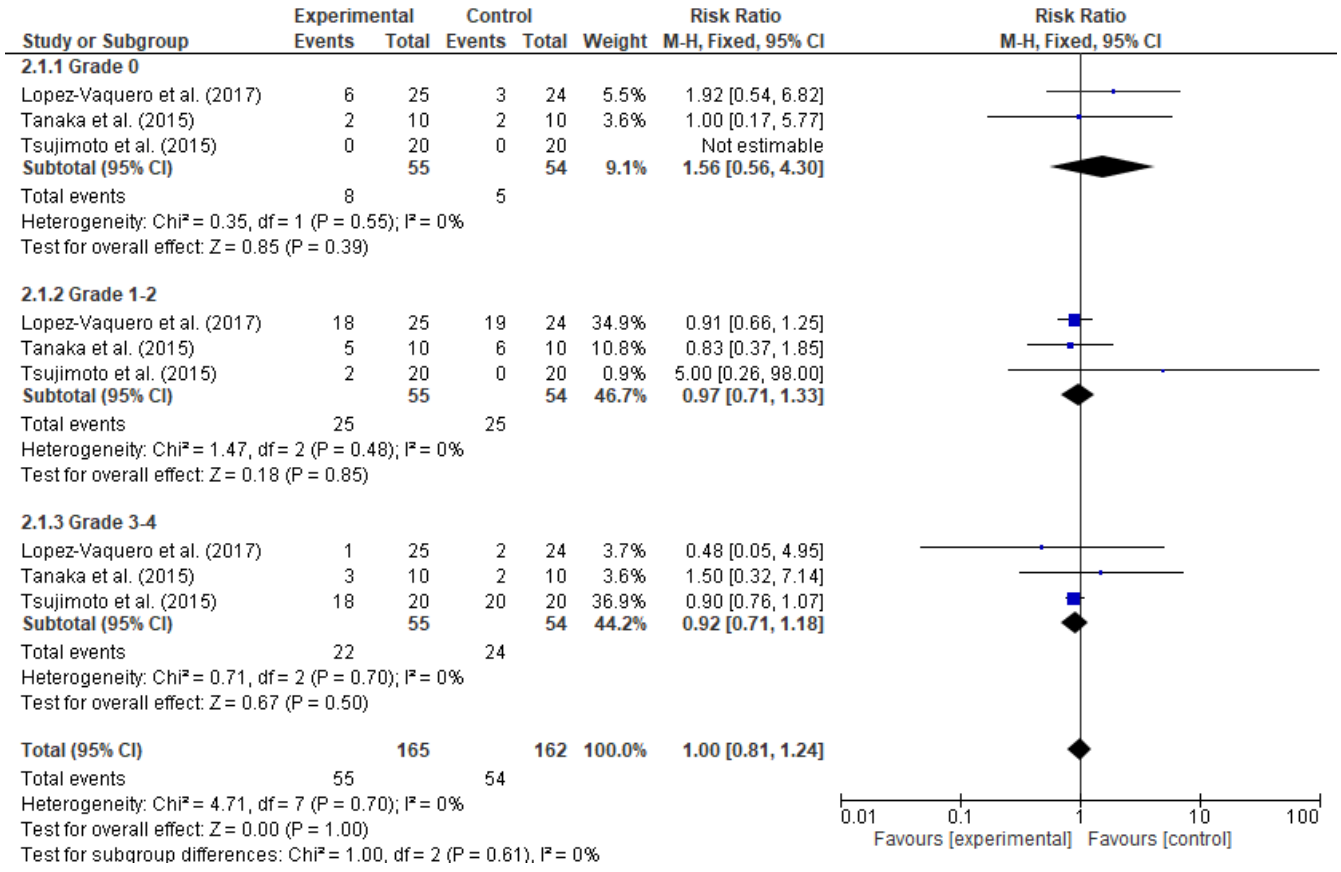

Figure 4 - Forest plot of glutamine vs. controls according to the grade of oral mucositis.

4.4.6 Risk of bias across studies

The quality of the evidence from the outcomes evaluated by the GRADE system was assessed as low for Zinc vs. controls according to occurrence of OM, and moderate for Glutamine vs. controls according to the grade of OM (Table 2), suggesting low and moderate confidence respectively in the estimated effect from the outcomes assessed. The important limitation in the studies was due to risk of bias since most studies were graded as unclear or high risk of bias leading to low quality of the evidence from studies evaluated.

Table 2 - GRADE assessment.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[intervention]**	**[comparison]**	**Relative (95% CI)**	**Absolute (95% CI)**		
Zinc vs. controls according to occurrence of oral mucositis												
5	RCT	serious [a]	serious [b]	not serious	not serious	none	65/185 (35.1%)	88/178 (49.4%)	**RR 0.76** (0.56 to 1.02)	**119 fewer per 1.000** (from 10 more to 218 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Glutamine vs. controls according to the grade of oral mucositis												
3	RCT	serious [c]	not serious	not serious	serious [d]	dose response gradient	22/55 (40.0%)	24/55 (43.6%)	**RR 1.00** (0.81 to 1.24)	**0 fewer per 1.000** (from 83 fewer to 105 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Most studies were graded as of unclear risk of bias

b. I^2 shows moderate heterogeneity

c. Most studies were graded as of unclear or high risk of bias

d. Risk relative shows that there was no statistical between intervention and control

4.5 DISCUSSION

OM is a complication due to antineoplastic therapy that may harm the patient's quality of life and health. However, OM in outpatients occurs with less intensity that in those hospitalized and receiving high doses of chemotherapy. OM due to chemotherapy and radiation therapy generates a considerable impact on the treatment and recovery of patients (10). Therefore, the synthesis of evidences to prevent and control OM is very important. This systematic review investigated the effect of oral supplementations to prevent and/or treat OM in cancer patients, since it may be an easy, efficient and low-cost source to manage OM. The search found three types of oral supplementations (Zinc, Glutamine and Elental) in 11 randomized clinical trials.

Zinc was the most frequent oral supplementation studied. Zinc is an essential element for multiple functions, normal growth, wound healing, immunity, and functions for cell proliferation (19, 41). It serves as a cofactor in numerous transcription factors and enzyme systems including zinc-dependent matrix metalloproteinases that augment autodebridement and keratinocyte migration during wound repair. Zinc confers resistance to epithelial apoptosis through cytoprotection against reactive oxygen species and bacterial toxins possibly through antioxidant activity of the cysteine-rich metallothioneins (46). Furthermore, recent *in vitro* study showed that cytotoxic effects and chromosomal damage observed in children suffering from protein-energy malnutrition, can be repaired with zinc sulfate supplementation (47).

However a previous review about natural agents for the management of OM have suggested that systemic zinc supplements administered orally may be of benefit in the prevention of OM in oral cancer patients receiving radiation therapy or chemoradiation (19), however our meta-analysis in this present review shown no significant difference to prevent OM with zinc administrated only as oral supplementation. In this present review, there was a heterogeneity related to dose prescribed ranging from 75 mg to 660 mg per day. However, independently of dose, zinc shows benefit to delay the occurrence of OM (36, 38), and to reduce the severity of OM (36, 38, 40, 41) in patients receiving chemoradiotherapy.

Incidence of OM is considerably high and more severe in patients receiving chemoradiotherapy compared with those receiving radiation therapy alone or only chemotherapy (48, 49). Zinc administrated as oral supplementation should be studied more, because it can be a relevant strategy for manage the OM.

Glutamine is an amino acid precursor for protein synthesis and cell proliferation primarily by mucosal cells which rapidly proliferate (50). It is a precursor for nucleotides, glutamate, and glutathione synthesis (51). Consequently, glutamine is important in nitrogen- and carbon-skeleton exchange among different tissues and fulfills other physiological functions (52). Clinical trials in humans have demonstrated that glutamine treatment decreases infectious complications, shortens hospital stays, and decreases hospital costs in a number of patient populations (53). Research in animal models of endotoxin shock, including severe injury models, demonstrated that glutamine supplementation improves survival, enhances immune and gut barrier function, decreases bacteremia, and inhibits gut mucosal atrophy (54). In addition, it attenuates proinflammatory cytokine release (54, 55). A recent *in vitro* study demonstrated that glutamine promoted growth, migration, and differentiation in human dental pulp cells through the BMP-2, Wnt, and MAPK pathways, leading to improved pulp repair and regeneration (56).

Previous cohort study has demonstrated that glutamine as an oral supplementation may delay the onset of OM and decreases the severity of OM in cancer patients (57). However, more studies with larger sample are needed to confirm the effect of glutamine, as shown in our meta-analysis. Glutamine, as oral supplementation, may decreases the risk and the severity of OM when it is associated with topical administration in patients undergoing radiation therapy or chemoradiotherapy (58).

Elental contains a well-balanced blend of amino acids and minerals. It has been proven to be effective against various gastrointestinal disorders, such as inflammatory bowel disease (59, 60). A recent prospective study of nutritional supplementation for preventing oral mucositis in cancer patients receiving chemotherapy, Elental showed a statistically significant reduction (p=0.020), while clinical examination showed insignificant reduction but shift toward lower grade. This study illustrates the effectiveness of oral elemental diet in preventing oral mucositis during chemotherapy. However, it is a preliminary report and further study with larger patient’s groups should be devoted to optimization of efficacy of Elental (42).

Reports of lower levels of pain associated to OM onset was observed in patients who underwent chemotherapy (35, 42), radiotherapy (43), and chemoradiotherapy (45), using different oral supplementations, such as Elental, Glutamine, and Zinc.

4.6 LIMITATIONS

Limitations of this review were the heterogeneity in doses and period of administration of oral supplementations, the heterogeneity of assessment criteria for OM, and the small samples size of the studies, leading to a difficult comparison between the interventions.

4.7 CONCLUSION

This systematic review and meta-analysis demonstrated that there was no strong evidence for oral supplementation for prevention and/or treatment of OM in cancer patients undergoing chemotherapy and/or radiation therapy. Zinc as an oral supplementation may be a promise strategy in the management of OM due to benefit to delay the occurrence and to reduce the severity of OM in some studies. Therefore, further researches are necessary to conduct more randomized clinical trials studies with well-designed and larger sample to evidence the best oral supplementation for prevention and/or treatment of the OM in cancer patients.

4.8 APPENDIX

4.8.1 Appendix 1 - Search Strategies in each database

Cinahl

Search	Search strategy	Results
#1	("oral supplementation" or "drugs supplementation" or supplement or supplementation or "Dietary supplements" or "Dietary Supplement" or "Dietary Supplementations" or "Food Supplementations" or "Food Supplements" or "Food Supplement" or "supplementary medicine" or "supplemental nutrition" or "multivitamin" or "vitamins" or "vitamin a" or "vitamin e" or "zinc" or "glutamine") AND ("mucositis" or Mucositides or "stomatitis" or Stomatitides or "Oral Mucositides" or Oromucositis or Oromucositides or "mouth mucosa" or "oral mucositis")	122

Cochrane

Search	Search strategy	Results
#1	("oral supplementation" or "drugs supplementation" or supplement or supplementation or "Dietary supplements" or "Dietary Supplement" or "Dietary Supplementations" or "Food Supplementations" or "Food Supplements" or "Food Supplement" or "supplementary medicine" or "supplemental nutrition" or "multivitamin" or "vitamins" or "vitamin a" or "vitamin e" or "zinc" or "glutamine") AND ("mucositis" or Mucositides or "stomatitis" or Stomatitides or "Oral Mucositides" or Oromucositis or Oromucositides or "mouth mucosa" or "oral mucositis")	223

Lilacs

Search	Search strategy	Results
#1	("mucosite oral" OR estomatite OR estomatitis OR stomatitis OR mucositis OR mucosite) AND ("suplementos nutricionais" OR "suplemento alimentar" OR "suplementos alimentares" OR "suplementos dietéticos" OR "dietary supplements")	55

PubMed

Search	Search strategy	Results
#1	("mucositis"[MeSH] OR Mucositides OR "stomatitis"[MeSH] OR Stomatitides OR "Oral Mucositides" OR Oromucositis OR Oromucositides OR "mouth mucosa"[MeSH] OR “oral mucositis") AND ("oral supplementation" OR "drugs supplementation" OR supplement OR supplementation OR "Dietary supplements" [MeSH Terms] OR "Dietary Supplement" OR "Dietary Supplementations" OR "Food Supplementations" OR "Food Supplements" OR "Food Supplement" OR "supplementary medicine" OR "supplemental nutrition" OR "multivitamin" OR "vitamins"[MeSH Terms] OR "vitamin a"[MeSH Terms] OR "vitamin e"[MeSH Terms] OR "zinc"[MeSH Terms] OR "glutamine"[MeSH Terms])	802

Scopus

Search	Search strategy	Results
#1	TITLE-ABS-KEY("Randomized controlled trials" OR "Randomized controlled trial" OR "Randomized clinical trial" OR "Randomized clinical trials" OR "clinical trials" OR "clinical trial" OR "random clinical trial" OR "random clinical trials" OR "controlled trials" OR "controlled trial") AND TITLE-ABS-KEY("mucositis" OR "stomatitis" OR "mouth mucosa" OR “oral mucositis”) AND TITLE-ABS-KEY(“oral supplementation” OR	361

	“drugs supplementation” OR “supplement” OR “supplementation” OR “Dietary supplements” OR “supplementary medicine” OR “supplemental nutrition” OR “multivitamin” OR "vitamins" OR "vitamin a" OR "vitamin e" OR "zinc" OR "glutamine")	

Web of Science

Search	Search strategy	Results
#1	("oral supplementation" or "drugs supplementation" or supplement or supplementation or "Dietary supplements" or "Dietary Supplement" or "Dietary Supplementations" or "Food Supplementations" or "Food Supplements" or "Food Supplement" or "supplementary medicine" or "supplemental nutrition" or "multivitamin" or "vitamins" or "vitamin a" or "vitamin e" or "zinc" or "glutamine") AND ("mucositis" or Mucositides or "stomatitis" or Stomatitides or "Oral Mucositides" or Oromucositis or Oromucositides or "mouth mucosa" or "oral mucositis")	548

Google Scholar

Search	Search strategy	Results
#1	("oral mucositis") AND ("oral supplementation" OR supplement)	100

Open Grey

Search	Search strategy	Results
#1	"oral mucositis" AND (treatment OR prevention)	9

ProQuest

Search	Search strategy	Results
#1	TI,AB("oran supplementation" OR "drubs supplementation" OR supplement OR supplementation OR "Dietary supplements" OR "Dietary Supplement" OR "Dietary Supplementations" OR "Food Supplementations" OR "Food Supplements" OR "Food Supplement" OR "supplementary medicine" OR "supplemental nutrition" OR "multivitamin" OR "vitamins" OR "vitamin a" OR "vitamin e" OR "zinc" OR "glutamine") AND TI,AB("mucositis" OR mucoses OR "stomatitis" OR stomatitis OR "oran mucoses" OR bronchitis OR Oromucoses OR "mouth mucosa" OR "oran mucositis") AND TI,AB("Randomized controlled trials" OR "Randomized controlled trial" OR "Randomized clinical trial" OR "Randomized clinical trials" OR "clinical trials" OR "clinical trial" OR "random clinical trial" OR "random clinical trials" OR "controlled trials" OR "controlled trial")	75

4.8.2 Appendix 2 - Full articles excluded (n = 25) from review with reasons.

Reference	Author, year	Reasons for exclusion
1	Assenat et al., 2011	4
2	Awidi et al., 2001	3
3	Chattopadhyay et al., 2014	3
4	Choi et al, 2007	3
5	Ferreira et al., 2004	3
6	Finocchiaro et al., 2014	4
7	Fukui et al., 2011	6
8	Gabison et al., 1995	4
9	Jebby et al., 1994	3
10	Kumabe et al., 2013	7
11	Li et al., 2006	2
12	Lin et al., 2004	4
13	Lin et al, 2010	8
14	Ogata et al., 2015	5
15	Okuno et al., 1999	3
16	Osaki et al., 1994	4
17	Pattanayak et al., 2016	3
18	Peterson et al., 2007	3
19	Reshma et al., 2012	3
20	Santos et al., 2009	4
21	Sarumathy et al., 2012	3
22	Saxena et al., 2008	3
23	Senesse et al., 2016	4
24	Ueta et al., 1994	6
25	Van Zaanen et al., 1994	3

(1) Studies evaluating oral mucositis secondary to blood marrow transplantation;

(2) Studies evaluating other types of mucosa different from oral mucosa (intestinal/bowel mucosa), or another treatment that does not involve CH or RT;

(3) Studies assessing only intervention that is not oral supplementation, such as topical mouthwashes, cryotherapy, and parenteral interventions;

(4) Reviews, letters, conference abstracts, personal opinions, book chapter, case reports or cases series;

(5) Non randomized clinical trial;

(6) Language restriction (non-roman languages);

(7) Full paper copy not available;

(8) Studies with the same sample.

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4.8.3 Appendix 3 - Cochrane's tool to assessed risk of bias in randomized controlled trials (32)

Author, year	Questions	Support for judgement	Risk of Bias
Arbabi-Kalati *et al.* 2012	Random sequence generation (selection bias)	Patients were divided by block randomization	Low
	Allocation concealment (selection bias)	The placebo capsules were similar in shape, taste, and color to the zinc sulfate capsules.	Low
	Blinding of participants and personnel (performance bias)	Insufficient information to permit judgement	Unclear
	Blinding of outcome assessment (detection bias)	The student and specialist who monitored the patients were blinded to the randomization and treatment.	Low
	Incomplete outcome data (attrition bias)	All participants completed the study	Low
	Selective reporting (reporting bias)	The study has been registered in the Iranian Registry of Clinical Trials, registry number: IRCT201101023133N3 and is available online	Low
	Other bias		Low
Ertekin *et al.* 2004	Random sequence generation (selection bias)	The study is randomized, however they do not give enough information about how the randomization was performed	Unclear
	Allocation concealment (selection bias)	The placebos were empty capsules bought from the same medicine firm to be identical to the zinc sulfate capsules	Low
	Blinding of participants and personnel (performance bias)	The study did not address this outcome	Unclear
	Blinding of outcome assessment (detection bias)	The study did not address this outcome	Unclear
	Incomplete outcome data (attrition bias)	It was described the number of patients that completed the study, as well as the reasons to patients that did not complete.	Low
	Selective reporting (reporting bias)	The published reports included all expected outcomes	Low
	Other bias		Unclear
Gorgu *et al.* 2013	Random sequence generation (selection bias)	The study is randomized, however they do not give enough information about how the randomization was performed	Unclear
	Allocation concealment (selection bias)	The study did not address this outcome	Unclear
	Blinding of participants and personnel (performance bias)	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding	High
	Blinding of outcome assessment (detection	No blinding or incomplete blinding, and the outcome is likely to be	High

	bias)	influenced by lack of blinding	
	Incomplete outcome data (attrition bias)	All participants completed the study	Low
	Selective reporting (reporting bias)	Insufficient information to permit judgement	Unclear
	Other bias		Unclear
Lin *et al.* 2006	Random sequence generation (selection bias)	Blocked randomization was used for all subjects to achieve balanced assignment. They adapted the RV.UNIFORM function in SPSS for Windows to generate random numbers and to assign distinct random permuted blocks to subjects.	Low
	Allocation concealment (selection bias)	The method of concealment is not described or not described in sufficient detail to allow a definite judgement	Unclear
	Blinding of participants and personnel (performance bias)	Insufficient information to permit judgement	Unclear
	Blinding of outcome assessment (detection bias)	The drug contents were not revealed, even to the principal investigator, until the end of the experiment	Low
	Incomplete outcome data (attrition bias)	It was described the number of patients that completed the study, as well as the reasons to patients that did not complete.	Low
	Selective reporting (reporting bias)	There are descriptions about all measurements in terms of means and standard deviation. There are values about all outcomes pre-specified.	Low
	Other bias		Low
Lopez-Vaquero *et al.* 2017	Random sequence generation (selection bias)	A randomization in 5 blocks of 10 patients with 1-to-1 assignment to groups was computer-generated by a statistician who was not working with the patients	Low
	Allocation concealment (selection bias)	The allocations were placed in sealed masked envelopes with a specific number group or an experimental group to receive a daily administration of oral glutamine or placebo	Low
	Blinding of participants and personnel (performance bias)	Both supplements were prepared in powder form packaged in single dosage pouches indistinguishable from each other, thus ensuring double-blind masking.	Low
	Blinding of outcome assessment (detection bias)	The study did not address this outcome	Unclear
	Incomplete outcome data (attrition bias)	It was described the number of patients that completed the study, as well as the reasons to patients that did not complete.	Low
	Selective reporting (reporting bias)	The study protocol was approved by the Ethics Committee of the	Low

		Puerta del Mar University Hospital, Cadiz, Spain and by the Spanish Agency for Drugs and Health Products (number of trial registry 2009-018103-40)	
	Other bias		Low
Mosalaei *et al.* 2010	Random sequence generation (selection bias)	Randomization was performed by using a random numbers table in a statistics textbook.	Low
	Allocation concealment (selection bias)	Placebo capsules were identical in shape and color to zinc sulphate and were filled with starch.	Low
	Blinding of participants and personnel (performance bias)	Insufficient information to permit judgement	Unclear
	Blinding of outcome assessment (detection bias)	Insufficient information to permit judgement	Unclear
	Incomplete outcome data (attrition bias)	All participants completed the study	Low
	Selective reporting (reporting bias)	There are descriptions about all measurements in terms of means and standard deviation. There are values about all outcomes pre-specified.	Low
	Other bias		Low
Moslemi *et al.* 2014	Random sequence generation (selection bias)	The study is randomized, however they do not give enough information about how the randomization was performed	Unclear
	Allocation concealment (selection bias)	Placebo capsules filled with starch and designed same medicine firm, form and color to zinc sulphate	Low
	Blinding of participants and personnel (performance bias)	Insufficient information to permit judgement	Unclear
	Blinding of outcome assessment (detection bias)	Insufficient information to permit judgement	Unclear
	Incomplete outcome data (attrition bias)	It was described the number of patients that completed the study, as well as the reasons to patients that did not complete.	Low
	Selective reporting (reporting bias)	It was registered in Iranian Registry of Clinical Trials (www.irct.ir) with ID No: IRCT201106116734N3	Low
	Other bias		Unclear
Okada *et al.* 2017	Random sequence generation (selection bias)	The study did not address this outcome	Unclear
	Allocation concealment (selection bias)	By using the enveloped method, the enrolled patients were randomized into two groups	Low

	Blinding of participants and personnel (performance bias)	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding	High
	Blinding of outcome assessment (detection bias)	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding	High
	Incomplete outcome data (attrition bias)	It was described the number of patients that completed the study, as well as the reasons to patients that did not complete.	Low
	Selective reporting (reporting bias)	The study has been registered in the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as number UMIN 000004898	Low
	Other bias		Unclear
Sangthawan *et al.* 2013	Random sequence generation (selection bias)	A block of four-randomization procedure was undertaken to achieve a balanced assignment. The trial statistician generated the randomization sequence via a computerized random number generator.	Low
	Allocation concealment (selection bias)	In order to conceal the allocation process, a pharmacy staff was responsible for keeping the randomization list and assigned participants to the trial group.	Low
	Blinding of participants and personnel (performance bias)	Patients and investigators were unaware of which treatment was administered	Low
	Blinding of outcome assessment (detection bias)	Patients and investigators were unaware of which treatment was administered	Low
	Incomplete outcome data (attrition bias)	It was described the number of patients that completed the study, as well as the reasons to patients that did not complete.	Low
	Selective reporting (reporting bias)	There are descriptions about all measurements in terms of means and standard deviation. There are values about all outcomes pre-specified.	Low
	Other Bias		Low
Tanaka *et al.* 2015	Random sequence generation (selection bias)	The study is randomized, however they do not give enough information about how the randomization was performed	Unclear
	Allocation concealment (selection bias)	The study did not address this outcome	Unclear
	Blinding of participants and personnel (performance bias)	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding	High
	Blinding of outcome assessment (detection bias)	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding	High
	Incomplete outcome data (attrition bias)	All participants completed the study	Low
	Selective reporting (reporting bias)	This trial was registered with the University Hospital Medical	Low

		Information Network Clinical Trials Registry (UMIN000008338)	
	Other bias		Unclear
Tsujimoto *et al.* 2015	Random sequence generation (selection bias)	An independent observer not involved in the study conduct randomly allocated eligible patients to either the glutamine group (group G) or the placebo group (group P).	Low
	Allocation concealment (selection bias)	The study did not address this outcome	Unclear
	Blinding of participants and personnel (performance bias)	All patients and medical staff, including physicians, nurses, pharmacists, nutrition support team (NST) members and investigators, were in compliance with the double-blind design	Low
	Blinding of outcome assessment (detection bias)	All patients and medical staff, including physicians, nurses, pharmacists, nutrition support team (NST) members and investigators, were in compliance with the double-blind design	Low
	Incomplete outcome data (attrition bias)	It was described the number of patients that completed the study, as well as the reasons to patients that did not complete.	Low
	Selective reporting (reporting bias)	The present study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000003991)	Low
	Other bias		Low

5. CONSIDERAÇÕES FINAIS

Cabe ressaltar a importância do manejo da OM nos pacientes com câncer submetidos à QT e/ou RT, visto que o grau da sua severidade impacta na qualidade de vida e no seguimento do tratamento oncológico. Nessa revisão sistemática, foram identificados na literatura onze ensaios clínicos randomizados que avaliaram os efeitos da suplementação oral na prevenção e/ou tratamento da OM em pacientes com câncer submetidos à QT e/ou RT.

Os estudo incluídos avaliaram Zinco, Glutamina e Elental como suplementações orais. Os estudos não demonstraram fortes evidências dos efeitos destas suplementações na prevenção e/ou tratamento da OM em pacientes com câncer submetidos à QT e/ou RT.

As limitações presentes nessa revisão incluem a heterogeneidade das doses e do período de administração das suplementações orais e a heterogeneidade das escalas de graduação da avaliação da OM, que dificultam a comparação entre as intervenções avaliadas. Em relação a amostra dos estudos individuais, o pequeno tamanho amostral, a inclusão de pacientes com diferentes tipos de câncer e as diferentes modalidades terapêuticas também são limitações que dificultam a comparação entre dos estudos.

No que concerne à avaliação do risco de viés, os estudos incluídos apresentaram risco de viés heterogêneo em diferentes domínios de avaliação. A ausência de dados que relatam detalhadamente o processo da pesquisa e dos resultados dos estudos dificultam o julgamento dos estudos incluídos. A qualidade metodológica dos estudos que utilizaram Zinco como suplementação oral foi baixa e dos estudos que utilizaram Glutamina como suplementação oral, apresentaram moderada qualidade metodológica, o que impacta na confiabilidade dos estudos.

Dessa forma, ressalta-se a necessidade de estudos futuros com amostras maiores com pacientes com câncer submetidos à QT e/ou RT, com maior rigor metodológico e bem delineados, que utilizem como intervenção as suplementações orais, que podem ser promissoras no manejo da OM, pela sua facilidade de acesso, benefícios e baixo custo.

6. CONCLUSÃO

Essa revisão sistemática com metanálise demonstrou que não há forte evidência dos efeitos da suplementação oral na prevenção e/ou tratamento da OM em pacientes com câncer submetidos à QT e/ou RT. O Zinco como suplementação oral pode ser uma estratégia promissora no manejo da OM, devido seu benefício na ocorrência e redução da severidade de OM em alguns estudos. Desse modo, ressalta-se a necessidade da condução de ensaios clínicos randomizados com maiores amostras, bem delineados, para evidenciar a melhor suplementação oral para prevenção e/ou tratamento da OM em pacientes com câncer submetidos à QT e/ou RT.

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