



Universidade de Brasília
Faculdade de Ciências da Saúde
Programa de Pós-Graduação em Ciências da Saúde

GEISA SANT'ANA

**TRATAMENTO TÓPICO DA MUCOSITE ORAL EM PACIENTES COM CÂNCER:
UMA REVISÃO SISTEMÁTICA DE ENSAIOS CLÍNICOS RANDOMIZADOS**

**"TOPICAL TREATMENT OF ORAL MUCOSITIS IN CANCER PATIENTS: A
SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS."**

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Orientadora: Prof. Dra Eliete Neves da Silva Guerra

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BANCA EXAMINADORA

Orientadora: Prof^ª. Dr^ª. Eliete Neves Silva Guerra (Universidade de Brasília)

Prof^ª. Dr^ª. Paula Elaine Diniz dos Reis (Universidade de Brasília)

Prof. Dr. Fabio Ferreira Amorim (Escola Superior de Ciências da Saúde)

Prof^ª. Dr^ª. Jamila Reis de Oliveira (Universidade de Brasília)

Prof. Dr. Levy Aniceto Santana (Escola Superior de Ciências da Saúde)

*Dedico este trabalho a Deus que provê todas as
graças e bençãos em minha vida.*

*Aos meus queridos filhos, fonte inesgotável
de amor, Nathália Sant'Ana de Rosa, Bruno
Sant'Ana de Rosa e meu neto Lucca Carvalho
Sant Ana de Rosa, pelo amor e paciência pelas
minhas ausências.*

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RESUMO

Objetivos: Os protocolos baseados em evidências de terapia tópica para Mucosite Oral (MO) induzida por quimiorradioterapia (QT e/ou RT)) são continuamente estabelecidos e atualizados. Assim, a presente revisão sistemática (RS) tem como objetivo avaliar a eficácia das intervenções tópicas no manejo clínico da mucosite oral em pacientes oncológicos submetidos à QT e/ou RT.

Materiais e Métodos: Esta revisão sistemática foi baseada na Lista de Verificação de Itens Preferenciais de Relatórios para Revisões Sistemáticas e Meta-Análises (PRISMA). Essa RS seguiu a abordagem de PICOS, incluindo pacientes adultos, em tratamento com intervenções tópicas nos estudos com ensaios clínicos randomizados. Para identificar a literatura publicada até 17/04/2019, estratégias de busca individual foram aplicadas nas seguintes bases de dados eletrônicas: CINAHL, Cochrane Library, LILACS, Livivo, PubMed, SCOPUS e Web of Science. A literatura cinzenta também foi avaliada no Google Scholar, Open Grey e ProQuest. O risco de viés nos estudos incluídos foi avaliado pela Ferramenta de risco de viés da Colaboração Cochrane. Os revisores compararam avaliações, resolveram as divergências e relataram suas avaliações usando o software Review Manage (RevMan 5.3). **Resultados:** Vinte e três ensaios clínicos randomizados (n = 1169 pacientes) preencheram os critérios de inclusão. Todos os artigos descreveram ensaios clínicos randomizados e foram publicados em inglês, no período de 1990 a 2017. O tamanho da amostra variou entre 09 a 142 pacientes nos estudos incluídos. O uso de metodologias semelhantes e robustas nos estudos incluídos, reduziu o potencial de má interpretação e foi considerado de risco moderado de viés, por esses motivos, considerados relativamente homogêneos em termos de características metodológicas. Vinte e três (23) agentes tópicos diferentes foram examinados e categorizados em cinco grupos: analgésicos (30,4%), agentes naturais (21,7%), outros agentes tópicos (21,7%), agentes antimicrobianos (17,4%) e fatores de crescimento (8,8%). Doze (12) estudos avaliaram o tratamento do câncer de cabeça e pescoço. Dos 23 estudos incluídos, 50% apresentaram resolução da MO em 14 dias. Os estudos incluídos geralmente demonstraram que pacientes tratados com enxaguatórios bucais apresentaram benefícios superiores em relação ao controle, dependendo da gravidade da MO. O enxaguatório bucal com fenitoína melhorou significativamente a dor e a qualidade de vida dos pacientes, pois os analgésicos tópicos são essenciais para o controle da dor, melhorando significativamente a ingestão alimentar e de líquidos, comunicação e conforto dos pacientes. Os agentes naturais tópicos produziram bons resultados, com redução da intensidade da MO (grau 3) e a dor, em 4-14 dias após a intervenção. Especialmente própolis e geleia real produziram resultados superiores, com tempo médio de resolução de 3 a 7 dias, sendo que 65% dos pacientes que usaram própolis como enxaguatório bucal foram completamente curados no dia 7 e 98% daqueles que usaram geleia real foram curados em 3-4 dias. **Conclusão:** Os agentes tópicos reduziram efetivamente a gravidade das lesões de MO e a intensidade da dor em pacientes recebendo QT e/ou RT, embora os efeitos variem por tipo de agente. No entanto, a heterogeneidade dos resultados encontrados nos estudos demonstra a necessidade de padronizar os instrumentos de avaliação validados que permitiram comparações e análises dos efeitos do tratamento com base em ensaios clínicos randomizados bem desenhados.

Relevância clínica: Os agentes tópicos foram efetivos em pacientes com lesões graves de MO em tratamento antineoplásico e, portanto, são uma boa alternativa de atendimento domiciliar em relação ao controle da dor, redução da inflamação e consequente melhoria na qualidade de vida.

Palavras-chave: intervenção tópica, quimioterapia, radioterapia, mucosite oral, ensaio clínico randomizado

ABSTRACT

Objectives: The evidence-based protocols for topical therapy for Oral Mucositis (OM) induced by chemoradiotherapy (QT and / or RT)) are continuously established and updated. Hence, the present systematic review (SR) aims to evaluate the effectiveness of topical interventions in the clinical management of oral mucositis in cancer patients undergoing QT and / or RT.

Materials and Methods: This systematic review was based on the Checklist of Preferred Items in Reports for Systematic Reviews and Meta-Analysis (PRISMA). This SR followed the PICOS approach, including adult patients being treated with topical interventions in studies with randomized clinical trials. To identify the literature published until 2019-04-17, individual search strategies were adopted in the following electronic databases: CINAHL, Cochrane Library, LILACS, Livivo, PubMed, SCOPUS and Web of Science. Grey literature was also evaluated on Google Scholar, Open Grey and ProQuest. The risk of bias in the studies included was assessed by the Cochrane Collaboration Bias Risk Tool. The reviewers compared reviews, resolved differences and reported their reviews using the Review Manage software (RevMan 5.3).

Results: Twenty-three randomized controlled trials (n = 1169 patients) met the inclusion criteria. All articles described randomized clinical trials and were published in English from 1990 to 2017. The size of the samples varied between 09 to 142 patients in the studies included. The use of similar and robust methodologies in the studies included reduced the potential for misinterpretation and it was considered of moderate risk of bias. For these reasons, they were considered relatively homogeneous in terms of methodological characteristics. Twenty-three (23) different topical agents were examined and categorized into five groups: analgesics (30.4%), natural agents (21.7%), other topical agents (21.7%), antimicrobial agents (17.4) % and growth factors (8.8%). Twelve (12) studies evaluated the treatment of head and neck cancer. Out of the 23 studies, 50% had resolution of the OM in 14 days. The studies included generally demonstrated that the patients treated with mouthwashes showed superior benefits over the control, depending on the severity of OM. The mouthwash with phenytoin improved patients' pain and quality of life significantly since topical analgesics are essential for pain control improving food and fluid intake, communication and patient comfort. Topical natural agents produced good results, with reduced OM intensity (grade 3) and pain in 4-14 days after the intervention. Propolis and royal jelly especially produced superior results, with an average resolution time of 3 to 7 days. The results were that 65% of the patients who used propolis as a mouthwash were completely cured on day 7 and 98% of those who used royal jelly were cured in 3 or 4 days. **Conclusion:** Topical agents effectively reduced the severity of OM injuries and the intensity of pain in patients receiving QT and / or RT, although the effects vary by type of agent. However, the heterogeneity of the results found in the studies demonstrates the need to standardize the validated assessment instruments that allowed comparisons and analyses of treatment effects based on well-designed randomized clinical trials. **Clinical relevance:** Topical agents were effective in patients with severe OM injuries undergoing antineoplastic treatment and, therefore, are a good alternative for home care in relation to pain control, reduction of inflammation and consequent improvement in quality of life.

Keywords: topical intervention; chemotherapy; radiotherapy; oral mucositis; randomized controlled trial

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LISTA DE ABREVIATURAS E SIGLAS

COX2=	<i>Ciclooxigenase 2</i>
CHT=	<i>Chemotherapy</i>
INOS-NO=	<i>óxido nítrico sintase induzível isoforma;</i>
ISOO-Soc =	<i>Sociedade Internacional de Oncologia Oral</i>
IL=	<i>Interleucina</i>
MASCC =	<i>Multinational Association of Supportive Care in Cancer</i>
MAPK =	<i>Proteína-Quinase Ativada por Mitógeno</i>
MMP=	<i>Metaloproteinase</i>
MO =	<i>Mucosite Oral</i>
NF-kB =	<i>Nuclear Factor Kappa B</i>
NO=	<i>óxido nítrico</i>
OMS=	<i>Organização Mundial de Saúde</i>
PAF=	<i>fator de ativação plaquetária</i>
PAMP=	<i>padrões moleculares associados a patógenos</i>
PRISMA=	<i>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</i>
PTK=	<i>Proteína Tirosina-Quinase</i>
QT =	<i>Quimioterapia</i>
ROS=	<i>Espécies Reativas de Oxigênio/Reactive Oxygen Species</i>
RT=	<i>Radioterapia</i>
TNF- α =	<i>Necrotic Tumor Factor</i>
WHO=	<i>World Health Organization</i>
IMRT=	<i>Intensity-Modulated Radiotherapy</i>

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1. INTRODUÇÃO

1.1 EPIDEMIOLOGIA

No mundo, todos os anos, as neoplasias malignas, comumente conhecidas como câncer, são responsáveis por aproximadamente 57 milhões das mortes, com 27% dos casos (Raessi et al., 2014). No *ranking* de mortes, são consideradas a segunda principal causa no mundo. Em 2015, 8,7 milhões de pessoas morreram de câncer e aproximadamente 410 mil (2,4%), dos 17,5 milhões de novos casos diagnosticados, eram câncer de lábio e cavidade oral. (Li et al., 2017; Shield et al., 2017). Já em 2018, foram responsáveis por 9,6 milhões de mortes, ou seja, uma em cada seis é relacionada à doença (Bray, 2018).

Em 2017, os registros de óbitos por câncer da cavidade oral entre homens foram 4.923, enquanto em mulheres foram 1.372, correspondendo ao risco de 4,88/100 mil em homens e 1,33/100 mil em mulheres. O câncer da cavidade oral envolve as regiões do lábio (localização primária), cavidade oral, glândulas salivares e orofaringe. Já em 2018, a estimativa foi de 246 mil casos novos de cânceres de língua e cavidade oral, com risco de 6,4/100 mil em homens e 2,9/100 mil em mulheres, sendo mais frequentes nos países do sul da Ásia.

A estimativa para o Brasil é que a cada ano do triênio 2020-2022 ocorram 625 mil casos novos de câncer, sendo que as neoplasias de cavidade oral serão responsáveis por 15.190 novos casos, com 11.180 casos em homens, ocupando a quinta posição, enquanto as mulheres aparecem com 4.010, ocupando o décimo terceiro mais frequente entre todos os cânceres. Existe uma variação na magnitude e nos tipos de câncer entre as diferentes regiões do Brasil. Entretanto, a distribuição mostra que a Região Sudeste concentra mais de 60% da incidência, seguida pelas regiões Nordeste (27,8%) e Sul (23,4%). (INCA, 2019; Ministério da Saúde, 2020).

Os locais mais comuns de câncer são: próstata (21%), pulmão e brônquios (14%), cólon e reto (8%) e melanoma (6%) nos homens; e mama (29%), pulmão e brônquios (13%), cólon e

reto (8%) e colo do útero (7%) em mulheres; esses quatro locais são responsáveis por 46% das mortes por câncer (DeSantis et al., 2014; Siegel et al., 2016).

Aproximadamente 70% das mortes por câncer ocorrem em países de baixa e média renda. Novos tratamentos aumentaram as taxas de sobrevivência, mas as diferenças na expectativa de vida entre países de baixa e alta renda contrastam com o desafio de proporcionar uma distribuição igual dos recursos de diagnóstico e tratamento (Li, et al., 2017; Shield et al., 2017).

1.2 MUCOSITE ORAL (MO)

A Mucosite Oral (MO), caracterizada por lesões nas superfícies da mucosa oral, tem sua descrição na história desde a descoberta do rádio, em 1897, por Madame Curie, seguindo próximo à Primeira Guerra Mundial, quando se tem o marco de início das aplicações de radiação no tratamento de câncer, e era referida como estomatite (Shankar et al., 2017).

Assim, o termo Mucosite Oral, ou estomatite, refere-se à reação inflamatória e às lesões ulcerativas da cavidade oral e orofaringe, que ocorrem secundariamente ao tratamento do câncer, incluindo quimioterapia citotóxica e/ou radioterapia, ou ambas (Dodd et al., 2003; Miranzadeh et al., 2015). A MO pode, em alguns casos, como em regimes quimioterápicos de tumores sólidos (casos como de mama ou colorretal), não evoluir para lesões severas. Sabe-se que os jovens apresentam taxas mitóticas basocelulares mais altas e, portanto, observa-se uma frequência maior de MO entre crianças do que em adultos (Sonis et al., 1994; Shankar et al., 2017).

Além disso, a etiologia da MO aumentou desde o advento da quimioterapia em 1940, mas sua patobiologia foi descoberta somente nas últimas duas décadas. A MO aguda resulta da hipoplasia e destruição do epitélio escamoso, esterilização de células estaminais da mucosa, inibição da proliferação de células de trânsito e ausência de regeneração celular. São consideradas semelhantes a indução da MO por radiação e/ou por quimioterapia (Shankar et al., 2017; Dodd et al., 2003; Miranzadeh et al., 2015).

Durante a terapia de câncer de cabeça e pescoço, faz-se necessário conhecer a microbiota oral dos pacientes para melhor compreensão do seu papel no desenvolvimento e progressão da MO. A cavidade oral saudável é composta de centenas de espécies bacterianas e fúngicas, que na sua maioria são comensais, mas podem se tornar patogênicas em resposta às alterações do ambiente, incluindo a higiene bucal. Estas podem associar-se para formar biofilmes que são resistentes à tensão mecânica ou a tratamento com antibióticos (Ribeiro et al., 2020).

Com isso, estudos analisaram a diversidade geral da flora oral e as mudanças durante a quimioterapia para determinar as relações com a MO. Identificaram, através de experimentos com queratinócitos orais *in vitro*, como os microrganismos afetam a cicatrização e que, durante a exposição à radiação, promovem alterações funcionais. Portanto, o papel da microbiota deve ser considerado em todas as fases da patogênese da MO e não somente como contribuidor passivo da fase ulcerativa. Assim, observa-se a necessidade de reduzir a carga microbiana, estimulando e orientando o paciente no cuidado com a higiene bucal e destacando-a como um fator primordial na prevenção e mitigação de lesões orais. As orientações de higiene oral incluem escovação, uso de fio dental e enxaguatórios bucais (Bowen, 2019; Shankar, 2017).

Na maioria dos casos, os pacientes em tratamento, com diagnóstico de câncer, desenvolvem frequentemente desde um ligeiro desconforto até uma dor intensa (sintoma primário da MO), xerostomia transitória ou permanente (sensação de boca seca), eritema e hipossalivação (redução objetiva no fluxo salivar) (Lalla, 2008; Sheibani et al., 2015; Sonis, 2004).

Alguns pacientes descrevem os estágios iniciais, ou a forma branda da MO, como uma sensação de queimação, semelhante à ingestão de alimento quente. Comumente, a formação de uma pseudomembrana vem acompanhada do aumento da dor e da incapacidade de tolerar alimentação corriqueira ou normal, levando, em muitos casos, o paciente a excluir a ingestão de alimentos sólidos. As úlceras de MO se diferenciam da estomatite aftosa em decorrência do

processo inflamatório atípico, levando, entre outras diferenças, a um anel periférico de eritema (Shankar et al., 2017).

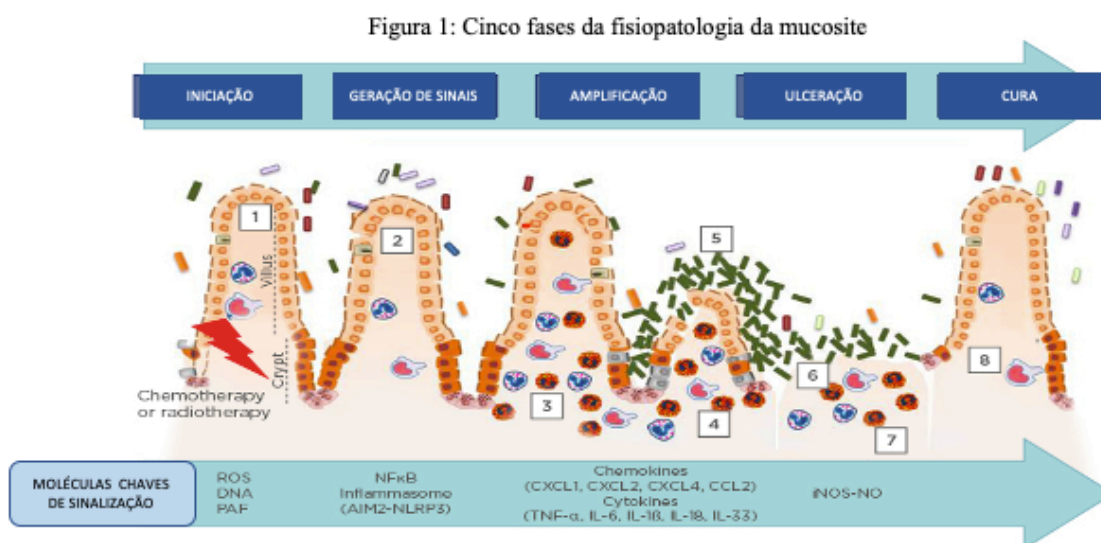
Toda a sintomatologia descrita, associada a outras características como eritema e ulceração da mucosa não queratinizada, desencadeia nutrição comprometida, hospitalização prolongada e infecções sistêmicas, fatores causadores de atrasos no tratamento e alteração do prognóstico terapêutico, o que afeta diretamente as remissões clínicas e chances de cura. As primeiras descobertas da MO, associadas à descrição de suas manifestações clínicas iniciais, precipitaram frustrações aos clínicos e pacientes devido à escassez de opções terapêuticas preventivas ou intervencionistas (Shankar et al., 2017; Münstedt et al., 2019).

Portanto, é importante enfatizar a necessidade de opções terapêuticas acessíveis, e nesse contexto promover a redução das diferenças de acesso aos tratamentos antineoplásicos entre países de baixa e alta renda que apresentam taxas de mortalidade global chegando a 70% (Li et al., 2017; Shield et al., 2017).

Pacientes com câncer de cabeça e pescoço (boca, nariz, faringe, laringe, seios paranasais ou glândulas salivares) em terapia antineoplásica têm prevalência de MO grave ou risco de vida relatado em até 66-85%, sendo, portanto, ainda um desafio a ser enfrentado, apesar dos avanços das pesquisas sobre o tema. Estudos demonstram os impactos econômicos significativos decorrentes da terapêutica da MO em pacientes oncológicos, correlacionando a gravidade da mucosite oral com um custo incremental de, pelo menos, \$ 1700-\$ 6000 por paciente (estimativas em dólares americanos de 2006). O tratamento do câncer de cabeça e pescoço com QT e/ou RT tem um custo médio estimado que excede \$39.000 em pacientes com MO em comparação aos sem MO com custos de aproximadamente \$21.000 (em dólares americanos de 2005) (Blakaj et al., 2019).

1.2.1 PATOGÊNESE

A patogênese da MO tem sido caracterizada como um complexo processo biológico, muito além do dano direto ao epitélio sozinho, que varia desde lesões eritematosas a quadros severos de ulceração e dor, o que na maioria das vezes interfere no tratamento antineoplásico, ou ainda mais grave, promove a interrupção do mesmo, levando à redução da qualidade de vida e/ou sobrevida do paciente (Lalla, 2008; Yoneda et al., 2007; Yen et al., 2012). Esse processo biológico tem sido dividido em cinco fases sequenciais: iniciação; geração de mensagem; sinalização e amplificação; ulceração e cicatrização (Figura 1) (Bossi et al., 2016; Lalla, 2008; Sonis, 2007; Al-Dasooqi et al., 2010).



Adaptado de Sonis ST. *The pathobiology of mucositis*. *Nat Rev Cancer*. 2004;4(4):277-84.

1) A geração de ROS e liberação de DNA de células danificadas e mediadores lipídicos, como o PAF durante a fase de iniciação; 2) Ativação do NFκB e da montagem de multiproteínas do inflamassoma, seguida pela indução de moléculas mensageiras, como TNF-α, IL-6 e CXCL1; 3) inflamação e apoptose dos tecidos relacionados ao tratamento durante a fase de regulação positiva / geração de mensageiros, caracterizada por influxo de neutrófilos, eosinófilos e macrófagos na lâmina própria; 4 e 5) NFκB induzida por microbiota e conjunto de múltiplas proteínas do inflamassoma, via PAMP, o que contribui para a amplificação da inflamação. A produção aprimorada de moléculas mensageiras na fase de amplificação e sinalização, desencadeada pela sinalização de citocinas, influxo de leucócitos e microbiota disbiótica, culmina em inflamação e apoptose aumentadas (3 e 4) e descontinuidade do epitélio e descontinuidade da barreira epitelial resultante da apoptose durante a fase ulcerativa (6), promovendo assim a translocação bacteriana (7). Uma fase de cicatrização espontânea é iniciada após a interrupção da quimioterapia (8), caracterizada por intensa proliferação celular.

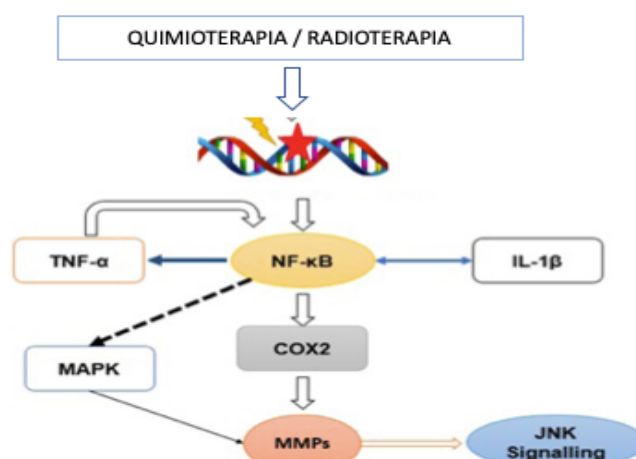
A fase de iniciação (fase 1) é caracterizada por lesões das células do epitélio basal e do conjuntivo subjacente (lâmina própria), induzidas após administração de quimioterapia (QT) ou radioterapia (RT). Essas lesões iniciais das células podem acontecer por dano direto ao DNA, ou mais comumente de forma indireta, por *espécies reativas de oxigênio* (ERO, *inglês* ROS), que

são importantes mediadores de eventos biológicos (Georgiou, 2012; Sonis, 2004). Na fase 2, geração de mensagem, RT, QT e *espécies reativas de oxigênio* (ERO, *inglês* ROS) ativam fatores de transcrição, sendo o mais importante o *fator nuclear* kB, em *inglês* *Nuclear Factor Kappa B* (NF-kB), até então inativado no citoplasma. Sua ativação carrega para o núcleo das células epiteliais, endoteliais e mesenquimais e macrófagos, levando à regulação positiva dos genes e à produção de citocinas pró-inflamatórias, incluindo o *fator necrótico do tumor* (TNF- α), a *interleucina* (IL-1 β) e a IL-6, resultando em danos aos tecidos. Nesta fase, os tecidos que parecem clinicamente normais têm alterações como a apoptose mediada por ceramida, provocando a morte de células endoteliais, além de células da submucosa como os fibroblastos. Associada a isso, teremos a geração de fibronectina, produção de metaloproteinases e apoptose adicional (Sonis, 2004; Sonis, 2009).

Na fase 3, a sinalização e amplificação do processo resultam também dos efeitos causados pela produção de proteínas. As citocinas, como a TNF- α , podem ativar o NF-kB em outras células, resultando na expressão de moléculas (transcrição de genes) que codificam a *Proteína-Quinase Ativada por Mitógeno* (MAPK), a ciclooxigenase 2 (COX2) e as moléculas sinalizadoras de *Proteína Tirosina-Quinase* (PTK) (Sonis, 2004; Kwon, 2016).

Na fase de ulceração (fase 4), as vias de sinalização ativam as metaloproteinases da matriz (MMPs) 1 e 3 nas células epiteliais e do conjuntivo subjacente, como fibroblastos, macrófagos e células endoteliais, o que resulta em lesões teciduais. Outra característica tardia das úlceras induzidas por MO é a angiogênese (Sonis, 2004; Kwon, 2016; Sonis, 2007). A inflamação resultante e os danos nos tecidos levam à ulceração e subsequente colonização bacteriana, alimentando ainda mais um círculo vicioso de dano mediado por citocinas inflamatórias. Esse processo potencializa genes pro-apoptóticos, que potencializam a lesão tecidual, gerando úlceras clinicamente visíveis (Figura 2) (Georgiou, 2012; Al-Ansari et al., 2015; Stringer & Logan, 2015).

Figura 2: Via de sinalização de mucosite



Adaptado de Shankar. *Current Trends in Management of Oral Mucositis in Cancer Treatment. Asian Pac J Cancer Prev.* 18 (8), 2019-2026

A fase final de cicatrização envolve sinalização via matriz extracelular, resultando em proliferação epitelial e epitelização, restabelecendo a barreira da mucosa (Georgiou, 2012).

1.3 TRATAMENTO ANTINEOPLÁSICO: QUÍMIO E RADIOTERAPIA

No tratamento da maioria dos cânceres, é geralmente usada a combinação de radioterapia, quimioterapia e outras terapias sistêmicas, como imunoterapia/bioterapia, direcionada ou hormonal. Embora as terapias antineoplásicas aumentem a sobrevida, sua administração está associada a efeitos colaterais que interferem na qualidade de vida, como náuseas e vômitos, MO com alteração do paladar, apetite e disfagia, supressão da medula óssea, imunossupressão, alopecia, toxicidade renal, cardiotoxicidade, toxicidade pulmonar, neurotoxicidade e lesão gonadal e esterilidade. Tais tratamentos são prescritos separadamente ou combinados, dependendo do tipo e estágio do câncer, e visam melhorar as taxas de sobrevivência, aliviar os sintomas e melhorar a qualidade de vida (American Cancer Society, 2019-2021; Miranzadeh et al., 2015; Bulsara et al., 2018).

Enquanto o tratamento cirúrgico do câncer tem como objetivo a ressecção da massa cancerosa e dos tecidos envolvidos na disseminação da doença, como linfonodos e órgãos endócrinos, a radioterapia e a quimioterapia atuam pela inibição do crescimento de células que se dividem rapidamente, interferindo especificamente na divisão celular. O sucesso do tratamento

do câncer de cabeça e pescoço está relacionado ao controle locorregional do tumor primário. Nesta situação, inclui-se a excisão de tumores com ressecção da margem de tecido clinicamente normal entre 1 e 2 cm (Bulsara et al., 2018).

A frequência da mucosite oral (MO) induzida pela quimioterapia é descrita de maneira diferente. No estudo de Raessi (2014), dos pacientes tratados com quimioterapia, pelo menos 30-40% experimentam algum grau de desconforto desse problema oral, que começa 5-10 dias após o início do regime do tratamento. No entanto, em outro estudo o autor descreve o início dos sintomas, como a sensação de irritação da mucosa começando 3-4 dias após a infusão da quimioterapia (Shankar et al., 2017).

A abordagem terapêutica com rádio ou químico é uma combinação de cirurgia oncológica (indução/neoadjuvante) ou pós-cirurgia (terapia adjuvante). Antes da cirurgia, tem como propósito reduzir a massa tumoral, possibilitando a remoção cirúrgica completa. Contudo, os estudos ainda não conseguiram demonstrar melhora na sobrevida com a adição de quimioterapia de indução (Shankar et al., 2017; Stafford, 2020).

Os agentes citotóxicos da quimioterapia afetarão todo o epitélio do trato gastrointestinal (boca, laringe e faringe), em rápida divisão celular por meio da replicação e reparo de DNA prejudicados, parada do ciclo celular, dano ao DNA e morte celular, sugerindo ainda que a microbiota oral, composta por uma grande variedade de microrganismos, estaria, nessas condições, contribuindo para o desenvolvimento da MO (Bowen et al., 2019).

Na radioterapia, normalmente, a MO leva mais tempo para se desenvolver e cicatrizar, com a ulceração aparecendo em torno de duas (02) semanas, em um ciclo de tratamento de sete (07) semanas e a resolução de três a quatro (3-4) semanas após o término do tratamento. Após o início do tratamento, a MO causa dor e dificuldades em comer, beber e falar, perda de peso e piora do estado geral. Atualmente, a radioterapia é administrada no pós-operatório (Sonis, 2009; Shaebjamee et al., 2015; Mogensen et al., 2017).

Nesse sentido, o tratamento de câncer oral, nos últimos anos, tem sido realizado por meio da *radioterapia com intensidade modulada (Intensity-Modulated Radiotherapy - IMRT)*, que usa doses de radiação mais altas que as terapias tradicionais, com uma melhor chance de controle locorregional do tumor alvo, poupando os tecidos normais e, conseqüentemente, minimizando as doses prejudiciais e os efeitos da radiação nos tecidos normais adjacentes, reduzindo a toxicidade ao tratamento e os efeitos colaterais em curto e longo prazo. (Bulsara et al., 2018).

Portanto, a ação da química e/ou radioterapia causa danos ao DNA e morte celular. O estresse oxidativo resulta na formação de *espécies reativas de oxigênio*, liberadas no interior de células epiteliais e endoteliais lesadas, aumentando o dano. Com isso, as membranas celulares estimulam macrófagos de transição e ativam o *fator nuclear (NF)-κB* e, conseqüentemente, sua ativação precede picos nas citocinas pró-inflamatórias como o TNF-α (fator necrótico do tumor), interleucina (IL)-6 e IL-1β, e regula positivamente a *ciclooxigenase-2 (COX-2)* em fibroblastos submucosos e células endoteliais. As vias independentes do NF-κB influenciam a produção de ceramida sintase, resultando na apoptose das células epiteliais basais e submucosas, levando à fase ulcerativa da MO (figura 1 e 2) (Bowen et al., 2019; Shankar et al., 2017).

1.4 DIAGNÓSTICO E TRATAMENTO

1.4.1 SAÚDE BUCAL

Estamos ainda diante da inconsistência no entendimento da epidemiologia da MO, considerada ainda incompleta. No entanto, progressos clínicos significativos foram alcançados quanto à patogênese da MO e, com isso, algumas medidas preventivas foram estabelecidas (Shankar et al., 2017).

Dessa forma, as ações para prevenção e tratamento da MO apresentam recomendações padronizadas para os cuidados com a saúde bucal, incluindo desde a aplicação de enxague bucal, a higiene dental, entre outros. Atendimento odontológico antes do início e durante a terapêutica do câncer são importantes para a saúde oral e os cuidados bucais, sendo descritos minimamente

com o uso de enxagues leves com o soro fisiológico e bicarbonato de sódio, ação considerada básica. A boa higiene bucal objetiva a manutenção da limpeza e a promoção do conforto na prevenção e tratamento da MO, reduzindo o risco de infecções orais. (McGuire et al., 2013).

Outro aspecto importante para a saúde bucal é o papel das dietas. Devido às alterações provocadas pela QT ou RT, os pacientes são orientados a eliminar alimentos que contenham açúcar processado, tabaco, álcool, produtos ácidos e condimentados, que podem exacerbar o desconforto da MO. Por esses motivos as dietas geralmente são moles e líquidas. No entanto, as recomendações alimentares precisam equilibrar a necessidade de manter a ingestão com o aumento do risco de doença bucal. A dieta adequada auxilia na redução dos sintomas da MO (Shankar et al., 2017; Kusiak, 2020).

A incidência da MO é influenciada por variáveis associadas ao paciente e ao tratamento antineoplásico. Estes fatores de risco influenciam a frequência e a gravidade da MO, alguns relacionados ao paciente, como idade (pacientes jovens), tipo de tumor (doença neoplásica), saúde bucal e dentária (higiene bucal precária antes e durante a quimioterapia), condição nutricional e sistêmica e a manutenção da função renal e hepática. Por sua vez, outros fatores de risco são associados ao medicamento administrado (citotoxicidade), à frequência de administração (prolongada ou repetida em baixa dose) e ao tratamento concomitante na forma de radiação e/ou transplante de medula óssea. Entre os agentes quimioterápicos mais estomatotóxicos, específicos do ciclo do DNA, destacamos metotrexato, bleomicina, fluorouracil (FU) e os medicamentos (por exemplo, metotrexato, etoposídeo) que aumentam o potencial de toxicidade por serem secretados na saliva (Robert et al., 2020; Chaveli-López, 2014; Chaveli-López, 2016).

1.4.2 DIAGNÓSTICO E TRATAMENTO DA MUCOSITE ORAL

Rotineiramente, a MO é diagnosticada conforme critérios comuns de toxicidade da Organização Mundial de Saúde (OMS), conforme descrito na Tabela 1 (Lalla, 2008; Yoneda et

al., 2007; Yen et al., 2012).

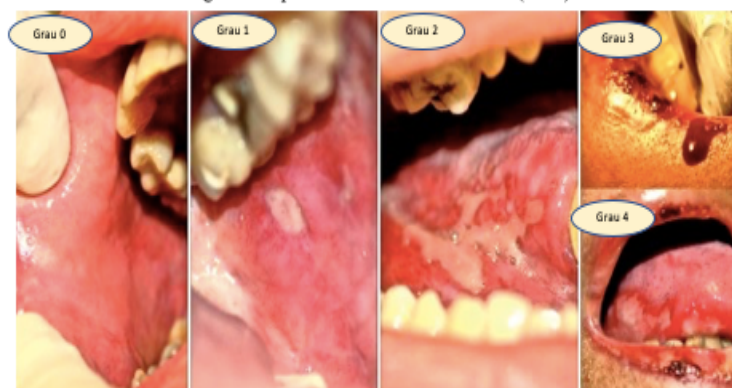
Tabela 1. Escala da Organização Mundial de Saúde (OMS) para Mucosite Oral

Grau 0	Nenhuma MO
Grau 1	Eritema e dor da mucosa
Grau 2	Ulceração irregular ou pseudomembrana
Grau 3	Ulcerações confluentes e sangramento com trauma menor
Grau 4	Necrose tecidual, sangramento espontâneo

Fonte: Lalla, 2008; Yoneda et al., 2007; Yen et al., 2012. Tradução.

A escala da OMS é considerada de fácil aplicabilidade na avaliação clínica. Importante destacar que no grau 2 observa-se o aparecimento de placas brancas descamativas; o grau 3 tem como característica marcante o aparecimento de crostas epiteliais e exsudato fibrinoso que levam à formação de pseudomembranas e ulcerações e o grau 4 é forma mais severa da MO, em que ocorre a exposição de estroma do tecido conjuntivo subjacente (Figura 3) (Lalla, 2008; Lalla et al., 2014).

Figura 3: Aspecto clínico da Mucosite Oral (OMS)



Adaptado de campos, L. et al [Laserterapia no tratamento da mucosite oral induzida por quimioterapia: relato de caso. Rev. Assoc. Paul. Cir. Dent., vol.67, n.2,](#)

Não existe consenso acerca de um protocolo de tratamento ou prevenção para a mucosite oral (MO), induzida por radioterapia sozinha (RT) ou quimioterapia concorrente (CCRT). Foram sugeridas, para o manejo dessa complicação, abordagens sistêmicas e tópicas, incluindo o uso de agentes anti-inflamatórios citoprotetores diretos, como sucralfato e antiprostaglandinas, antioxidantes, agentes não esteroides, terapia a *laser* de baixo nível, glutamina ou fatores estimulantes de colônias, drogas imunossupressoras e citoprotetores indiretos, como fatores de crescimento hematopoieticos e agentes antimicrobianos (Sahebamee et al., 2015; Yen et al., 2012).

O Grupo de Estudo da *Multinational Association of Supportive Care in Cancer* e a Sociedade Internacional de Oncologia Oral (MASCC / ISOO-Soc) desenvolveram as diretrizes da prática clínica para o manejo da MO e destacam que embora as intervenções terapêuticas direcionadas estejam sendo desenvolvidas, a profilaxia, ou mesmo seu tratamento, continuam até hoje sendo paliativos ou de suporte, e são divididos em grupos como: suporte nutricional, controle da dor, descontaminação oral, palição da boca seca, manejo da hemorragia oral e intervenções terapêuticas para mucosite oral (Lalla, 2008). Já em 2014, o MASCC / ISOO, em sua segunda revisão das diretrizes de práticas clínicas para MO, categorizou as intervenções usadas em 1) cuidados bucais básicos / boas práticas clínicas; 2) fatores de crescimento e citocinas; 3) agentes anti-inflamatórios; 4) antimicrobianos, agentes de revestimento das mucosas, anestésicos e analgésicos; 5) *laser* e outras terapias leves; 6) crioterapia; 7) agentes naturais e diversos (Lalla et al., 2014).

As intervenções terapêuticas tópicas, que foram desenvolvidas para aliviar os sintomas e combater a mucosite oral, incluem soluções de enxaguamento bucal como alopurinol, benzidamina (Lalla et al., 2014; Tsavaris et al., 1991; Abbasi et al., 2007), clorexidina (Kin-Fong and Ka Tsui, 2006; Diaz-Sanches et al., 2015; Dodd et al., 2000), sucralfato (Dodd et al., 2003), difenildramina e morfina (Cerchietti et al., 2003), fenitoina (Baharvand et al., 2010; Baharvand et al., 2015), glutamina (Dodd et al., 2000; Anderson et al., 1989), hidróxido de alumínio, pallifermina, própolis (Akhavankarbassi et al., 2016), entre outros. Esses agentes infelizmente atendem apenas a aspectos limitados e específicos da condição e são ineficazes sobre os outros. Com isso, os resultados conflitantes dos ensaios clínicos estimulam a avaliação de novos estudos (Dodd et al., 2003; Baharvand et al., 2010).

Dessa maneira, o objetivo desta revisão sistemática foi responder à seguinte pergunta focada: Qual é a eficácia das intervenções tópicas em comparação com os controles para o tratamento da mucosite oral, em pacientes com câncer?

2.OBJETIVO

2.1 Objetivo Geral

Avaliar a eficácia das intervenções tópicas no manejo clínico da mucosite oral em pacientes com câncer submetidos à QT e/ou RT.

2.2 Objetivos Específicos

Avaliar a eficácia das intervenções tópicas na redução da gravidade da MO (grau de MO) e intensidade da dor;

Avaliar e comparar a eficácia entre os diversos agentes tópicos aplicados como alternativa terapêutica para a mucosite oral, considerando o escore de eritema, ferimentos, alimentação e capacidade de beber.

3.ARTIGO

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Topical Treatment of Oral Mucositis in Cancer Patients: A Systematic Review of Randomized Clinical Trials

REVIEW

Editorial Process: Submission:02/16/2020 Acceptance:07/14/2020

Topical Treatment of Oral Mucositis in Cancer Patients: A Systematic Review of Randomized Clinical Trials

Geisa Sant Ana^{1*}, Ana Gabriela Costa Normando¹, Isabela Porto de Toledo^{1,2}, Paula Elaine Diniz dos Reis¹, Eliete Neves Silva Guerra¹

Abstract

Background and Purpose: Evidence-based protocols of topical therapy for oral mucositis (OM) induced by chemoradiotherapy (CRT) are continuously established and updated. Thus, the present systematic review aims to evaluate the scientific literature in terms of effectiveness of topical treatment of OM in cancer patients undergoing CRT. **Materials and Methods:** This systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist. Randomized clinical trials were identified through electronic database searches on CINAHL, Cochrane Library, LILACS, Livivo, PubMed, SCOPUS, and Web of Science. Grey literature was also assessed on Google Scholar, Open Grey, and ProQuest. The risk of bias in the included studies was assessed by the Cochrane Collaboration Risk of Bias Tool. **Results:** Twenty-three randomized clinical trials (n=1169 patients) met the inclusion criteria. Twenty-three different topical agents were examined and categorized into five groups: analgesics (30.4%), natural agents (21.7%), other topical agents (21.7%), antimicrobial agents (17.4%), and growth factors (8.8%). Of the included studies, 50% presented a resolution of OM within 14 days. Topical natural agents yielded good results with average resolution time of 3–7 days. The included studies generally demonstrated that patients treated with mouthwashes presented superior benefits compared to the control, depending on OM severity. **Conclusion:** Topical agents effectively reduced the severity of OM lesions and pain intensity in patients receiving chemoradiotherapy, although the effects varied by agent type. However, the heterogeneity in the results of these topical intervention studies underscores the need for standardized clinical trial methodologies. **Clinical Relevance:** Topical agents were effective in patients with severe OM lesions receiving chemoradiotherapy and are a good alternative of home care in relation to pain control, reduction of inflammation and consequent improvement in quality of life.

Keywords: Topical intervention- chemotherapy- radiotherapy- oral mucositis- randomized controlled trial

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Introduction

Oral mucositis (OM) is one of the most prevalent adverse effect of head and neck radiotherapy (RT) and chemotherapy (CT) that is characterized by an inflammatory response of the oral cavity and oropharynx. OM affects 20–40% of patients receiving conventional CT, up to 80% of patients undergoing hematopoietic stem cell transplantation and receiving high doses of CT and almost all patients undergoing head and neck RT (Dodd et al., 2003; Miranzadeh et al., 2015; Sheibani et al., 2015; Lalla et al., 2014). Generally, patients undergoing CT experience some degree of oral discomfort within 5–10 days after treatment initiation (Nagarajan, 2015), while those undergoing RT usually develop OM within 1–2 weeks of treatment. Generally, OM causes great discomfort during eating, drinking, and speaking consequently resulting in weight loss and a decline in general health condition (Sahebamee et al., 2015; Mogensen et al., 2017).

Recent reports have described the complex pathogenic mechanisms of OM, which extends beyond immediate tissue damage to involve erythematous lesions that affect the entire epithelium, leading to severe ulceration, pain, submucosal hemorrhage, and infection. OM may interfere with antineoplastic treatment, leading to treatment interruption, a decreased quality of life, and compromised patient survival (Yoneda et al., 2007; Yen et al., 2012; Lalla et al., 2008; Raber-Durlacher et al., 2010; Ferreira et al., 2017; Trotti et al., 2003). Moreover, OM leads to a considerable economic burden, since it increases costs related to symptoms management, nutritional support, secondary infection treatment, and hospitalizations (Elting et al., 2007).

Currently, OM management mainly involves pain control, oral decontamination, inflammation reduction, oral hemorrhage management, and nutritional support (Lalla et al., 2014; Lalla et al., 2008). The Mucositis Study Group of the Multinational Cancer Support

¹Health Sciences Faculty, University of Brasilia, Brasilia, Brazil. ²Brazilian Centre of Evidence Based Research, University of Santa Catarina, Florianopolis, Brazil. *For Correspondence: geisa.s.ana@gmail.com

Care Association and the International Society of Oral Oncology (MASCC/ISOO) has proposed clinical practice guidelines for the management of OM that include palliative care and assumed future targeted therapeutic interventions (Lalla et al., 2014). Several studies have investigated alternative topical interventions that may reduce the symptoms and severity of OM, including allopurinol, benzydamine (Lalla et al., 2014; Tsavaris et al., 1991; Abbasi et al., 2007), chlorhexidine (Kin-Fong and Ka Tsui, 2006; Diaz-Sanches et al., 2015; Dodd et al., 2000), sucralfate (Dodd et al., 2003), diphenhydramine, morphine (Cerchiotti et al., 2003), phenytoin (Baharvand et al., 2010; Baharvand et al., 2015), glutamine (Dodd et al., 2000; Anderson et al., 1989), aluminum hydroxide, palifermin, and propolis (Akhavankarbassi et al., 2016). Still, no evidence supports a standard systemic or topical therapy or preventive measure for OM induced by CT and/or RT.

Taking into account that in many health services, patients do not have access to strategies for the prevention of OM, it is necessary that they have an alternative of home care in relation to pain control, reduction of inflammation and consequent improvement in quality of life. Given that topical agents are more easily applied, relatively inexpensive and have fewer side effects when compared to systemic therapies, the present systematic review aimed to summarize the scientific evidence available in the literature regarding the clinical practice of using topical agents as a therapeutic alternative for OM in patients undergoing cancer treatment.

Materials and Methods

Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist (Moher et al., 2009; Shamseer et al., 2015). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under registration number CRD42017073116 (Prospero, 2017).

Study Design and terminology definition

The present study is a systematic review of randomized controlled trials that assessed topical agents for OM treatment in cancer patients undergoing CT and/or RT. Topical intervention was defined as any treatment applied to the oral mucosa with local effects, including mouthwashes, creams, ointments, and jellies.

Eligibility criteria

Inclusion criteria

This systematic review followed the PICOS (population, intervention, comparison, outcome, and study design) approach in order to define the inclusion criteria. Only randomized clinical studies (S) assessing the effects of topical agents (I) for OM treatment (O) in cancer patients aged ≥ 18 years who underwent CT and/or RT (P). Any comparisons were considered for inclusion and only full-text articles were considered.

Exclusion criteria

The exclusion criteria were (1) patient age < 18 years; (2) topical intervention for OM prevention; (3) non-randomized clinical trials; (4) reviews, letters, personal opinions, book chapters, and conference abstracts; (5) language restrictions; (6) full text unavailability; (7) studies with the same sample; and (8) use of hematopoietic stem cell transplantation as a treatment modality.

Information sources and search strategy

To identify literature published until April 17, 2019, individual search strategies were applied to the following electronic databases: CINAHL EBSCO, Cochrane Library, LILACS, Livivo, PubMed, SCOPUS, and Web of Science (Appendix 1). A gray literature search on Google Scholar, Open Grey, and ProQuest Dissertations and Theses Global was also performed. The references of included studies were manually screened for potential studies that could have been missed on database search. Duplicate references were removed using Rayyan, a reference manager software (Ouzzani et al., 2016).

Study selection

During a two-phase study selection process, two authors (GSA and AGCN) independently reviewed the titles and abstracts of identified articles in Phase 1 and selected those appearing to meet the inclusion criteria. In Phase 2, these authors independently read the full texts of all selected articles and excluded those that did not meet the inclusion criteria (Appendix 2). Disagreements between evaluators were resolved by consensus, with final decisions by a third reviewer (IPT) if needed.

Data collection process

One author (GSA) collected key data from each selected article, which were crosschecked for accuracy by a second reviewer (AGCN). Disagreements were resolved by discussion and mutual agreement among GSA, AGCN, and IPT. The following information was recorded for all included studies: author(s), publication year, country, patients' ages (years), cancer type, cancer treatment, intervention type, control type, sample size (cases and controls), follow-up period, and main conclusions (Tables 1 and 2).

Risk of bias in individual studies

The risk of bias of included trials was assessed by the Cochrane Risk of Bias (RoB) tool. "High," "low," or "unclear" risk scores were based on the randomization method; allocation concealment; blinding of participants, personnel, and outcome assessors; completeness of outcome data; and selective reporting (Higgins and Green, 2011). The reviewers compared evaluations, resolved disagreements and reported their RoB assessments using Review Manager software (RevMan 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark).

Summary measures

The primary outcome of this systematic review was a reduction in the OM severity grade based on the World Health Organization assessment scale. The secondary

outcomes were the scores for erythema, wound healing, pain intensity, and eating and drinking ability. Any type of outcome measurement was considered in this review (categorical and continuous variables).

Risk of bias across studies

Individuals using novel topical interventions for OM management were compared with individuals using placebo and/or routine mouthwashes. Clinical heterogeneity (by comparing variability among the participant's characteristics and outcomes assessed), methodological (by comparing the variability in study design and risk of bias), and statistical heterogeneity were considered in order to critically analyze the results.

Results

Study selection

In phase 1, 994 citations were identified in seven electronic databases, and 480 remained after removing duplicates. Any references were included from gray literature. After screening the titles and abstracts, 376 references were excluded as irrelevant to the research question. One more reference was included after an updated search. A manual search of the reference lists yielded no additional studies. The full texts of 105 articles were screened (phase 2), and 81 were excluded (Appendix 2). Finally, 23 were selected for the descriptive analysis. A flow chart of the study identification, inclusion, and exclusion process is shown in Figure 1.

Study characteristics

The 23 included studies (n=1,169 patients) were performed in 10 countries: Argentina (Cerchiatti et al., 2003), Austria (Sprinzl et al., 2001; Hejna et al., 2001), China (Lin et al., 2015), Iran (Miranzadeh et al., 2015; Baharvand et al., 2016; Baharvand et al., 2015; Akhavankarbassi et al., 2016; Mansouri et al., 2016; Sarvizadeh et al., 2015), Italy (Porta et al., 1994), India (Satheeshkumar et al., 2010), Spain (Cabrera-Jaime et al., 2018) Switzerland (Wayne-Bossert et al., 2010), Turkey (Erdem et al., 2014; Erden and Ipekoban, 2017), Taiwan (Yen et al., 2012), and USA (Dodd et al., 2000; Dodd et al., 2003; Leenstra et al., 2014; Limaye et al., 2013; Rothwell et al., 1990; Wadleigh et al., 1992). All articles described randomized clinical trials and were published in English during 1990–2017. The majority (47%) of the evaluated patients (552 patients) were diagnosed with head and neck cancer, followed by gastrointestinal, blood, breast, lymphatic, urinary tract, hepatocellular, and other/unknown cancers. The study sample sizes ranged from 9 (Wayne-Bossert et al., 2010) to 142 (Dodd et al., 2000).

Twenty-two studies mentioned the follow-up duration (mean, 14 days; range, <1–45 days). Different topical interventions were classified as analgesics (30.4%), natural agents (21.7%), other topical agents (21.7%), antimicrobial agents (17.4%), and growth factors (8.8%). Here, intervention refers to the provided experimental treatments, while control refers to placebo and/or routine mouthwash. Table 1 summarizes the descriptive characteristics of studies assessing patients undergoing

CT exclusively. Table 2 summarizes the descriptive characteristics of studies assessing patients undergoing chemoradiotherapy and RT.

Risk of bias within studies

Six studies had a high RoB due to one or more domains which compromised the reliability of the results (Cerchiatti et al., 2003; Sprinzl et al., 2001; Lin et al., 2015; Satheeshkumar et al., 2010; Limaye et al., 2013; Hejna et al., 2001). Five studies had a low RoB in all evaluated domains (Miranzadeh et al., 2015; Baharvand et al., 2010; Baharvand et al., 2015; Sarvizadeh et al., 2015; Cabrera-Jaime et al., 2018) and could be considered more reliable studies (Figure 2). “Unclear risk,” defined as insufficient or missing data that difficult the assessment of the original study, occurred in the “random sequence generation” and “allocation concealment” domains of 11 (Dodd et al., 2003; Yen et al., 2012; Cerchiatti et al., 2003; Sprinzl et al., 2001; Erden and Ipekoban, 2017; Lin et al., 2015; Porta et al., 1994; Erdem et al., 2014; Limaye et al., 2013; Rothwell and Spektor, 1990; Wadleigh et al., 1992) and 12 studies (Yen et al., 2012; Cerchiatti et al., 2003; Anderson et al., 1989; Sprinzl et al., 2001; Erden and Ipekoban, 2017; Porta et al., 1994; Satheeshkumar et al., 2010; Wayne-Bossert et al., 2010; Erdem and Güngörmüş, 2014; Wadleigh et al., 1992; Hejna et al., 2001; Mansouri et al., 2012), respectively. “High risk” in the “blinding of participants and personnel” domain occurred in six studies (Cerchiatti et al., 2003; Sprinzl et al., 2001; Lin et al., 2015; Satheeshkumar et al., 2010; Limaye et al., 2013; Hejna et al., 2001). Most studies (n=18, 78.3%) had a low RoB in the domains of “incomplete outcome data” and “selective reporting” (Miranzadeh et al., 2015; Yen et al., 2012; Cerchiatti et al., 2003; Baharvand et al., 2015; Erden and Ipekoban, 2017; Lin et al., 2015; Mansouri et al., 2016; Sarvizadeh et al., 2015; Porta et al., 1994; Satheeshkumar et al., 2010; Wayne-Bossert et al., 2010; Erdem et al., 2014; Leenstra et al., 2014; Limaye et al., 2013; Rothwell and Spektor, 1990; Hejna et al., 2001; Cabrera-Jaime et al., 2018; Cerchiatti et al., 2002).

Results of individual studies

All 23 articles described different types of topical agents for OM treatment. Despite heterogeneity in the evaluated topical interventions, most patients receiving CT and/or RT exhibited reduced OM severity (i.e., grade) and/or pain intensity.

Synthesis of results

Treatment characteristics

The treatment characteristics are shown in Tables 1 and 2. More than half (n=63,2%) of the included patients received CT alone (Table 1), while almost 46% (n=537) received RT and/or CT (Table 2). Most studies of different cancer treatments identified the incidence of mucositis as a secondary outcome. Twelve studies evaluated the treatment of head and neck cancer, while 11 included several types of cancer (Tables 1 and 2). Of the 23 topical agents evaluated in this descriptive analysis, natural agents, analgesics, antimicrobial agents, growth factors, and others were applied to 209, 148, 98, 32, and

outcomes were the scores for erythema, wound healing, pain intensity, and eating and drinking ability. Any type of outcome measurement was considered in this review (categorical and continuous variables).

Risk of bias across studies

Individuals using novel topical interventions for OM management were compared with individuals using placebo and/or routine mouthwashes. Clinical heterogeneity (by comparing variability among the participant's characteristics and outcomes assessed), methodological (by comparing the variability in study design and risk of bias), and statistical heterogeneity were considered in order to critically analyze the results.

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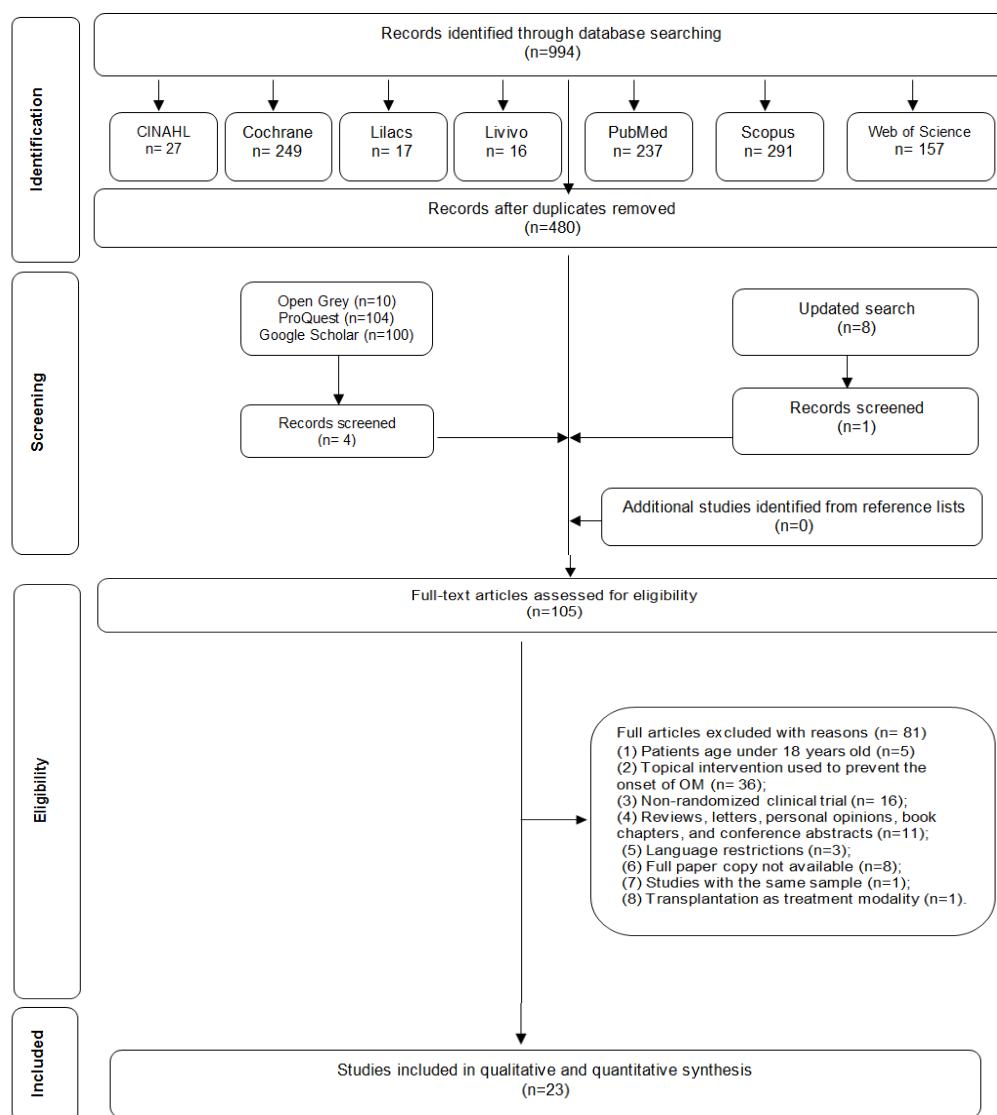


Figure 1. Flow Diagram of Literature Search and Selection Criteria Adapted from PRISMA.

65 patients, respectively (Table 3).

Effects of interventions

Studies on natural topical agents evaluated propolis (Akhavankarbassi et al., 2016), royal jelly (Erdem and Güngörmüş, 2014), Aloe vera gel (Mansouri et al., 2016), Achillea millefolium distillate (Miranzadeh et al., 2015), dioctahedral smectite and iodine glycerin (Lin et al., 2015), and Plantago major extract (Cabrera-Jaime et al., 2018). These agents reduced OM intensity (grade 3) and pain within 4–14 days after the intervention (Miranzadeh et al., 2015; Akhavankarbassi et al., 2016; Lin et al., 2015; Mansouri et al., 2016; Erdem and Güngörmüş, 2014). Natural topical agents, especially propolis (Akhavankarbassi et al., 2016) (n=20) and royal jelly (Erdem and Güngörmüş, 2014) (n=51), yielded

superior results, with mean OM resolution times of 3–7 days (Table 4). Moreover, 65% of patients using propolis were completely healed by day 7, while 98% of those using royal jelly were completely healed in 3–4 days. Both treatments were administered as mouthwashes (Akhavankarbassi et al., 2016; Erdem and Güngörmüş, 2014). Like propolis, honey was associated with rapid recovery times and quicker healing than control treatments in patients with CT- and RT-induced mucositis (Aghamohammadi and Hosseinimehr, 2016; Tonkaboni et al., 2015; Maria et al., 2017; Zakaria, 2017). Honey also significantly reduced the severity of radiation-induced grade 3–4 mucositis (Amanat et al., 2017).

Topical analgesics are essential for pain control, and consequently for an appropriate food and fluid intake, communication, and sleep (Quinn et al., 2017). Studied

Table 1. Summary of the Descriptive Characteristics of Studies that Assessed Patients Undergoing Chemotherapy for Various Types of Cancers (n=11)

Study characteristics	Population characteristics			Intervention characteristics			Main conclusions
	Author Year Country	Age Mean/range (years)	Cancer type	Cancer treatment	Intervention (# of cases)	Control (# of controls)	
Baharvand et al. 2010 Iran	C: 38.8±13.8 K: 33.3±14.8	Solid tumors (2) Blood malignancies (10)	Chemotherapy	0.5% Phenytoin mouthwash (6)	Placebo mouthwash (6)	14	Two weeks after study initiation, mucositis severity was significantly lower in the treatment group than in the control group. Lesions persisted for 4.5 days in the treatment group and 3–7 days in the control group. The minimum duration of lesion healing in the intervention group was 6 days, and 2 subjects required >14 days. The mucositis grade was determined using the WHO scale, and pain intensity was measured using an NRS.
Cabrera-Jaime et al. 2018 Spain	59.5±14.3	Solid tumors	Chemotherapy	NaHCO ₃ -Plantain (15)	NaHCO ₃ -NaHCO ₃ (16) NaHCO ₃ -Chlorhexidine (19)	7–14	There were no statistically significant differences in healing time or pain intensity among the three treatment groups. This study was the first to assess Plantago major for the treatment of OM in cancer patients. The intervention was not superior to sodium bicarbonate or chlorhexidine. However, a double dose of sodium bicarbonate (in mouthwash) was associated with a shorter healing time (5 vs. 7 days). This finding supports the use of alkaline oral care products as an evidence-based therapeutic approach to OM prevention and treatment and provides a focus for future research and care strategies. The mucositis grade was determined using the WHO scale, and pain intensity was measured using VAS.
Dodd et al. 2000 USA	C: 59.24±14.89 K1: 59.47±14.27 K2: 57.39±14.62	Breast Colon Non-Hodgkin lymphoma Other	Chemotherapy	0.12% Chlorhexidine gluconate mouthwash (51)	"Magic" mouthwash (42) Salt and soda (49)	12	No significant differences in the time to OM sign and symptom resolution (P=0.59) or the patients' pain ratings over time were observed among the three mouthwash groups. All three oral rinses appeared to provide no value other than the benefit of systematic oral hygiene protocol. Pain intensity was measured using an NRS. The study was limited by the lack of description of the mucositis grading scale.
Erden et al. 2017 Turkey	≥18	Gastric Colon Pancreatic Rectal Metastatic cancer Unknown etiology	Chemotherapy	Chlorhexidine mouthwash (30)	Control group: cryotherapy (water mouthwash) (30)	21	There was a statistical difference in the moment of transition to oral nutrition for patients in the experimental groups. The time of oral nutrition time in the first experimental group that applied chlorhexidine was lower than in the group that applied cryotherapy and the control group (P<0.01). Chlorhexidine mouthwash is recommended for the treatment of OM. The mucositis grade was determined using the WHO scale. The study was limited by the lack of description of the pain measurement scale.
Hejna et al. 2001 Austria	C: 58 (39–77) K: 73 (48–80)	Colorectal Gastric Pancreatic Breast Cholangiocellular	Chemotherapy	GM-CSF mouthwash (15)	AA mouthwash (16)	2.8 ± 0.7 (2–4)a	Topical GM-CSF treatment significantly reduced the duration and time to resolution of OM, including the pretreatment plus treatment periods (P=0.0008), as well as the duration of treatment until the complete remission of lesions (P<0.0001) when compared with AA. Topical GM-CSF may therefore be the treatment of choice for OM induced by standard cytotoxic chemotherapy. The mucositis grade was measured using the WHO scale. The study was limited by the lack of description of the pain measurement scale.
Limaye et al. 2013 USA	C: 1x/day: 61(42–66) 3x/day: 54 (26–64) 6x/day: 52 (42–56) K: 54 (18–63)	Head and neck	Chemotherapy	AG013 (ActoBiotic) mouthwash (17) 1x/day (5) 3x/day (6) 6x/day (6)	Placebo mouthwash (8)	14	AG013 appeared to effectively reduce mucositis induced by PF (cisplatin, 5-fluorouracil) or TPF (docetaxel, cisplatin, 5-fluorouracil), but additional studies with larger sample sizes are recommended. Subjects treated with AG013 exhibited a 35% decrease in the mean percentage of days with UOM (WHO grade >2) vs. placebo. Furthermore, 29% of subjects who received AG013 had 0 or 1 day of UOM, whereas all subjects who received placebo experienced at least 2 days of UOM. The mucositis grade was determined using the WHO scale. The study was limited by the lack of description of the pain measurement scale.
Lin et al. 2015 China	53.0 (19–78)	Lymphoma Breast Colorectal	Chemotherapy	DSIG (dioctahedral smectite and iodine glycerin) cream (63)	Topical mouthwash (gentamicin, saline and Vitamin B12) (67)	5	DSIG cream significantly reduced the duration of OM and relieved symptoms. A significant downward trend in mucosal lesions was observed in the DSIG cream subgroup vs. the topical buccal rinse group after 5 days of treatment. The DSIG cream also significantly reduced the OM repair time (4.68±0.98 vs. 8.76±1.80 days, P<0.001). The mucositis was measured using the OAG. The study was limited by the lack of description of the pain measurement scale.

Table 1. Continued

Study characteristics		Population characteristics			Intervention characteristics		
Author Year Country	Age Mean/range (years)	Cancer type	Cancer treatment	Intervention (# of cases)	Control (# of controls)	Follow-up (days)	Main conclusions
Mansouri et al. 2016 Iran	C: 46.25±18.17 K: 47.78±18.28	Acute myeloid leukemia Acute lymphocytic leukemia	Chemotherapy	Aloe vera mouthwash (32)	Routine mouthwash: normal saline, chlorhexidine, and nystatin (32)	3–14	The 2 groups differed significantly in terms of stomatitis intensity and pain between days 3 and 14 (P<0.05 and P=0.013, respectively), thus confirming the study hypothesis and demonstrating that Aloe vera could effectively reduce stomatitis intensity and pain. The mucositis grade was measured using the WHO scale. Pain intensity was measured using a VAS.
Miranzadeh et al. 2015 Iran	C: 56.46±14.32 K: 55.54±14.01	Gastrointestinal Leukemia Lung Bone Kidney Breast	Chemotherapy	Achillea millefolium distillate mouthwash (28)	Routine mouthwash: lidocaine, dexamethasone, sucralfate, diphenhydramine solution (28)	14	The severity of OM was reduced on days 7 and 14 after the intervention, with only 3.6% and 0% of the experimental group exhibiting grade 3 or 4 OM, respectively, vs. more than 60% of the control group. A. millefolium distillate mouthwash reduced the severity of OM without side effects and could be used by patients during chemotherapy. The mucositis grade was measured using the WHO scale. The study was limited by a lack of description of the pain measurement scale.
Porta et al. 1994 Italy	57.8 (30–68)	Colon Gastric Rectal	Chemotherapy	Allopurinol mouthwash (22)	Placebo mouthwash (22)	7	Allopurinol mouthwash completely or partially resolved OM in 40.9% and 45.4% of patients, respectively. OM persisted for an average of 4 days in the allopurinol group, vs. 7.5 days in the control group. Allopurinol appears to be simple and cost-effective. The study was limited by a lack of description of the scales used to measure the mucositis grade and pain.
Wadleigh et al. 1992 USA	39–71 years	Head and neck Esophageal Hepatocellular Acute myelogenous leukemia	Chemotherapy	Vitamin E topical oil (9)	Placebo oil (coconut and soybean oils) (9)	5	Six of 9 patients in the vitamin E group achieved a complete resolution of their lesions within 4 days of initiating therapy (median: 3 days), whereas 8 of 9 patients receiving placebo did not achieve a complete resolution during the 5-day study period (P=0.025). The topical administration of vitamin E may be effective for the treatment of chemotherapy-induced mucositis. The mucositis grade was measured using WHO scale. Pain intensity was measured using a VAS.

WHO, World Health Organization; NRS, numeric rating scale; C, case; K, control; VAS, visual analogue scale; OAG, Oral Assessment Guideline; OM, oral mucositis; GM-CSF, granulocyte-macrophage colony-stimulating factor; UOM, ulcerative oral mucositis.

topical analgesics included 0.5% or 1% phenytoin (Baharvand et al., 2010; Baharvand et al., 2015), 1% or 2% morphine (Cerchietti et al., 2003; Sarvizadeh et al., 2015; Vayne-Bossert et al., 2010), doxepin (Leenstra et al., 2014), and sucralfate (Dodd et al., 2003). Phenytoin mouthwash significantly improved patients' pain and quality of life (Baharvand et al., 2010; Baharvand et al., 2015). Only one study on topical morphine described pain relief 28 minutes after the first use of mouthwash, with an average duration of relief of 216 minutes (Cerchietti et al., 2003). Doxepin rinse significantly reduced mouth and throat pain due to OM caused by RT and CT for HNC (P<0.001), however no significant correlation was found between this topical intervention and OM severity (Leenstra et al., 2014). Similarly, the use of topical sucralfate had no significant impact on OM severity (P=0.85) or pain reduction (P=0.54) (Dodd et al., 2003), suggesting the need for further randomized clinical trials with these agents.

The studied topical antimicrobials included chlorhexidine gluconate (Dodd et al., 2000; Erden and Ipekoban, 2017), nystatin + diphenhydramine + tetracycline + hydrocortisone (Rothwell and Spektor, 1990), and triclosan (Satheeshkumar et al., 2010). Erden (2017) evaluated the efficacy of chlorhexidine on oral nutrition transition times in patients with CT-induced OM and observed a significant difference in days for OM resolution between the chlorhexidine (8.53±1.04) and control

groups (13.53±1.69). In contrast, Dodd (2000) found no significant differences in the time of OM resolution (P=0.59) or in patients' pain ratings over time among chlorhexidine and control mouthwashes groups. The use of oral rinse containing nystatin, diphenhydramine, tetracycline and hydrocortisone resulted in reduced OM severity compared to control group (Rothwell and Spektor, 1990), as well as the use of triclosan was also capable of reducing the severity and duration of OM (Satheeshkumar et al., 2010).

Regarding growth factors, two studies on human granulocyte and macrophage colony-stimulating factor (GM-CSF) (Sprinzl et al., 2001; Hejna et al., 2001) yielded conflicting results. Hejna et al., (2001) recommended the topical use of GM-CSF for the treatment of CT-induced OM in patients with head and neck cancer since this topical treatment was effective on reducing the time of resolution of OM (P=0.0008) when compared to control. On the other hand, Sprinzl et al., (2001) did not recommend this application since there was no statistical difference between GM-CSF and conventional mouthwash in terms of OM severity. This difference may have probably occurred because in the study by Hejna et al., (2001) the patients were submitted to CT only, while in the study by Sprinzl et al., (2001) the patients were submitted to an association of CT and head and neck RT, causing a more severe mucositis.

Other topical agents included vitamin E oil (Wadleigh

Table 2. Summary of the Descriptive Characteristics of Studies that Assessed Patients Receiving Chemoradiotherapy and Radiotherapy for Head and Neck Cancer and Various Types of Cancer (n=12).

Study characteristics	Population characteristics			Intervention characteristics			Main Conclusions
	Author Year Country	Age Mean/range (years)	Cancer type	Cancer treatment	Intervention (# of cases)	Control (# of controls)	
Akhavan-Karbassi et al. 2016 Iran	≥18	Head and neck	Chemotherapy and radiotherapy	Propolis mouthwash (20)	Placebo mouthwash (sterile water with allowed additives) (20)	7	On day 7 of the trial, 65% of patients in the propolis group were completely healed. There were significant differences in the incidence of OM, wound, and erythema between the propolis and placebo groups, but no significant differences in eating and drinking abilities. Propolis-based mouth rinse is safe and effective for the treatment of RT-induced mucositis. The mucositis grade was determined using the WHO scale. The study was limited by a lack of description of the pain measurement scale.
Baharvand et al. 2015 Iran	C: 52.75±13.23 K: 56±14.65	Head and neck	Chemotherapy and radiotherapy	1% Phenytoin mouthwash (8)	Normal saline mouthwash (8)	21	The quality of life improved in both groups, but this outcome was significantly more obvious in the phenytoin group vs. the normal saline group (P<0.001). Although both groups achieved pain relief, it was more pronounced with phenytoin. Both groups experienced similar decreases in mucositis severity (P=0.154). The mucositis grade was determined using the WHO scale. Pain intensity was measured using an NRS.
Cerchietti et al. 2003 Argentina	First block: 56.9 (44–69) Second block: 55.6 (47–78)	Head and neck	Chemotherapy and radiotherapy	1% and 2% morphine mouthwash (First block: 10) (Second block: 22)	Water mouthwash (32)	First block: 1 (60 minutes) Second block: 1 (15, 30, 60, 120, 180 minutes)	A 2% morphine solution yielded better pain relief than a 1% solution (P=0.0238). Patients enrolled in the second block received a 2% morphine mouthwash, and the time to good or complete pain relief was 28 min after the first mouthwash, with an average duration of relief of 216 min. Topical morphine mouthwashes could be useful for alleviating painful chemoradiotherapy-induced stomatitis. The mucositis grade was measured using the WHO scale. Pain intensity was measured using an NRS.
Dodd et al. 2003 USA	C: 53.7 (18.1) K: 56.6 (13.0)	Head and neck	Chemotherapy and radiotherapy	Sucralfate mouthwash (14)	Salt + soda mouthwash (16)	30	The average worst severity ratings and average pain intensity scores did not differ significantly between the two mouthwash groups (P=0.85 and 0.54, respectively). Moreover, salt and soda are less expensive than micronized sucralfate. The study was limited by a lack of description of the scales used to measure the mucositis grade and pain intensity.
Erdem et al. 2014 Turkey	C: 53.8 (13.08) K: 50.69 (25.42)	Various types of malignancies	Chemotherapy and radiotherapy	Royal jelly (51)	Benzylamine hydrochloride and nystatin mouthwashes (52)	14	Royal jelly improved the signs and symptoms of OM and considerably reduced the time to healing, such that after 3–4 days all lesions had resolved in the jelly group, except for 1 case of grade 2 mucositis. The mucositis grade was determined using the WHO scale. The study was limited by a lack of description of the pain measurement scale and a lack of specification of the type(s) of cancer for which patients received treatment.
Leenstra et al. 2014 USA	C: 62 (39–93) K: 60 (37–86)	Head and neck	Chemotherapy and radiotherapy	Doxepin mouthwash (69)	Placebo mouthwash (71)	1 (5, 15, 30, 60, 120, 240 minutes)	Compared with placebo, doxepin yielded greater mean reductions in mouth and throat pain (-4.7 vs. -9.1; P<0.001). A doxepin rinse was significantly superior to placebo for treating OM pain due to RT ± chemotherapy for HNC. Further study is needed to fully elucidate this use of a doxepin rinse. The mucositis grade was determined using the WHO scale. Pain intensity was measured using an NRS.
Rothwell et al. 1990 USA	45–73	Head and neck	Radiotherapy	Test mouthwash (nystatin, diphenhydramine, tetracycline, and hydrocortisone) (5)	Cherry syrup containing sorbitol, magnesia and alumina suspension, and vitamins (7)	42	The topical application of nystatin, diphenhydramine, tetracycline, and hydrocortisone may reduce the incidence of RT-associated mucositis. Although the experimental group of patients developed mucositis, their symptoms were less severe and were not exacerbated beyond the third week of therapy. Pain intensity was measured on a scale of 0–5. The study was limited by a lack of description of the scale used to determine the mucositis grade.

Table 2. Continued

Study characteristics	Population characteristics			Intervention characteristics			Main Conclusions
	Author Year Country	Age Mean/range (years)	Cancer type	Cancer treatment	Intervention (# of cases)	Control (# of controls)	
Sarvzadeh et al. 2015 Iran	C: 47.5±14.6 K: 52.1±11.0	Head and neck	Chemotherapy and radiotherapy	2% Morphine mouthwash (15)	Magic mouthwash (magnesium aluminum hydroxide, viscous lidocaine, and diphenhydramine) (13)	6	Topical morphine effectively reduced the severity of OM in head and neck cancer patients. On day 6, a significant reduction in mucositis severity was observed in patients who received morphine, compared to those receiving the magic solution (P=0.045). Further studies with larger sample sizes and longer follow-ups are needed prior to the recommendation of routine topical morphine use. The mucositis grade was determined using the WHO scale. The study was limited by a lack of description of the pain measurement scale.
Satheeskumar et al. 2010 India	C: 63.67±11.5 K: 65.9±12.9	Head and neck	Radiotherapy	Triclosan mouthwash (12)	Sodium bicarbonate mouthwash (12)	45	Triclosan may be effective for the management of RT-induced OM. There was no significant statistical difference between the intervention and control groups until the likelihood of progressing from grade 2-3 (P>0.05). Only one patient (8%) in the intervention group progressed to grade 4 mucositis, compared to 10 patients (83%) in the control group. A triclosan mouth rinse was superior to a sodium bicarbonate mouth rinse for the control of OM in terms of severity and duration. The mucositis grade was determined using the WHO scale. Pain intensity was measured using a VAS.
Sprinzel et al. 2001 Austria	C: 60 (49-82) K: 57 (42-75)	Head and neck	Chemotherapy and radiotherapy	GM-CSF mouthwash (Leukomax) (17)	Conventional mouthwash (pantocain, hydrocortisone acid, cional kreussler, and bepanthen) (18)	21	In a statistical analysis, GM-CSF was not superior to conventional mouthwash in terms of OM, pain perception, incidence of secondary infection, and abnormal hematological parameters. Therefore, topical GM-CSF is not recommended for the treatment of OM induced by chemoradiotherapy in patients with HNC. The mucositis grade was determined using the WHO scale. Pain intensity was measured using a VAS.
Vayne-Bossert et al. 2010 Switzerland	55.1±3.0	Head and neck	Chemotherapy and radiotherapy	2% Morphine mouthwash (4)	Placebo mouthwash (quinine diHCl) (5)	7	A morphine mouthwash yielded a mean (±SD) pain relief duration of 124±98 min vs. 126±81 minutes for placebo (P>0.01). It was not possible to conclude that local morphine via mouthwash can effectively treat local pain associated with OM. This result is distinct from the good peripheral analgesic effects of local opioids when applied to painful malignant and non-malignant skin ulcers. The mucositis grade was determined using the WHO scale. The study was limited by a lack of description of the pain measurement scale.
Yen et al. 2012 Taiwan	C: 51.1 (10.6) K: 54.8 (12.1)	Head and neck	Chemotherapy and radiotherapy (HNC)	5% Phenylbutyrate mouthwash (17)	Placebo mouthwash (same base as intervention) (19)	Patients began treatment after randomization and continued until 4 weeks after completion of RT	The intensity of ulceration in response to a cumulative RT dose of 6000-7000 cGy, which induced the most devastating phase of mucositis, was significantly lower in patients who received phenylbutyrate vs. those who received placebo (P=0.0485). Phenylbutyrate mouthwash appeared to significantly decrease the impact of OM in patients receiving RT or chemoradiotherapy for HNC. The mean duration of severe mucositis (WHO ≥ 3) was 2 days in the phenylbutyrate group and 12 days in the placebo group. The mucositis grade was determined using the WHO scale. The study was limited by a lack of description of the pain measurement scale.

WHO, World Health Organization; NRS, numeric rating scale; C, case; K, control; VAS, visual analogue scale; OM, oral mucositis; GM-CSF, granulocyte and macrophage colony-stimulating factor; RT, radiotherapy; HNC: head and neck cancer; SD, standard deviation

et al., 1992), allopurinol (Porta et al., 1994), AG013 (ActoBiotic) (Limaye et al., 2013), and 5% phenylbutyrate (Yen et al., 2012). Topical vitamin E oil, which has antioxidant effects, was reported by Wadleigh et al., (1992) that found 66% of patients receiving vitamin E

intervention experienced a complete resolution of their lesions within 4 days of treatment initiation (median: 3 days), became asymptomatic, and were able to eat. The major pharmacological effects of allopurinol and its main metabolite, alloxanthin, involve the inhibition of xanthine

Table 3. Evidence of the Efficacies of Different Topical Interventions for Chemotherapy/Radiotherapy-Induced Oral Mucositis

Group	Topical intervention (n)	Objective	Oral mucositis model	Sex (% female)	Follow-up (days)	Most significant result	Proposed mechanism	Ref.
Topical natural agents	Propolis mouthwash (20)	This study aimed to determine the ability of propolis treatment to reduce the OM score, oral cavity erythema, and wound formation and to restore normal eating and drinking abilities in patients undergoing chemotherapy for head and neck carcinoma	Clinical studies of chemotherapy (methotrexate)-induced mucositis in patients with head and neck cancer	Not estimated	7	All variables (erythema, wound formation, eating and drinking ability, and mucositis) improved significantly with propolis. Wound and OM scores decreased significantly in the placebo group. Interestingly, 65% of patients in the propolis group were completely healed at day 7 of the trial.	Anti-inflammatory, antibacterial, analgesic, collagen synthesis	Akhavan-Karbassi et al.
	Royal jelly mouthwash (51)	This study was conducted to evaluate the effect of royal jelly administered via mouthwash on oral mucositis in patients undergoing radiotherapy and chemotherapy.	Clinical studies of chemoradiotherapy-induced mucositis in cancer patients	61%	4	Times to healing: 3–4 days for most grades in the royal jelly group vs 13–14 days for mucositis grades 2–3 in the control group	Anti-inflammatory, antioxidant, antibiotic	Erdem et al. 2014
	Aloe vera mouthwash (32)	The study aimed to evaluate the effectiveness of Aloe vera for reducing pain intensity and oral mucositis scores.	Clinical studies of chemotherapy-induced mucositis in patients with acute myeloid leukemia and acute lymphocytic leukemia	70%	3–14	The two groups differed significantly in terms of the intensity of stomatitis and pain between days 3 and 14 ($P < 0.05$ and 0.013 , respectively).	Antioxidant (polysaccharides, anthraquinone, lectin, superoxide dismutase and glycoprotein, amino acids, vitamins C and E and minerals)	Mansouri et al. 2016
	Achillea millefolium distillate mouthwash (28)	This study was designed to investigate the effect of A. millefolium distillate-containing solution on chemotherapy-induced oral mucositis.	Clinical studies of chemotherapy-induced mucositis in patients with gastrointestinal, lung, bone, kidney, breast, and blood (leukemia) cancers	57.10%	14	In the experimental group, the average healing time for OM grade 3 or 4 was 14 days. However, at this time, the rate of patients with OM grade 3 or 4 was increased to over 60% in the control group.	Anti-inflammatory, antimicrobial	Miranzadeh et al. 2015
	DSIG (dioctahedral smectite and iodine glycerin) cream (63)	This study aimed to compare the efficacy of DSIG cream with a topical mouth rinse (containing saline, gentamicin, and Vitamin B12) for treating chemotherapy-induced oral mucositis.	Clinical studies on chemotherapy-induced mucositis in patients with lymphoma, breast cancer, colorectal cancer	27.70%	5	In the experimental group, on day 5, 85.7% of patients had achieved complete regression of oral mucositis ($P < 0.001$). However, only two patients (3.0%) obtained completed OM regression in the control group.	Naturally adsorbent DSIG (antimicrobial)	Lin et al. 2015
	Plantain (Plantago major extract) mouthwash (15)	This study aimed to evaluate the efficacy of a Plantago major extract mouthwash versus 0.12% chlorhexidine or 5% sodium bicarbonate (aqueous) for the treatment of oral mucositis symptoms in cancer patients with solid tumors.	Clinical studies on the symptomatic treatment of chemotherapy-induced oral mucositis in patients with solid malignancies.	Not estimated	14	Plantago major extract was no more beneficial than a sodium bicarbonate or chlorhexidine solution for the treatment of oral mucositis.	Anti-inflammatory	Cabrera-Jaime et al. 2018
Topical Analgesics	0.5% Phenytoin mouthwash (6)	This study aimed to compare a phenytoin mouthwash, an analgesic and wound-healing agent, with placebo for the treatment of chemotherapy-induced oral mucositis.	Clinical studies of chemotherapy-induced mucositis in solid tumors and blood malignancies.	58.30%	14	A minimum duration of 6 days was required for lesion healing in the experimental group. The proportion of patients with grade 2–3 oral mucositis was reduced to 0% after 1 week.	Analgesic and wound healing agent; "Phenytoin promotes wound healing by a number of mechanisms including stimulation of fibroblast proliferation, facilitation of collagen deposition by inhibiting the activity of collagenase enzymes, and antibacterial activity. Furthermore, by stabilizing neural fiber membranes and reducing the inflammatory response, phenytoin contributes to the topical pain relief.	Baharvand et al. 2010

Table 3. Continued

Group	Topical intervention (n)	Objective	Oral mucositis model	Sex (% female)	Follow-up (days)	Most significant result	Proposed mechanism	Ref.
	1% Phenytoin mouthwash (8)	This study aimed to investigate the effectiveness of a 1% phenytoin mouthwash in patients undergoing chemotherapy or radiotherapy for head and neck carcinoma.	Clinical studies of chemoradiotherapy-induced mucositis in various head and neck cancers, including oropharyngeal squamous cell carcinoma (SCC), tongue SCC, laryngeal SCC, mucoepidermoid carcinoma of the submandibular gland, and supraglottic SCC	Not estimated	21	Initially, seven patients presented with grade 2 mucositis; after 3 weeks, this number was reduced to four patients. The mucositis severity decreased in both groups, but this difference was not significant.	Analgesic and wound-healing agent; quality of life evaluation	Baharvand et al. 2015
	1% and 2% Morphine mouthwash (first block: 10)	This study aimed to analyze the effect of a topical morphine mouthwash on damaged tissues in patients with head and neck cancer who developed mucositis induced by chemotherapy or radiation therapy.	Clinical studies on chemoradiotherapy-induced mucositis in patients with head and neck cancer	28.10%	First block: 1 (60 minutes) Second block: 1 (15, 30, 60, 120, 180 minutes)	After treatment (2% morphine mouthwash; second block), the mean duration of severe swallowing-related pain was 5.17±1.47 days, and the duration of severe functional impairment was 1.52±1.31 days. Results indicate that for patients with radiotherapy-induced stomatitis, morphine mouthwashes may be an effective and safe therapy to relieve pain and shorten the duration of functional impairment.	Systemic analgesic	Cerchietti et al. 2003
	2% Morphine mouthwash (15)	This study aimed to investigate the efficacy of topical morphine in comparison with a routine therapy (i.e., magic mouthwash) for the management of oral mucositis in patients with head and neck cancer.	Clinical studies of chemoradiotherapy-induced mucositis in patients with head and neck cancer	63.30%	6	On day 6, a significant reduction in mucositis severity was observed in patients who received morphine vs. those who received the magic solution (P=0.045).	Systemic analgesic; "Some evidence verified that opioid receptors are expressed on oral epithelial cells and morphine can accelerate the cell migration, which in turn can help to the wound healing process."	Sarvzadeh et al. 2015
	2% Morphine mouthwash (4)	This study aimed to determine whether a morphine-containing mouthwash solution could decrease oral pain associated with radiotherapy- and/or chemotherapy-induced oral mucositis.	Clinical studies of chemoradiotherapy induced mucositis in patients with head and neck or breast cancer	77.80%	7	The symptom intensities did not differ statistically over the 6-day study period or between the two arms (analysis of variance).	Systemic analgesic (pain alleviation)	Vayne-Bossert et al. 2010
	Doxepin mouthwash (69)	This study aimed to test the efficacy of a doxepin oral rinse as an anesthetic/analgesic for oral mucositis pain caused by the treatment of head and neck cancer.	Clinical studies of chemoradiotherapy-induced mucositis in patients with head and neck cancer	19–21%	<1	In the second phase, the reported use of additional analgesia at the 2- and 4-hour time points did not differ between the doxepin and placebo arms.	Systemic analgesic	Leenstra et al. 2014
	Sucralfate mouthwash (14)	This study compared the efficacy of micronized sucralfate (Carafate R) mouthwash versus salt + soda mouthwash in terms of the severity of mucositis and mucositis-related pain the and time required for lesion healing in in patients with head and neck carcinoma who developed radiotherapy-induced mucositis.	Clinical studies of radiotherapy-induced mucositis in patients with head and neck cancer	30%	30	No significant differences in the average pain intensity scores were observed between the two mouthwash groups (t=0.63, P= 0.54).	Increased prostaglandin and mucus production, increased mucosal blood flow, increased growth factor binding due to sucralfate, a basic albumin salt of sucrose octasulfate	Dodd et al. 2003
Topical antimicrobial	0.12% Chlorhexidine gluconate mouthwash (51)	This study analyzed the effectiveness of three mouthwashes used to treat chemotherapy-induced mucositis.	Clinical studies of chemotherapy-induced mucositis in patients with breast and colon cancer and non-Hodgkin lymphoma	64%	12	The three groups had similar times to the cessation of mucositis signs and symptoms (mean: 6.6–7.17 days).	Antimicrobial, anti-inflammatory	Dodd et al. 2000

Table 3. Continued

Group	Topical intervention (n)	Objective	Oral mucositis model	Sex (% female)	Follow-up (days)	Most significant result	Proposed mechanism	Ref.
	Chlorhexidine mouthwash (30)	This study aimed to compare the effects of chlorhexidine vs. a control on oral nutrition transition times in patients with chemotherapy-induced oral mucositis.	Clinical studies of chemotherapy-induced mucositis in patients with gastric, colon, pancreatic, rectal, and metastatic cancer (unknown cause)	50%	7–14	The mean transition time for oral nutrition differed significantly between the chlorhexidine group (8.53 ± 1.04 days) and the control groups (13.53 ± 1.69 days). This finding was statistically significant ($P < 0.05$).	Antimicrobial, anti-inflammatory	Erden et al. 2016
	Nystatin, diphenhydramine, tetracycline, and hydrocortisone mouthwash (5)	This study aimed to analyze the effectiveness of an oral rinse comprising hydrocortisone, nystatin, tetracycline, and diphenhydramine for controlling radiation-related mucositis.	Clinical studies of radiotherapy-induced mucositis in patients with head and neck cancer	33%	42	As expected, the control group exhibited increasingly severe mucositis with increasing exposure to irradiation throughout the course of therapy. Mucositis severity increased in the experimental group during the first 3 weeks, but then decreased during the last 3 weeks of therapy.	Antimicrobial, anti-inflammatory	Rothwell et al. 1990
	Triclosan mouthwash (12)	This study aimed to determine the effectiveness of triclosan for the management of radiation-induced oral mucositis and to compare the effectiveness of a triclosan mouth rinse with that of a conventional sodium bicarbonate mouth rinse. Mucositis grade, body weight, food intake, and pain were assessed during weekly follow-ups throughout and after radiation treatment.	Clinical studies of radiotherapy-induced mucositis in patients with oral carcinoma	even distribution between men and women.	24	A triclosan mouth rinse was superior to a sodium bicarbonate mouth rinse for reducing the severity and duration of oral mucositis. The groups differed in terms of the recovery of mucositis from grade 3 to grade 0, which required a mean of 23.6 days in the intervention group vs. 36.5 days in the control group.	Antimicrobial, anti-inflammatory	Satheeshkumar et al. 2010
Topical growth factors	GM-CSF mouthwash (15)	This study aimed to analyze the efficacy of topical GM-CSF (molgramostim) vs. the combined topical use of an antiseptic agent (povidone-iodine) and amphotericin B (AA) in patients with chemotherapy-induced mucositis (World Health Organization; WHO) grades I–III.	Clinical studies of chemotherapy-induced mucositis in patients with head and neck cancer	54.80%	2–4	The ranges of therapy duration until complete remission of oral mucositis were 2–4 days in the GM-CSF group and 5–8 days in the AA group. Therefore, topical GM-CSF was recommended for the treatment of chemotherapy-induced oral mucositis in patients with head and neck cancer.	Growth factor activity	Hejna et al. 2001
	GM-CSF mouthwash (Leukomax) (17)	This study compared GM-CSF with a conventional mouthwash (pantocain, hydrocortisone acid, cional kreussler, and bepanthen).	Clinical studies of chemoradiotherapy-induced mucositis in patients with advanced carcinoma (stage III–IV) of the oral cavity, oropharynx, and hypopharynx.	44%	21	GM-CSF was not superior to the conventional mouthwash in terms of oral mucositis, pain perception, the incidence of secondary infection, or hematological abnormalities. Therefore, topical GM-CSF was not recommended for the treatment of chemoradiotherapy-induced oral mucositis in patients with head and neck cancer	Growth factor activity	Sprinzel et al. 2001
Other topical agents	Vitamin E topical oil (9)	This study compared the efficacy of Vitamin E topical oil with that of a placebo oil (coconut and soybean oils).	Clinical studies of chemotherapy-induced mucositis in patients with head and neck, esophageal, and hepatocellular cancers and myelogenous leukemia	Not estimated	5	In the intervention group, 66% of patients experienced complete lesion resolution within 4 days of initiation (median: 3 days). Patients who responded to treatment became asymptomatic and were able to eat.	Antioxidant	Wadleigh et al. 1990

Table 3. Continued

Group	Topical intervention (n)	Objective	Oral mucositis model	Sex (% female)	Follow-up (days)	Most significant result	Proposed mechanism	Ref.
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	Nystatin, diphenhydramine, tetracycline, and hydrocortisone mouthwash (5)	This study aimed to analyze the effectiveness of an oral rinse comprising hydrocortisone, nystatin, tetracycline, and diphenhydramine for controlling radiation-related mucositis.	Clinical studies of radiotherapy-induced mucositis in patients with head and neck cancer	33%	42	As expected, the control group exhibited increasingly severe mucositis with increasing exposure to irradiation throughout the course of therapy. Mucositis severity increased in the experimental group during the first 3 weeks, but then decreased during the last 3 weeks of therapy.	Antimicrobial, anti-inflammatory	Rothwell et al. 1990
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	GM-CSF mouthwash (Leukomax) (17)	This study compared GM-CSF with a conventional mouthwash (pantocain, hydrocortisone acid, cional kreussler, and bepanthen).	Clinical studies of chemoradiotherapy-induced mucositis in patients with advanced carcinoma (stage III–IV) of the oral cavity, oropharynx, and hypopharynx.	44%	21	GM-CSF was not superior to the conventional mouthwash in terms of oral mucositis, pain perception, the incidence of secondary infection, or hematological abnormalities. Therefore, topical GM-CSF was not recommended for the treatment of chemoradiotherapy-induced oral mucositis in patients with head and neck cancer	Growth factor activity	Sprinzi et al. 2001
Other topical agents	Vitamin E topical oil (9)	This study compared the efficacy of Vitamin E topical oil with that of a placebo oil (coconut and soybean oils).	Clinical studies of chemotherapy-induced mucositis in patients with head and neck, esophageal, and hepatocellular cancers and myelogenous leukemia	Not estimated	5	In the intervention group, 66% of patients experienced complete lesion resolution within 4 days of initiation (median: 3 days). Patients who responded to treatment became asymptomatic and were able to eat.	Antioxidant	Wadleigh et al. 1990

Table 3. Continued

Group	Topical intervention (n)	Objective	Oral mucositis model	Sex (% female)	Follow-up (days)	Most significant result	Proposed mechanism	Ref.
	Allopurinol mouthwash (22)	This study analyzed the efficacy of an allopurinol mouthwash for the treatment of 5-fluorouracil-induced stomatitis.	Clinical studies of chemotherapy-induced mucositis in patients with colon, gastric, and rectal cancers	Not estimated	4	Allopurinol mouthwashes resolved stomatitis completely in 40.9% of patients, with responses seen in 86.3%. The duration of oral mucositis was 4 days in the allopurinol group vs. 7 days in the control group.	Enzyme inhibition	Porta et al. 1994
	AG013 (ActoBiotic) mouthwash (17)	This study evaluated the safety and tolerability of orally applied AG013 at three daily dosages.	Clinical studies of chemotherapy-induced mucositis in patients with head and neck cancer	24%	30	AG013 reduced the mean percentage of days with ulcerative oral mucositis by 35%, compared to the placebo, and reduced the number of unplanned office and emergency room visits. Moreover, 29% of subjects who received AG013 had 0–1 day of ulcerative oral mucositis, compared to at least 2 days overall.	Biotherapeutic activity	Limaye et al. 2013
	5% Phenylbutyrate mouthwash (17)	This study evaluated the safety and efficacy of a 5% phenylbutyrate mouthwash used to mitigate oral mucositis during radiation therapy or concurrent chemoradiotherapy in patients with head and neck cancer.	Clinical studies of chemoradiotherapy-induced mucositis in patients with oral cavity carcinoma, nasopharyngeal carcinoma, oropharyngeal carcinoma, and hypopharyngeal carcinoma	35%	21	During the most devastating phase of mucositis (radiotherapy), the intensity of ulceration was significantly lower in patients receiving phenylbutyrate mouthwash vs. those receiving placebo (P=0.0485). Patients treated with phenylbutyrate were more likely to retain the ability to intake food orally vs. controls (9.0% vs. 3.8%, P=0.0085, chi-square test).	Histone deacetylase (HDAC) inhibitor	Yen et al. 2012

GM-CSF, granulocyte-macrophage colony-stimulating factor; OM, oral mucositis;

Table 4. Mucositis frequency and time for healing by cancer treatment and topical intervention agent

Cancer treatment	Topical intervention (n)	Cancer type	Time to healing (days)	References
Chemoradiotherapy	Royal jelly mouthwash (51)	Various types of malignancies	3–4	Erdem et al. 2014
Chemotherapy	Aloe vera mouthwash (32)	Acute myeloid leukemia, acute lymphocytic leukemia	3–14	Mansouri et al. 2016
Chemotherapy	DSIG (dioctahedral smectite and iodine glycerin) cream (63)	Lymphoma, breast cancer, colorectal cancer	5	Lin et al. 2015
Chemotherapy	Allopurinol mouthwash (22)	Colon, gastric, rectal cancers	5	Porta et al. 1994
Chemotherapy	Vitamin E topical oil (9)	Head and neck, esophageal, and hepatocellular cancers; acute myelogenous leukemia	5	Wadleigh et al. 1992
Chemoradiotherapy	1–2% Morphine mouthwash (51)	Head and neck cancer	6–7	Sarvizadeh et al. 2015; Cerchetti et al. 2003; Vayne-Bossert et al. 2010
Chemoradiotherapy	Propolis mouthwash (20)	Head and neck cancer	7	Akhavan-Karbassi et al. 2016
Chemotherapy	NaHCO ₃ -plantain (15)	Solid tumors	7–14	Cabrera-Jaime et al. 2018
Chemotherapy	0.12% Chlorhexidine gluconate mouthwash (51)	Breast, colon, and other cancers; non-Hodgkin lymphoma	12	Dodd et al. 2000
Chemotherapy	Achillea millefolium distillate mouthwash (28)	Gastrointestinal leukemia; lung, bone, kidney, and breast cancers	14	Miranzadeh et al. 2015
Chemotherapy	0.5% Phenytoin mouthwash (6)	Solid tumors, blood malignancies	14	Baharvand et al. 2010
Chemotherapy	AG013 (ActoBiotic) mouthwash (17)	Head and neck	14	Limaye et al. 2013

* Including only topical interventions associated with resolutions ≤ 14 days.

Table 3. Continued

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	5% Phenylbutyrate mouthwash (17)	This study evaluated the safety and efficacy of a 5% phenylbutyrate mouthwash used to mitigate oral mucositis during radiation therapy or concurrent chemoradiotherapy in patients with head and neck cancer.	Clinical studies of chemoradiotherapy-induced mucositis in patients with oral cavity carcinoma, nasopharyngeal carcinoma, oropharyngeal carcinoma, and hypopharyngeal carcinoma	35%	21	During the most devastating phase of mucositis (radiotherapy), the intensity of ulceration was significantly lower in patients receiving phenylbutyrate mouthwash vs. those receiving placebo (P=0.0485). Patients treated with phenylbutyrate were more likely to retain the ability to intake food orally vs. controls (9.0% vs. 3.8%, P=0.0085, chi-square test).	Histone deacetylase (HDAC) inhibitor	Yen et al. 2012

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* Including only topical interventions associated with resolutions ≤14 days.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Akhavan-Karbassi et al. 2016	+	?	+	+	+	+	+
Baharvand et al. 2010	?	+	+	+	+	+	+
Baharvand et al. 2015	+	+	+	+	+	+	+
Cabrera-Jaime et al. 2018	+	+	+	+	+	+	+
Cerchiatti et al. 2003	+	?	-	-	+	+	+
Dodd et al. 2000	+	+	+	+	+	+	+
Dodd et al. 2003	?	+	+	+	?	?	+
Erdem et al. 2014	?	?	+	+	+	+	+
Erden et al. 2016	?	?	?	?	+	+	+
Hejna et al. 2001	+	?	-	?	+	+	+
Leenstra et al. 2014	+	+	+	?	?	?	+
Limaye et al. 2013	?	+	-	?	+	+	+
Lin et al. 2015	?	-	-	?	+	+	+
Mansouri et al. 2016	+	?	?	+	+	+	+
Miranzadeh et al. 2015	+	+	+	+	+	+	+
Porta et al. 1994	?	?	+	?	?	+	+
Rothwell et al. 1990	?	+	+	+	+	+	+
Sarvizadeh et al. 2015	+	+	+	+	+	+	+
Satheeshkumar et al. 2010	+	?	-	-	+	+	+
Sprinzel et al. 2001	?	?	-	-	?	?	+
Vayne-Bossert et al. 2010	+	?	+	?	+	+	+
Wadleigh et al. 1992	?	?	+	?	?	?	+
Yen et al. 2012	?	?	+	?	+	+	+

Figure 2. Risk of Bias Summary: review authors' judgements about each risk of bias item for each included study (+ = low; - = high; ? = unclear).

oxidase (Porta et al., 1994; Fields et al., 1996). Porta et al., (1994) reported that all patients receiving CT developed grade 2–3 stomatitis, which resolved completely or partially by allopurinol mouthwash in 40.9% and 86.3% of patients, respectively. AG013 is an oral rinse containing the recombinant *L. lactis* strain engineered to secrete the mucosal protectant hTFF1. Limaye et al., (2013) reported that treatment with AG013 led to a 35% reduction in the mean duration of ulcerative OM (UOM) vs. placebo and reduced the numbers of unplanned office and emergency room visits. Furthermore, 29% of individuals receiving AG013 had none or 1 day of UOM; all other participants had ≥2 days of UOM. Yen et al., (2012) demonstrated that patients receiving a mouthwash containing phenylbutyrate and histone deacetylase inhibitor had significantly lower intensity of OM ulceration than those receiving a placebo (p=0.0485); suggesting that phenylbutyrate enhanced oral nutrition intake compared to the control (P=0.0085).

Twenty-one of 23 topical agents were administered as mouthwashes while one study used as a cream vehicle (Lin et al., 2015). Treatment with mouthwashes containing

the following 15 agents were effective on reducing the duration of severe OM (functional impairment): propolis (Akhavankarbassi et al., 2016), royal jelly (Erdem and Güngörmüş, 2014), Aloe vera gel (Mansouri et al., 2016); Achillea millefolium distillate (Miranzadeh et al., 2015), 0.5% phenytoin (Baharvand et al., 2015), chlorhexidine gluconate (Dodd et al., 2000), chlorhexidine (Erden and Ipekoban, 2017), nystatin+diphenhydramine+tetracycline and hydrocortisone, triclosan (Satheeshkumar et al., 2010), GM-CSF (Hejna et al., 2001), allopurinol (Porta et al., 1994), AG013 (Limaye et al., 2013), and 5% phenylbutyrate (Yen et al., 2012).

Risk of bias across studies

The use of similar and robust methodologies in the included studies reduced the potential for misinterpretation. All included studies were randomized controlled trials and the majority were considered to be of moderate risk of bias, for these reasons, were considered to be relatively homogeneous in terms of methodological characteristics. When it comes to clinical aspects, the studies were considered similar in terms of participant characteristics and outcomes, but considerably heterogeneous in relation to topical interventions, consequently impacting the unfeasibility of a meta-analysis. Nevertheless, the results of our review could be considered consistent and trustworthy.

Discussion

Summary of evidence

Cancer is one of the most common causes of death worldwide and its incidence has been gradually increasing, mainly due to both aging and growth of the population, as well as changes in the prevalence and distribution of the main risk factors for cancer (Bray et al., 2018). Its treatment depends on several factors that include the type of the tumor, the location, the clinical and pathological staging as well as the patient's health status. Currently, there are several types of CT and RT that can be used alone or in combination to manage the disease. Both therapies are extremely effective in destroying tumor cells but as a result they end up causing side effects so damaging that treatment often needs to be interrupted. One of the most prevalent side effects is oral mucositis, which affects around 40% of patients undergoing chemotherapy, such as Methotrexate, Cisplatin and 5-Fluorouracil, and almost 100% of patients undergoing head and neck RT (Sonis, 2009; Scully et al., 2003).

The pathobiology of oral mucositis is divided into 5 phases: initiation, signaling, amplification, ulceration and healing. Once the chemotherapeutic drug or radiotherapy contacts the mucosa, several chemical changes occur in the tissue, resulting in the release of reactive oxygen species that in turn activate transcription factors capable of amplifying the production and release of inflammatory cytokines. This amplification causes a cycle of constant production of cytokines that result in clinically evident and painful ulceration susceptible to bacterial colonization and secondary infection (Sonis, 2009). Thus, the need of early intervention is fundamental in order to reduce the severity

of the injury. Although many therapeutic agents have been investigated, no effective prevention or treatment standard protocol has been completely successful to handle OM (Dos Santos Filho et al., 2018).

It is not uncommon in clinical dentistry practice for patients to ask for medications that they can apply at home in order to reduce pain and control inflammation. Prevention with photobiomodulation has been widely accepted and applied, but, unfortunately, in many health services such therapy is still inaccessible to many patients (Zadik et al., 2019). Thus, topical therapeutic alternatives for OM are necessary, which are cost-effective, easily applicable and cause less additional side effects in patients who are already systemically compromised.

For the best of our knowledge, this is the first systematic review of randomized clinical trials that compiled the highest level of scientific evidence available in the literature in terms of efficacy of topical agents for OM in patients with cancer. The included studies generally demonstrated that patients treated with mouthwash presented superior benefits when compared to the control, depending on mucositis severity.

In the case of natural agents, royal jelly treatment was effective during the initial but not final stages of OM, and the corresponding control group benefited from benzydamine hydrochloride and nystatin mouthwash (Erdem and Güngörmüş, 2014). Moreover, propolis mouthwash improved oral health in patients undergoing CT (Akhavankarbassi et al., 2016), thus reinforcing the recommendations for therapeutic mouthwashes to promote oral hygiene, prevent/treat infections, moisten the oral cavity, and provide pain relief (Quinn et al., 2017). Both honey and propolis exert various anti-inflammatory effects, antioxidant activity, prostaglandin synthesis-inhibiting activity in mucosal tissue, pro-immune effects via the stimulation of phagocytic activity and cellular immunity, and healing effects in epithelial tissues. Propolis is rich in iron and zinc, which are important elements in collagen synthesis (Akhavankarbassi et al., 2016; Erdem and Güngörmüş, 2014; Zakaria, 2017). The anti-inflammatory agents *Achillea millefolium* distillate (Miranzadeh et al., 2015) and *Plantago major* extract (Cabrera-Jaime et al., 2018) yielded different responses. *Achillea millefolium* mouthwash improved the mean healing time of grade 3–4 OM to 14 days, whereas *Plantago major* extract was not superior to control treatment (sodium bicarbonate or chlorhexidine). However, *Plantago major* extract reduced the healing time from 7 to 5 days when combined with sodium bicarbonate in a mouthwash. Accordingly, strategies involving oral hygiene products are evidence-based therapeutic approaches to mucositis prevention and treatment (Cabrera-Jaime et al., 2018). The antioxidant activity of topical Aloe vera gel is mediated by polysaccharides, anthraquinone, lectin, superoxide dismutase, glycoproteins, amino acids, vitamins C and E, and minerals. Mansouri et al., (2016) reported significantly reduced pain and OM intensity between 3 and 14 days after the use of Aloe vera mouthwash ($p < 0.05$ and 0.013 , respectively).

Among topical analgesics, phenytoin mouthwash yielded significant improvements in pain and quality of

life (Baharvand et al., 2010; Baharvand et al., 2015). The topical antimicrobial chlorhexidine exhibited activity against gram-positive and gram-negative bacteria and fungi and had minimal systemic adverse reactions when used at a low concentration, which reduced absorption in the gastrointestinal tract (Dodd et al., 2000; Erden and Ipekoban, 2017).

GM-CSF is a hematopoietic growth factor that promotes neutrophil proliferation and differentiation. Previously, Liang et al., (2017) reported that GM-CSF could prevent and treat CT- and RT-induced OM in patients with head and neck cancer. In our review, two studies reported conflicting results regarding the efficacy of topical GM-CSF for OM (Sprinzl et al., 2001; Hejna et al., 2001), although this discrepancy might have been related to the use of RT. Specifically, RT-induced OM begins with inflammation of the oral mucosa, tongue, and pharynx, followed by a normal tissue lesion for 7–98 days (Limaye et al., 2013; Maria et al., 2017; Sonis, 2010).

In addition to the primary outcome of the present review, which was to assess the effect of topical therapies currently available on OM control, some studies have contemplated other secondary outcomes. Nine included studies discussed the importance of oral hygiene, monitoring and controlling of opportunistic infections via antimicrobial treatments and preventive dental protocols, including selective extractions, restorations, and fluoride programs. These randomized controlled trials addressed the reduction of the incidence of sepsis in patients with OM, a considerable risk factor reported in most studies (Dodd et al., 2003; Akhavankarbassi et al., 2016; Sprinzl et al., 2001; Erden and Ipekoban, 2017; Mansouri et al., 2016; Sarvizadeh et al., 2015; Satheeshkumar et al., 2010; Rothwell and Spektor, 1990; Hejna et al., 2001).

Limitations

This review had some limitations that should be considered. First, the methodological quality was overall moderate, mainly due to heterogeneity of the studies as a consequence of the large number of topical interventions. Second, there was also heterogeneity in terms of presentation of results among the studies, as some analyzed treatment evolution according to OM severity while others presented results with medians. Moreover, there was a wide variation on duration of the interventions, ranging from 1 day to 4 weeks. Due to all this considerable heterogeneity among reviewed studies, a meta-analysis could not be conducted. The absence of pain measurement scales was also a limitation.

In conclusion, in this review, the efficacy of topical agents for OM in cancer patients undergoing CT and/or RT was evaluated. Particularly, topical natural agents yielded good results and significant improvements in the patients' quality of life. Generally, topical agents reduced the OM severity and pain intensity in patients receiving CT and RT, although the effects varied among interventions. However, the heterogeneity of the studies' results demonstrates the need to standardize the validated assessment instruments and similar interventions that would enable comparisons and analyses of treatment effects based on well-designed randomized clinical trials.

Acknowledgments

Compliance with Ethical Standards

Ethical approval This article does not contain any studies involving human participants or animals that were performed by any of the authors.

Informed consent Formal consent is not required for this type of study.

Conflict of Interest

The authors declare that they have no conflict of interest.

Abbreviations

OM, oral mucositis; CT, chemotherapy; RT, radiotherapy; RoB, risk of bias; GM-CSF, granulocyte and macrophage colony-stimulating factor; UOM, ulcerative oral mucositis.

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4. CONSIDERAÇÕES FINAIS

Considerando os pressupostos da demanda cada vez mais necessária por qualidade máxima do cuidado em saúde, e mais especificamente na melhoria das condições de saúde do paciente oncológico comprometido pela MO, que é responsável pelo aumento dos custos hospitalares e redução da qualidade de vida dos pacientes, surgiu a proposta desta revisão sistemática. Sabendo, ainda que em muitos serviços de saúde os pacientes não têm acesso a estratégias de prevenção da MO, consideramos na proposta da RS a necessidade de buscar alternativas no cuidado domiciliar em relação ao controle da dor, redução da inflamação e consequente melhora na qualidade de vida. Nesta perspectiva, os agentes tópicos são mais facilmente aplicados, relativamente baratos e apresentam menos efeitos colaterais quando comparados às terapias sistêmicas.

Portanto, os objetivos desse estudo consistiam resumir as evidências científicas disponíveis na literatura sobre a prática clínica do uso de agentes tópicos como alternativa terapêutica para MO em pacientes em tratamento de câncer submetidos à QT e/ou RT. Envolveria avaliar a eficácia das intervenções tópicas na redução da inflamação/gravidade da MO (grau de MO), intensidade e controle da dor, escore de eritema, capacidade de deglutição, fatores envolvidos no gerenciamento da MO.

Dos 23 estudos incluídos na RS, destacamos que a geleia real (mel) e aloe vera, agentes tópicos naturais, apresentaram o menor tempo de cura da MO, variando entre 3 a 4 dias. Outro agente natural a ser citado é a própolis com tempo de cura em até 7 dias, melhorando a saúde bucal de pacientes submetidos a quimiorradioterapia.

No que concerne às limitações desse estudo, foi observado uma heterogeneidade quanto apresentação dos resultados entre os estudos, pois alguns analisaram a evolução do tratamento

de acordo com a gravidade da MO, enquanto outros apresentaram resultados com medianas. Além disso, houve uma grande variação na duração das intervenções, com intervalo entre 1 dia a 4 semanas. Devido a toda essa heterogeneidade considerável entre os estudos revisados, uma meta-análise não pôde ser conduzida. A ausência de escalas de mensuração da dor também foi uma limitação.

5. CONCLUSÃO

Particularmente, os agentes naturais tópicos produziram bons resultados e melhorias significativas na qualidade de vida dos pacientes. Além do desfecho primário da presente revisão, que foi avaliar a efeito das intervenções tópicas atualmente disponíveis no controle da MO, alguns estudos contemplaram outros desfechos secundários. Geralmente, os agentes naturais tópicos reduziram a gravidade da MO (grau 3) e a intensidade da dor em pacientes que receberam QT e RT. Não é incomum na prática clínica odontológica os pacientes solicitarem medicamentos que possam aplicar em casa para reduzir a dor e controlar a infecção.

Assim, esses achados se destacam como alternativa terapêutica tópica para MO, com baixo custo, de fácil aplicação, menos efeitos colaterais e acessível a toda população brasileira. E assim, reforçam as recomendações de enxaguatórios bucais terapêuticos para promover a higiene oral, prevenir / tratar infecções, umedecer a cavidade oral e proporcionar alívio da dor.

Os resultados deste estudo contribuem como alternativa para resolubilidade terapêutica nos tratamentos da mucosite oral com custo-benefício, propiciando aos pacientes oncológicos comprometidos pela MO a melhoria das condições de saúde, que é responsável pelo aumento dos custos hospitalares, ampliando o acesso aos pacientes assistidos pelo Sistema Único de Saúde (SUS).

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1.Apêndice

Appendix.1 Search strategies with appropriated key words and MeSH terms

Database	Search (January 31st, 2018; updated on April 17, 2019)
CINAHL	("mucosal inflammation" OR "inflamed mucous membranes" OR mucositis OR "oral mucositis" OR "mouth ulcer" OR stomatitis OR "radiation induced mucositis" OR "mucosa irritation" OR "mucosal irritation" OR mucositis OR "mucosal barrier injury" OR "MBI" OR "mucosal injury") AND (neoplasm OR neoplasms OR cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies OR lymphoma OR leukemia OR "hematological malignancies") AND ("Sucralfate Mouth Wash" OR "Phenytoin mouthwash" OR "benzydamine oral rinse" OR "benzydamine mouthwash" OR "Xinjingjie mouthrinse" OR "Caphosol mouthwash" OR "Doxepin rinse" OR "supersaturated calcium phosphate mouth rinse" OR "Phenylbutyrate mouthwash" OR "Allopurinol mouth rinse" OR "Colchicine mouthwash" OR "Doxepin rinse" OR "Morphine mouthwashes" OR "Sucralfate mouthwash" OR "Povidone-iodine" OR "chamomile mouthwash" OR "chlorhexidine mouthwash" OR "Allopurinol mouthwashes" OR mouthwash OR "mouth wash" OR honey OR propolis OR "propolis extract" OR beeswax OR "matricaria recutita" OR "manuka honey" OR glutamine OR chlorhexidine OR zinc OR "aloe vera" OR peppermint OR "calendula officinalis" OR chamomile OR "topical agents" OR "topical treatment" OR "topical application" OR "topical interventions") AND ("Randomized controlled trials" OR "Randomized controlled trial" OR "Randomized clinical trial" OR "clinical trials" OR "clinical trial" OR "random clinical trial" OR "random clinical trials" OR "controlled trials" OR "controlled trial")
Cochrane Library	<i>("mucosal inflammation" OR "inflamed mucous membranes" OR mucositis OR "oral mucositis" OR "mouth ulcer" OR stomatitis OR "radiation induced mucositis" OR "mucosa irritation" OR "mucosal irritation" OR mucositis OR "mucosal barrier injury" OR "MBI" OR "mucosal injury") in Title, Abstract, Keywords AND (neoplasm OR neoplasms OR cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies OR lymphoma OR leukemia OR "hematological malignancies") in Title, Abstract, Keywords AND ("Sucralfate Mouth Wash" OR "Phenytoin mouthwash" OR "benzydamine oral rinse" OR "benzydamine mouthwash" OR "Xinjingjie mouthrinse" OR "Caphosol mouthwash" OR "Doxepin rinse" OR "supersaturated calcium phosphate mouth rinse" OR "Phenylbutyrate mouthwash" OR "Allopurinol mouth rinse" OR "Colchicine mouthwash" OR "Doxepin rinse" OR "Morphine mouthwashes" OR "Sucralfate mouthwash" OR "Povidone-iodine" OR "chamomile mouthwash" OR "chlorhexidine mouthwash" OR "Allopurinol mouthwashes" OR mouthwash OR "mouth wash" OR honey OR propolis OR "propolis extract" OR beeswax OR "matricaria recutita" OR "manuka honey" OR glutamine OR chlorhexidine OR zinc OR "aloe vera" OR peppermint OR "calendula officinalis" OR chamomile OR "topical agents" OR "topical treatment" OR "topical application" OR "topical interventions") in Title, Abstract, Keywords in Trials.</i>
LILACS	("mucosite oral" OR "oral mucositis" OR mucosite OR mucositis)) AND (tw:(câncer OR cancer OR neoplasma OR neoplasm OR tumor)) AND (tw:(mel OR honey OR camomila OR chamomile OR "enxagatório bucal" OR mouthwash OR glutamine OR chlorhexidine OR zinc OR "aloe vera" OR peppermint OR "calendula officinalis" OR "topical agents" OR "topical treatment" OR "agentes tópicos"))
LIVIVO	TI=("mucosal inflammation" OR "inflamed mucous membranes" OR mucositis OR "oral mucositis" OR "mouth ulcer" OR stomatitis OR "radiation induced mucositis" OR "mucosa irritation" OR "mucosal irritation" OR mucositis OR

	<p>"mucosal barrier injury" OR "MBI" OR "mucosal injury") AND TI=(neoplasm OR neoplasms OR cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies OR lymphoma OR leukemia OR "hematological malignancies") AND TI=("Sucralfate Mouth Wash" OR "Phenytoin mouthwash" OR "benzylamine oral rinse" OR "benzylamine mouthwash" OR "Xinjingjie mouthrinse" OR "Caphosol mouthwash" OR "Doxepin rinse" OR "supersaturated calcium phosphate mouth rinse" OR "Phenylbutyrate mouthwash" OR "Allopurinol mouth rinse" OR "Colchicine mouthwash" OR "Doxepin rinse" OR "Morphine mouthwashes" OR "Sucralfate mouthwash" OR "Povidone-iodine" OR "chamomile mouthwash" OR "chlorhexidine mouthwash" OR "Allopurinol mouthwashes" OR mouthwash OR "mouth wash" OR honey OR propolis OR "propolis extract" OR beeswax OR "matricaria recutita" OR "manuka honey" OR glutamine OR chlorhexidine OR zinc OR "aloe vera" OR peppermint OR "calendula officinalis" OR chamomile OR "topical agents" OR "topical treatment" OR "topical application" OR "topical interventions")</p>
PubMed	<p>("Mucositis"[Mesh Terms] OR "mucosal inflammation" OR "inflamed mucous membranes" OR mucositis OR "oral mucositis" OR "mouth ulcer" OR stomatitis OR "radiation induced mucositis" OR "mucosa irritation" OR "mucosal irritation" OR mucositis OR "mucosal barrier injury" OR "MBI" OR "mucosal injury") AND ("Neoplasms"[Mesh Terms] OR neoplasm OR neoplasms OR cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies OR lymphoma OR leukemia OR "hematological malignancies") AND ("Sucralfate Mouth Wash" OR "Phenytoin mouthwash" OR "benzylamine oral rinse" OR "benzylamine mouthwash" OR "Xinjingjie mouthrinse" OR "Caphosol mouthwash" OR "Doxepin rinse" OR "supersaturated calcium phosphate mouth rinse" OR "Phenylbutyrate mouthwash" OR "Allopurinol mouth rinse" OR "Colchicine mouthwash" OR "Doxepin rinse" OR "Morphine mouthwashes" OR "Sucralfate mouthwash" OR "Povidone-iodine" OR "chamomile mouthwash" OR "chlorhexidine mouthwash" OR "Allopurinol mouthwashes" OR mouthwash OR "mouth wash" OR honey OR propolis OR "propolis extract" OR beeswax OR "matricaria recutita" OR "manuka honey" OR glutamine OR chlorhexidine OR zinc OR "aloe vera" OR peppermint OR "calendula officinalis" OR chamomile OR "topical agents" OR "topical treatment" OR "topical application" OR "topical interventions") AND ("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")</p>
Scopus	<p>TITLE-ABS-KEY("mucosal inflammation" OR "inflamed mucous membranes" OR mucositis OR "oral mucositis" OR "mouth ulcer" OR stomatitis OR "radiation induced mucositis" OR "mucosa irritation" OR "mucosal irritation" OR mucositis OR "mucosal barrier injury" OR "MBI" OR "mucosal injury") AND TITLE-ABS-KEY(neoplasm OR neoplasms OR cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies OR lymphoma OR leukemia OR "hematological malignancies") AND TITLE-ABS-KEY("Sucralfate Mouth Wash" OR "Phenytoin mouthwash" OR "benzylamine oral rinse" OR "benzylamine mouthwash" OR "Xinjingjie mouthrinse" OR "Caphosol mouthwash" OR "Doxepin rinse" OR "supersaturated calcium phosphate mouth rinse" OR "Phenylbutyrate mouthwash" OR "Doxepin rinse" OR "Allopurinol mouth rinse" OR "Colchicine mouthwash" OR "Doxepin rinse" OR "Morphine mouthwashes" OR "Sucralfate mouthwash" OR "Povidone-iodine" OR "chamomile mouthwash" OR "chlorhexidine mouthwash" OR "Allopurinol mouthwashes" OR mouthwash OR "mouth wash" OR honey OR propolis OR "propolis extract" OR beeswax OR "matricaria recutita" OR "manuka honey" OR glutamine OR chlorhexidine OR zinc OR "aloe vera" OR peppermint OR "calendula officinalis" OR chamomile OR "topical agents" OR "topical treatment" OR "topical application" OR "topical interventions") AND TITLE-ABS-KEY("Randomizes controlled trials" OR "Randomized controlled trial" OR "Randomized clinical</p>

	<i>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 (LIMITTO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “sh”) OR LIMIT-TO (DOCTYPE, “ip”))</i>
Web of Science	TS=("mucosal inflammation" OR "inflamed mucous membranes" OR mucositis OR "oral mucositis" OR "mouth ulcer" OR stomatitis OR "radiation induced mucositis" OR "mucosa irritation" OR "mucosal irritation" OR mucositis OR "mucosal barrier injury" OR "MBI" OR "mucosal injury") AND TS=(neoplasm OR neoplasms OR cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies OR lymphoma OR leukemia OR "hematological malignancies") AND TS=("Sucralfate Mouth Wash" OR "Phenytoin mouthwash" OR "benzylamine oral rinse" OR "benzylamine mouthwash" OR "Xinjingjie mouthrinse" OR "Caphosol mouthwash" OR "Doxepin rinse" OR "supersaturated calcium phosphate mouth rinse" OR "Phenylbutyrate mouthwash" OR "Allopurinol mouth rinse" OR "Colchicine mouthwash" OR "Doxepin rinse" OR "Morphine mouthwashes" OR "Sucralfate mouthwash" OR "Povidone-iodine" OR "chamomile mouthwash" OR "chlorhexidine mouthwash" OR "Allopurinol mouthwashes" OR mouthwash OR "mouth wash" OR honey OR propolis OR "propolis extract" OR beeswax OR "matricaria recutita" OR "manuka honey" OR glutamine OR chlorhexidine OR zinc OR "aloe vera" OR peppermint OR "calendula officinalis" OR chamomile OR "topical agents" OR "topical treatment" OR "topical application" OR "topical interventions") AND TS=("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")
Google Scholar	Search 1: "oral mucositis" AND (cancer OR neoplasm) AND (mouthwash OR "topical treatment" OR honey OR chlorhexidine OR chamomile OR peppermint OR zinc OR glutamine OR "aloe vera" OR propolis OR beeswax) AND ("randomized controlled trials" OR "clinical trials") Search 2: all in the title: mouthwash OR "topical treatment" OR honey OR chlorhexidine OR chamomile OR peppermint OR zinc OR glutamine OR "aloe vera" OR propolis OR beeswax "oral mucositis"
Open Grey	"oral mucositis" AND treatment
ProQuest	TI,AB("mucosal inflammation" OR "inflamed mucous membranes" OR mucositis OR "oral mucositis" OR "mouth ulcer" OR stomatitis OR "radiation induced mucositis" OR "mucosa irritation" OR "mucosal irritation" OR mucositis OR "mucosal barrier injury" OR "MBI" OR "mucosal injury") AND TI,AB(neoplasm OR neoplasms OR cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies OR lymphoma OR leukemia OR "hematological malignancies") AND TI,AB("Sucralfate Mouth Wash" OR "Phenytoin mouthwash" OR "benzylamine oral rinse" OR "benzylamine mouthwash" OR "Xinjingjie mouthrinse" OR "Caphosol mouthwash" OR "Doxepin rinse" OR "supersaturated calcium phosphate mouth rinse" OR "Phenylbutyrate mouthwash" OR "Allopurinol mouth rinse" OR "Colchicine mouthwash" OR "Doxepin rinse" OR "Morphine mouthwashes" OR "Sucralfate mouthwash" OR "Povidone-iodine" OR "chamomile mouthwash" OR "chlorhexidine mouthwash" OR "Allopurinol mouthwashes" OR mouthwash OR "mouth wash" OR honey OR propolis OR "propolis extract" OR beeswax OR "matricaria recutita" OR "manuka honey" OR glutamine OR chlorhexidine OR zinc OR "aloe vera" OR peppermint OR "calendula officinalis" OR chamomile OR "topical agents" OR "topical treatment" OR "topical application" OR "topical interventions") 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")

2. Apêndice

appendix.2 Excluded articles and reasons for exclusion (N=81)

Reference	Author/Year	Reasons for exclusion
1	Abdulrhman <i>et al.</i> 2012	1
2	Anderson <i>et al.</i> , 1998	1
3	Anderson <i>et al.</i> , 1998	1
4	Askarifar <i>et al.</i> , 2016	2
5	Atay <i>et al.</i> 2015	3
6	Bardy <i>et al.</i> , 2012	2
7	Bez <i>et al.</i> , 1999	3
8	Boers-Doets <i>et al.</i> , 2015	4
9	Bolouri <i>et al.</i> , 2015	2
10	Bolouri <i>et al.</i> , 2015	4
11	Braga <i>et al.</i> , 2013	4
12	Cerchietti L, 2006	4
13	Chattopadhyay <i>et al.</i> , 2014	2
14	Cheng & Yuen, 2006	2
15	Diaz-Sanchez <i>et al.</i> , 2015	2
16	DeVries, A. <i>et al.</i> , 2000	4
17	El-Sayed <i>et al.</i> , 2002	2
18	Epstein <i>et al.</i> 2001	3
19	Epstein <i>et al.</i> , 2008	3
20	Epstein <i>et al.</i> , 2011	2
21	Elzawawy A, 1991	6
22	Francis & Williams, 2014	6
23	Feber T, 1996	2
24	Ferreira <i>et al.</i> , 2004	2
25	Finocchiaro <i>et al.</i> , 2014	4
26	Foncuberta <i>et al.</i> , 2001	3
27	Foote <i>et al.</i> , 1994	2
28	Girdler <i>et al.</i> , 1995	3
29	Han <i>et al.</i> , 2014	5
30	Hawley <i>et al.</i> , 2014	2
31	Huang <i>et al.</i> , 2000	2
32	Hunter <i>et al.</i> , 2007	6
33	Hunter <i>et al.</i> , 2009	2
34	Ibrahim <i>et al.</i> , 1998	3
35	Ishii <i>et al.</i> , 1990	5
36	Jayalekshmi <i>et al.</i> , 2016	2
37	Khanal <i>et al.</i> , 2010	2
38	Kiprian <i>et al.</i> , 2017	3
39	Kong <i>et al.</i> , 2016	2
40	Kostrica <i>et al.</i> , 2002	6
41	Kuk, J. <i>et al.</i> , 2011	4

Reference	Author/Year	Reasons for exclusion
42	Lang <i>et al.</i> , 2015	4
43	Madan <i>et al.</i> , 2008	2
44	Maddocks-Jennings <i>et al.</i> , 2009	2
45	Mansourian <i>et al.</i> , 2015	2
46	Markiewicz <i>et al.</i> , 2012	2
47	Meeradevi & Sivaraman, 2014	4
48	Miranzadeh <i>et al.</i> , 2014	7
49	Mogensen <i>et al.</i> , 2016	3
50	Nazari <i>et al.</i> , 2007	2
51	Nct, 2011	6
52	Nottage <i>et al.</i> , 2003	2
53	Okuno <i>et al.</i> , 1997	2
54	Papila <i>et al.</i> , 1999	6
55	Papila <i>et al.</i> , 2003	6
56	Pfeiffer <i>et al.</i> , 1990	2
57	Prince <i>et al.</i> , 2005	3
58	Puataweepong <i>et al.</i> , 2009	2
59	Putwatana <i>et al.</i> , 2009	2
60	Raessi <i>et al.</i> , 2014	1
61	Roopashri <i>et al.</i> 2011	3
62	Rovirosa <i>et al.</i> , 1998	3
63	Sahebjamee <i>et al.</i> , 2015	2
64	Samaranayake <i>et al.</i> , 1998	2
65	Samdariya <i>et al.</i> , 2015	4
66	Sarumathy <i>et al.</i> 2012	2
67	Schubert & Newton, 1987	6
68	Sheibani <i>et al.</i> , 2015	2
69	Spijkervet <i>et al.</i> , 1989	2
70	Tiemann <i>et al.</i> , 2007	3
71	Tomazevic & Jazbec, 2013	1
72	Tsavaris <i>et al.</i> , 1991	3
73	Turhal <i>et al.</i> , 2000	3
74	Valcárcel <i>et al.</i> , 2002	8
75	Vokurka <i>et al.</i> 2005	2
76	Wasko Grabowska <i>et al.</i> , 2011	3
77	Wong <i>et al.</i> , 2017	2
78	Xu, X. <i>et al.</i> , 2014	5
79	Yoneda <i>et al.</i> , 2007	2
80	You <i>et al.</i> , 2009	2
81	Zannier <i>et al.</i> , 2015	4

- (1) Patients younger than 18 years (n=5)
- (2) Topical intervention used to prevent the onset of oral mucositis (n=36)
- (3) Non-randomized clinical trial (n=16)
- (4) Reviews, letters, personal opinions, book chapters, and conference abstracts (n=11)

- (5) Language restrictions (n=3)
- (6) Full paper copy not available (n=8)
- (7) Studies with the same sample (n=1)
- (8) Transplantation as a treatment modality (n=1)

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