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Interventions to Chemotherapy and Radiotherapy Induced Oral Mucositis: a Systematic Review and Meta-analysis

Intervencije u slučaju oralnoga mukozitisa prouzročenog kemoterapijom i radioterapijom: sustavni pregled i metaanaliza

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Abstract
Introduction: Oral mucositis is a common adverse effect of chemotherapy and radiotherapy, characterized by erythematous lesions, edema, ulceration, atrophy, or even hemorrhage. Current evidence highlights the complexity of its management and the importance of tailoring therapeutic approaches to the individual patient profile in order to improve quality of life during cancer treatment. **Objectives:** To access the efficacy of pharmacological and non-pharmacological interventions for the prevention and treatment of chemotherapy- and/or radiotherapy-induced oral mucositis. **Materials and Methods:** A systematic review with meta-analysis of 27 articles published between 2019 and 2024 was also performed, aiming to characterize and contextualize therapeutic interventions for oral mucositis. **Results and Discussion:** This systematic review and meta-analysis suggests that various non-pharmacological interventions (such as cryotherapy and photobiomodulation) and pharmacological interventions, particularly natural agents (such as honey, curcumin, green tea), are effective for the prevention and treatment of oral mucositis. **Conclusion:** Oral mucositis is a highly prevalent adverse effect in patients undergoing chemotherapy and/or radiotherapy, with significant functional, nutritional, and treatment adherence implications. The systematic review with meta-analysis demonstrated the efficacy of non-pharmacological and natural interventions.

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Introduction

Description of the condition

Oral mucositis (OM) is one of the most common side effects of chemotherapy and head and neck radiotherapy, affecting over 75% of high-risk patients (1-4). When induced by combined chemotherapy and radiotherapy, this percentage increases to approximately 90–100% (1, 2, 4, 5).

OM triggered by oncological treatment presents as erythematous lesions accompanied by edema, ulceration, atrophy, or even bleeding, characterizing significant inflammation of the oral cavity. This side effect represents a considerable challenge for both patients and oncology healthcare professionals (6–9). Symptom severity ranges from mild discomfort to painful erythema. In more severe cases, OM has a substantial impact on quality of life, particularly due to

Uvod

Opis stanja

Oralni mukozitis (OM) jedna je od najčešćih nuspojava kemoterapije i radioterapije glave i vrata, a pogađa više od 75 % pacijenata s visokim rizikom (1 – 4). Kada se inducira kombiniranom kemoterapijom i radioterapijom, taj se postotak povećava na približno 90 do 100 % (1, 2, 4, 5).

OM izazvan onkološkim liječenjem manifestira se kao eritematozne lezije praćene edemom, ulceracije, atrofija ili čak krvarenje, što karakterizira izraženu upalu usne šupljine. Ta je nuspojava velik izazov i za onkološke pacijente i za zdravstveno osoblje (6 – 9). Težina simptoma kreće se od blage nelagode do bolnog eritema. U težim slučajevima OM znatno utječe na kvalitetu života, posebno zbog ograničenja u bitnim funkcijama poput jedenja, hidratacije i komunika-

limitations in essential functions such as eating, hydration, and communication. In extreme situations, OM may lead to weight loss, nutritional deficiencies, secondary infections, prolonged hospitalization, and increased associated healthcare costs. It is also important to consider that dose reductions or even forced interruptions of treatment may become necessary, which can negatively affect disease prognosis (1–3, 10–12).

OM is frequently classified according to the World Health Organization (WHO) oral mucositis scale, which considers both objective and functional criteria – such as the presence of erythema or ulceration and the patient's ability to eat – with symptom severity graded from 0 to 4 (13). Although the WHO scale is widely used, other classification systems also play an important role in the assessment of OM, namely the Radiation Therapy Oncology Group (RTOG) scale and the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), (1, 13-15).

Currently, the studies on chemotherapy and radiotherapy induced OM are mainly focused on symptom management and treatment effectiveness. Although no standardized protocol exists, scientific evidence increasingly supports the efficacy of various therapeutic approaches (1, 16, 17). In 2020, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) published clinical guidelines proposing evidence-based recommendations for the prevention and treatment of OM (17). These were grouped into eight categories: basic oral care (including oral habits and patient education); anti-inflammatory agents (such as benzydamine); low-level laser photobiomodulation therapy; cryotherapy; antimicrobials, coating agents, anesthetics, and analgesics (including topical morphine or lidocaine rinses); growth factors and cytokines; natural and miscellaneous agents (such as honey and glutamine); interventions for gastrointestinal mucositis.

In cases of severe pain, the use of opioids may be necessary. It is up to the clinician to determine the most appropriate approach for symptom management (1, 4, 7, 9, 16–19). This evidence-based framework underscores the complexity of OM management. However, the MASCC/ISOO recommendations are now five years old, and since then additional data and expert consensus have emerged. In particular, the 2025 international expert consensus provided updated perspectives on both pharmacological and non-pharmacological interventions, highlighting the need to reassess and compare the robustness of existing guidelines (20).

Why it is important to do this review

Given the clinical burden of OM and the evolving landscape of therapeutic approaches, an updated systematic review and meta-analysis is essential to synthesize current evidence, identify the most effective interventions, and guide oncology practice.

Objective

The objective of this review was to assess the current landscape of pharmacological and non-pharmacological in-

cije. U ekstremnim situacijama OM može potaknuti gubitak tjelesne težine, nutritivne nedostatke, sekundarne infekcije, produljene hospitalizacije i povećane povezane troškove zdravstvene zaštite. Također je važno uzeti u obzir da mogu postati nužni za smanjenje doze ili čak prisilni prekid liječenja, što može negativno utjecati na prognozu bolesti (1 – 3,10 – 12).

OM se često klasificira prema ljestvici oralnoga mukozitisa Svjetske zdravstvene organizacije (WHO) koja uzima u obzir i objektivne i funkcionalne kriterije – poput eritema ili ulceracija i sposobnosti pacijenta da jede – s težinom simptoma ocjenjivanom od 0 do 4 (13). Iako se ljestvica WHO-a najčešće primjenjuje, drugi klasifikacijski sustavi također su važni u procjeni OM-a, a to su ljestvica Skupine za onkološku radioterapiju (RTOG) i Zajednički terminološki kriteriji za štetne događaje Nacionalnoga instituta za rak (NCI-CTCAE) (1, 13 – 15).

Trenutačno su studije o OM-u prouzročenom kemoterapijom i radioterapijom uglavnom usmjerene na upravljanje simptomima i učinkovitost liječenja. Iako nema standardiziranoga protokola, znanstveni dokazi sve češće podupiru učinkovitost različitih terapijskih pristupa (1, 16, 17). Godine 2020., studijska skupina za mukozitis Multinacionalnog udruženja za potpornu skrb kod raka i Međunarodnoga društva za oralnu onkologiju (MASCC/ISOO) objavila je kliničke smjernice s preporukama na temelju dokaza za prevenciju i liječenje oralnoga mukozitisa (OM) (17). Smjernice su grupirane u osam kategorija: osnovna oralna skrb (uključujući oralne navike i edukaciju pacijenata), protuupalna sredstva (kao što je benzidamin), terapija fotobiomodulacijom laserom niskoga intenziteta, krioterapija, antimikrobna sredstva, sredstva za premazivanje, anestetici i analgetici (uključujući topikalno ispiranje morfinom ili lidokainom), faktori rasta i citokini, prirodni i razni agensi (med i glutamin) i intervencije za gastrointestinalni mukozitis.

U slučaju jake boli mogu biti potrebni opioidi. Na kliničaru je da odredi najprikladniji pristup za upravljanje simptomima (1, 4, 7, 9,16 – 19). Taj okvir temeljen na dokazima ističe složenost liječenja OM-a. Međutim, preporuke MASCC/ISOO-a predložene su prije pet godina, a od tada su se pojavili dodatni podatci i stručni konsenzus. Konkretno, ističući potrebu za ponovnom procjenom i usporedbom postojećih smjernica, međunarodni stručni konsenzus ažurirao je 2025 perspektivu o farmakološkim i nefarmakološkim intervencijama. (20)

Zašto je važno napraviti ovaj pregled

S obzirom na klinički teret onkološke encefalopatije i promjenjive terapijske pristupe, ažurirani sustavni pregled i metaanaliza ključni su za sintezu aktualnih dokaza, identificiranje najučinkovitijih intervencija i usmjeravanje onkološke prakse.

Svrha

Procijeniti aktualne farmakološke i nefarmakološke intervencije za prevenciju i liječenje oralnoga mukozitisa prou-

terventions for the prevention and treatment of chemotherapy and/or radiotherapy-induced oral mucositis.

Methods

This systematic review and meta-analysis were conducted according to the methodological expectations for Cochrane intervention reviews (MECIR) [21] when conducting the review and PRISMA 2020 (22) for the reporting. The review protocol was registered in PROSPERO, under registration number CRD42024554737.

Criteria for considering studies for this review

Eligibility criteria

Inclusion criteria

Eligibility criteria were defined according to the Population, Intervention, Comparator, and Outcomes (PICO) framework:

Population: Adults (≥18 years old) with cancer undergoing chemotherapy and/or radiotherapy, presenting with varying degrees of oral mucositis severity, classified according to standard grading systems (e.g., WHO, NCI-CTCAE, RTOG).

Interventions and Comparators: Any pharmacological or non-pharmacological intervention for the prevention or treatment of oral mucositis. Interventions included the categories defined by the MASCC/ISOO Mucositis Study Group (MSG): basic oral care, growth factors and cytokines, anti-inflammatory agents, antimicrobials, analgesics and anesthetics, mucosal coating agents, natural agents, cryotherapy, photobiomodulation/laser therapy, and amifostine (17). Comparisons included placebo, standard/routine care, no treatment, or head-to-head trials between interventions. For efficacy analyses, trials comparing an intervention to placebo were prioritized.

Outcomes: Primary outcomes were the severity and/or incidence of oral mucositis, assessed by validated grading scales (WHO, RTOG, NCI-CTCAE, PROMS).

Exclusion criteria

Studies were excluded if they met one of the following criteria: 1) Oral mucositis not resulting from chemoradiotherapy; 2) non-randomized clinical trials; 3) reviews, letters, case reports, personal opinions, book chapters, and conference abstracts; 4) languages restrictions; 5) full-text unavailability.

Types of outcome measures

Primary outcome: Oral mucositis incidence and severity. Severity was graded on a 0–4 scale (none to severe) and dichotomized as follows: any mucositis (0 vs ≥1), moderate-to-severe mucositis (0–1 vs ≥2), and severe mucositis (0–2 vs ≥3).

Secondary outcome: Pain intensity, time to onset, and remission of mucositis.

The core outcome set for oral mucositis, developed by Bellm in 2002 and registered in COMET (23), was considered for reporting consistency.

zročenog kemoterapijom i/ili radioterapijom.

Metode

Ovaj sustavni pregled i metaanaliza provedeni su u skladu s metodološkim očekivanjima za Cochranove intervencijske pregledne radove (MECIR) (21) pri obavljanju pregleda i PRISMA-e 2020. (22) za izvještavanje. Protokol preglednoga rada registriran je u PROSPERO-u, pod registracijskim brojem CRD42024554737.

Kriteriji za razmatranje studija za ovaj pregled

Kriteriji za uključivanje

Kriteriji za sudjelovanje

Kriteriji za sudjelovanje definirani su prema okviru populacije, intervencije, usporedbe i ishoda (PICO),

Populacija: odrasli (≥ 18 godina) s rakom koji se podvrgavaju kemoterapiji i/ili radioterapiji, s različitim stupnjevima oralnoga mukozitisa, klasificirani prema standardnim sustavima ocjenjivanja (WHO, NCI-CTCAE, RTOG).

Intervencije i usporedbe: bilo koja farmakološka ili nefarmakološka intervencija za prevenciju ili liječenje oralnoga mukozitisa. Intervencije su uključivale kategorije koje je definirao MASCC/ISOO Mucositis Study Group (MSG): osnovna oralna skrb, faktori rasta i citokini, protuupalni agensi, antimikrobni lijekovi, analgetici i anestetici, sredstva za premazivanje sluznice, prirodni agensi, krioterapija i fotobiomodulacija/laserska terapija i amifostin (17). Usporedbe su obuhvaćale placebo, standardnu/rutinsku skrb, bez liječenja ili izravna ispitivanja između intervencija. Za analize učinkovitosti prioritet su bila ispitivanja koja su uspoređivala intervenciju s placebom.

Ishodi: primarni ishodi bili su težina i/ili incidencija oralnoga mukozitisa procijenjena validiranim ljestvicama (WHO, RTOG, NCI-CTCAE, PROMS).

Kriteriji za isključivanje

Studije su isključene ako su ispunjavale jedan od sljedećih kriterija: 1) oralni mukozitis koji nije posljedica kemo ili radioterapije; 2) nerandomizirana klinička ispitivanja; 3) pregledi, pisma, prikazi slučajeva, osobna mišljenja, poglavlja u knjigama i sažetci s konferencija; 4) jezična ograničenja; 5) nedostupnost cjelovitoga teksta.

Vrste ishoda

Primarni ishod: **i**ncidencija i težina oralnoga mukozitisa. Težina je ocjenjivana na ljestvici od 0 do 4 (od nema do teškoga) i dihotomizirana na sljedeći način: bilo koji mukozitis (0 nasuprot ≥ 1), umjereni do teški mukozitis (0 – 1 nasuprot ≥ 2) i teški mukozitis (0 – 2 nasuprot ≥ 3).

Sekundarni ishod: **i**ntenzitet bola, vrijeme do početka i remisija mukozitisa.

Radi dosljednosti izvješćivanja uzet je u obzir osnovni skup ishoda za oralni mukozitis koji je predložio Bellm 2002. godine i registriran je u COMET-u (23).

Search methods

Electronic searches

A comprehensive search was conducted in PubMed, Scopus, Cochrane Library, and Google Scholar from inception to July 18, 2024, including articles published between 2019 and 2024. The full search strategies are provided in Table 1. Reference lists of relevant reviews and included studies were screened to identify additional eligible articles. Trial registries and gray literature were not considered.

Metode pretraživanja

Elektroničko pretraživanje

Sveobuhvatno pretraživanje obavljeno je u PubMedu, Scopusu, Cochrane Libraryju i Google Scholaru od početka do 18. srpnja 2024., uključujući članke tiskane između 2019. i 2024. Potpune strategije pretraživanja navedene su u tablici 1. Popisi referencija relevantnih preglednih radova i uključenih studija pregledani su kako bi se identificirali dodatni odgovarajući članci. Registri ispitivanja i siva literatura nisu uzeti u obzir.

Table 1. Search protocol used in the systematic review.
Tablica 1. Protokol pretraživanja korišten u sustavnom pregledu.

Search strategy	Database/Results
"pharmacological interventions" AND "oral mucositis"	PubMed: 50 SCOPUS: 193 Cochrane Library: 18 Google Scholar: 976
"pharmacological interventions" AND "ulceration related to oral mucositis"	PubMed: 4 SCOPUS: 54 Cochrane Library: 3 Google Scholar: 670
"pharmacological interventions AND pain related to oral mucositis"	PubMed: 4 SCOPUS: 107 Cochrane Library: 5 Google Scholar: 980
"oral mucositis" OR "oral mucositis treatment" OR "oral mucositis prevention" OR "oral mucositis therapy" OR "chemotherapy adverse events" OR "radiotherapy adverse events" OR "oral mucositis classification"	PubMed: 17 705 SCOPUS: 991 Cochrane Library: 9837 Google Scholar: 17 300

Study selection

Two reviewers independently screened all titles and abstracts. Full texts of potentially relevant articles were retrieved and assessed against inclusion/exclusion criteria. Discrepancies were resolved through discussion or, when necessary, consultation with a third reviewer in cases of persistent disagreement or uncertainty.

Data Extraction and Management

Data were independently extracted by two reviewers using a standardized form. Extracted data included study details (author, year, country), design, sample size, participant characteristics (mean age, % female, cancer type), treatment regimen, intervention and comparator details (category, agent, dose, route, frequency, duration), outcomes (mucositis scale, pain scale, time points, means/SDs or events), and risk of bias items.

Risk of Bias Assessment

Risk of bias was assessed independently by two reviewers using the Cochrane Risk of Bias tool for randomized trials (RoB 1.0). The level of agreement between reviewers was quantified using Cohen's Kappa index (24). Disagreements were resolved through discussion or by consulting a third reviewer (25, 26).

Odabir studija

Dva recenzenta neovisno su pregledala sve naslove i sažetke. Preuzeti su cjeloviti tekstovi iz potencijalno relevantnih članaka i procijenjeni prema kriterijima uključivanja/isključivanja. Neslaganja su riješena raspravom ili, ako je bilo potrebno, konzultacijama s trećim recenzentom u slučaju upornog neslaganja ili nesigurnosti.

Ekstrakcija i upravljanje podatcima

Podatke su, koristeći se standardiziranim modelom, neovisno izdvojila dva recenzenta. Izdvojeni podatci uključivali su detalje studije (autor, godina, zemlja), dizajn, veličinu uzorka, karakteristike sudionika (prosječna dob, postotak žena, vrsta raka), način liječenja, detalje o intervenciji i usporedbi (kategorija, sredstvo, doza, put primjene, učestalost, trajanje), ishode (ljestvica mukozitisa, ljestvica boli, vremenske točke, srednje vrijednosti / SD ili događaji) i rizik od pristranosti.

Procjena rizika od pristranosti

Rizik od pristranosti neovisno su procijenila dva recenzenta, a koristili su se Cochraneovim alatom za procjenu rizika od pristranosti za randomizirana ispitivanja (RoB 1.0). Razina slaganja između recenzenata kvantificirana je s pomoću Cohenova kappa indeksa (24). Neslaganja su riješena raspravom ili konzultacijama s trećim recenzentom (25, 26).

Statistical Analysis

For dichotomous outcomes (severe and non-severe OM), odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using raw event counts. For continuous outcomes (e.g., mean mucositis severity), mean differences (MDs) with standard errors were computed based on report means, standard deviations, and sample sizes.

For studies reporting multiple post-baseline time points, a multilevel random-effects meta-analysis model was fitted using maximum likelihood estimation, with random intercepts for each study to account for within-study correlations among repeated measurements. Best linear unbiased predictions (BLUP) were extracted as the study-specific estimates for these studies. For single post-baseline time point, a conventional random-effects meta-analysis was applied.

All study-specific OR or MD were combined in a meta-analysis using an inverse-variance weighted random-effects model. Heterogeneity was assessed using the I^2 statistic.

Subgroup-specific pooled effects were estimated using separate random-effects meta-analyses within each subgroup. To formally test for differences between subgroups, mixed-effects meta-regression models were fitted with the subgroup variable as a categorical moderator, and the likelihood ratio test was used to assess statistical significance. Pairwise comparisons between subgroups were conducted, with p-values adjusted using the Holm method to account for multiple testing.

Publication bias was evaluated with funnel plots and the trim-and-fill method. All analyses were performed in R (metaphor package), (27). Forest plots and funnel plots were generated using package ggplot2. In the forest plots, each point represents an individual study estimate, with marker size proportional to study weight. Circles denote studies with a single follow-up, while squares indicate studies with multiple follow-ups (BLUP estimates).

A two-sided significance level of 5% was used for all statistical tests.

Results

Study Selection

A total of 3064 records were identified through electronic database searches. After removing 1173 duplicates, 1891 unique records remained for screening. Following title and abstract screening, 1816 records were excluded because they did not meet the eligibility criteria.

The full texts of 66 articles were assessed for eligibility. Of these, 39 articles were excluded for the following reasons: not a randomized controlled trial (n = 6) (28-33), studies conducted in animals (n = 2) (34,35), *in vitro* studies (n = 5) (36-40), participants not undergoing chemotherapy or radiotherapy (n = 4) (41-44), literature reviews (n = 2) (45,46), unfinished trials (n = 4) (47-50), not reporting effect measures

Statistička analiza

Za dihotomne ishode (teški i ne teški OM), omjeri vjerojatnosti (OR) s 95 % intervalima pouzdanosti (CI) izračunati su korištenjem sirovoga broja događaja. Za kontinuirane ishode (npr., prosječna težina mukozitisa), srednje razlike (MD) sa standardnim pogreškama izračunate su na temelju srednjih vrijednosti izvješća, standardnih devijacija i veličina uzorka.

Za studije koje izvještavaju o više vremenskih točaka nakon početnog razdoblja, model metaanalize s više razina slučajnih učinaka prilagođen je korištenjem procjene maksimalne vjerojatnosti, sa slučajnim odsječcima za svaku studiju kako bi se uzele u obzir korelacije unutar studije među ponovljenim mjerenjima. Najbolja linearna nepristrana predviđanja (BLUP) izdvojena su kao procjene specifične za ove studije. Za pojedinačnu vremensku točku, nakon početnoga razdoblja, primijenjena je konvencionalna metaanaliza slučajnih učinaka.

Svi OR-i ili MD-i specifični za studiju kombinirani su u metaanalizi korištenjem modela slučajnih učinaka ponderiranog inverznom varijancom. Heterogenost je procijenjena korištenjem I^2 statistike.

Sveukupni učinci specifični za podskupinu procijenjeni su korištenjem zasebnih metaanaliza slučajnih učinaka unutar svake podskupine. Kako bi se formalno testirale razlike između podskupina, modeli metaregresije s miješanim efektima prilagođeni su varijablom podskupine kao kategoričkim moderatorom, a test omjera vjerojatnosti korišten je za procjenu statističke značajnosti. Provedene su parne usporedbe između podskupina, s p-vrijednostima prilagođenima Holmovom metodom kako bi se uzelo u obzir višestruko testiranje.

Pristranost objavljivanja procijenjena je ljevkastim dijagramima i metodom obrezivanja i popunjavanja. Sve analize provedene su u R-u (tzv. metafor paket) (27). Šumski dijagrami i ljevkasti dijagrami generirani su s pomoću paketa ggplot2. U šumskim dijagramima svaka točka označava procjenu pojedinačne studije, s veličinom markera proporcionalnog težini studije. Krugovi označavaju studije s jednim praćenjem, a kvadrati studije s više praćenja (procjene BLUP).

Za sve statističke testove korištena je dvostrana razina značajnosti od 5 %.

Rezultati

Odabir studija

Pretraživanjem elektroničkih baza podataka ukupno su identificirana 3064 zapisa. Nakon uklanjanja 1173 duplikata, za probir je ostao 1891 jedinstveni zapis. Nakon probira naslova i sažetka, 1816 zapisa je isključeno jer nisu ispunjavali kriterije prihvatljivosti.

Cjeloviti tekstovi 66 članaka procijenjeni su prema prihvatljivosti. Od toga je 39 isključeno iz sljedećih razloga: nije randomizirano kontrolirano ispitivanje (n = 6) (28 –33), studije su provedene na životinjama (n = 2) (34, 35), studije su *in vitro* (n = 5) (36 – 40), sudionici koji nisu podvrgnuti kemoterapiji ili radioterapiji (n = 4) (41 – 44), pregledi literature (n = 2) (45, 46), nedovršena ispitivanja (n = 4) (47 – 50), neiz-

of interest (n = 11) (51-61), and absence of a control group (n = 5) (62-66).

Ultimately, 27 studies met all inclusion criteria and were included in the qualitative synthesis (67-93). Several articles reported more than treatment arm, resulting in a total of 30 studies included in the meta-analysis.

The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Characteristics of Included Studies

A total of 30 studies, reported in 27 publications between 2019 and 2024, were conducted across 11 countries and included 1499 participants. The median sample size per study was 50 (range: 20–100). The proportion of female participants ranged from 6.5% to 100%, and the mean age of participants ranged from 44.7 to 66.9 years. Sixteen studies evaluated outcomes at more than one post-baseline time point (67-93).

The interventions evaluated were grouped into three main categories: anti-inflammatory, antimicrobial, and coating agents; natural agents or non-pharmacological interventions. Anti-inflammatory, antimicrobial, and coating agents included RRx-001 and dexamethasone (69), polyacrylate silver salt (70), triamcinolone acetonide (83), chlorhexidine (84), metformin (87), clotrimazole lozenges (90) and benzydamine (91). Natural agents included honey (67,74,77), green tea (68), probiotics (71,82), curcumin (72,73,78,81,92), vitamin E (75), plantago ovata-based herbal compound (76), ayurvedic (85), saline mouthwash (86) and compound Kushen (88). Non-pharmacological interventions included cryotherapy (79, 89), phototherapy (72, 80) and early nutritional intervention [93]. Interventions were also classified into two broader categories: pharmacological and non-pharmacological (intervention type). The delivery method was also considered, including capsules or pills (71,73,75,78,87), topical pharmacological interventions (such as mouthwashes or gels) (67,68,70,72,74,76,77,81-86,90-92) and topical non-pharmacological interventions (72,79,80,89). The scale used to assess oral mucositis and the type of cancer treatment received by participants was also considered.

Regarding countries of origin, five main regional groups were created to account for cultural differences and allow for more homogeneous comparisons. The East and South Asian group included Korea (89), China (71,88,93), Taiwan (70), and Indonesia (75) (five studies); the Middle East and North Africa group included Egypt (87) and Iran (73,76,78,83) (five studies); the South American group included Brazil (72,74,76,81) and Argentina (68) (six studies); the South Asian group included India (67,77,79,82,84,85,90-92) and the Maldives (86) (ten studies); and finally, three studies were published in the United States of America (69).

The inter-observer agreement was evaluated through Cohen's Kappa coefficient (24), with a resulting value of 0.85, indicating a substantial degree of consistency between raters.

Further details of included studies can be found in Table 2.

vješćivanje o mjerama učinka od interesa (n = 11) (51 – 61) i odsutnost kontrolne skupine (n = 5) (62 – 66).

Konačno, 27 studija ispunilo je sve kriterije i uključene su u kvalitativnu sintezu (67 – 93). U nekoliko članaka izviješteno je o više od jedne skupine liječenja, što je rezultiralo s ukupno 30 studija uključenih u metaanalizu.

Proces odabira studija sažet je u dijagramu toka PRISMA-e (slika 1.).

Značajke uključenih studija

Ukupno 30 studija, objavljenih u 27 publikacija između 2019. i 2024. godine, provedeno je u 11 zemalja i uključivale su 1499 sudionika. Srednja veličina uzorka po studiji bila je 50 (raspon: 20 – 100). Udio sudionika kretao se od 6,5 do 100 %, a prosječna dob bila je od 44,7 do 66,9 godina. U 16 studija procijenjeni su ishodi u više od jedne vremenske točke nakon početka istraživanja (67 – 93).

Procijenjene intervencije grupirane su u tri glavne kategorije: protuupalna, antimikrobna sredstva i sredstva za oblaganje te prirodni agensi ili nefarmakološke intervencije. Protuupalna, antimikrobna i sredstva za oblaganje uključivala su RRx-001 i deksametazon (69), poliakrilatnu srebrnu sol (70), triamcinolon acetonid (83), klorheksidin (84), metformin (87), klotrimazol pastile (90) i benzidamin (91). Prirodni agensi uključivali su med (67, 74, 77), zeleni čaj (68), probiotike (71, 82), kurkumin (72, 73, 78, 81, 92), vitamin E (75), biljni spoj na bazi plantago ovate (indijski trputac) (76), adjurvandski (85), fiziološku otopinu za ispiranje usta (86) i spoj dobiven od kineske biljke kushen (*Sophora flavescens*) (88). Nefarmakološke intervencije uključivale su krioterapiju (79, 89), fototerapiju (72, 80) i ranu nutritivnu intervenciju (93). Intervencije su također klasificirane u dvije šire kategorije: farmakološke i nefarmakološke (vrsta intervencije). Također je uzeta u obzir metoda primjene, uključujući kapsule ili tablete (71, 73, 75, 78, 87), lokalne farmakološke intervencije (vodice za ispiranje usta ili gelovi) (67, 68, 70, 72, 74, 76, 77, 81 – 86, 90 – 92) i lokalne nefarmakološke intervencije (72, 79 ,80, 89). Također su uzete u obzir ljestvica korištena za procjenu oralnoga mukozitisa i vrsta liječenja raka koju su sudionici primili.

Kad je riječ o zemljama podrijetla, stvoreno je pet glavnih regionalnih skupina kako bi se uzele u obzir kulturne razlike i omogućile homogenije usporedbe. Istočnoazijska i južnoazijska skupina obuhvaćale su Koreju (89), Kinu (71, 88, 93), Tajvan (70) i Indoneziju (75) (pet studija); skupina Bliskog istoka i Sjeverne Afrike obuhvaćala je Egipat (87) i Iran (73, 76, 78, 83) (pet studija); južnoamerička skupina obuhvaćala je Brazil (72, 74, 76, 81) i Argentinu (68) (šest studija); južnoazijska skupina obuhvaćala je Indiju (67, 77, 79, 82, 84, 85, 90 – 92) i Maldive (86) (deset studija) i konačno, tri studije objavljene su u Sjedinjenim Američkim Državama (69).

Slaganje između promatrača procijenjeno je Cohenovim kappa koeficijentom (24), s rezultirajućom vrijednošću od 0,85, što pokazuje znatan stupanj dosljednosti između ocjenjivača.

Više detalja o uključenim studijama vidi u tablici 2.

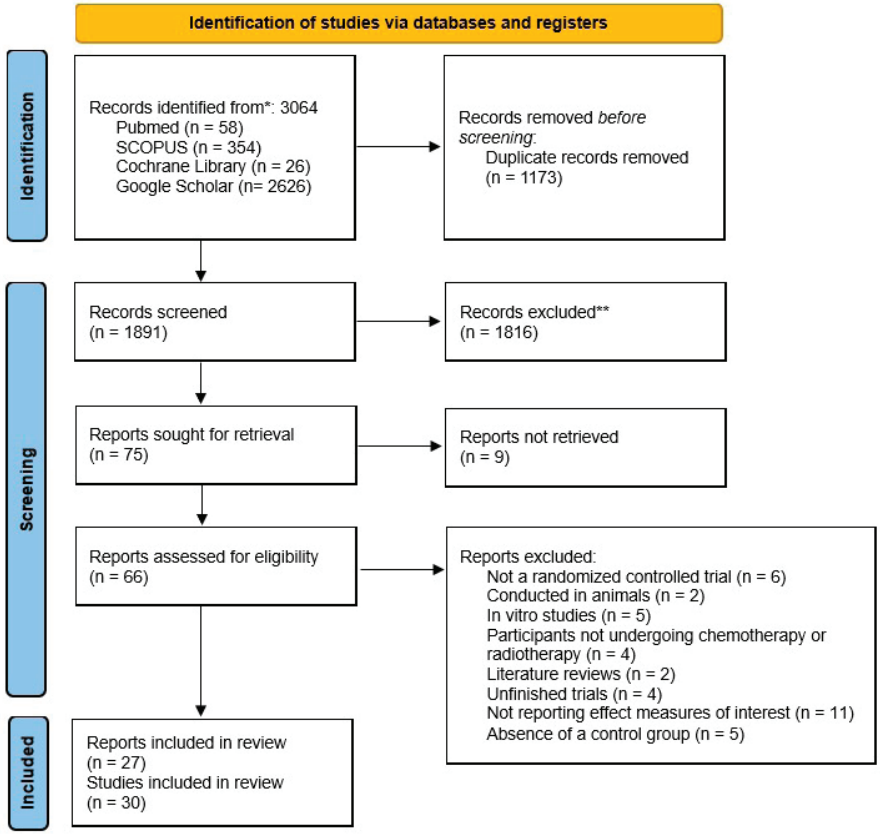


Figure 1. PRISMA flow diagram.
Slika 1. Dijagram toka PRISMA.

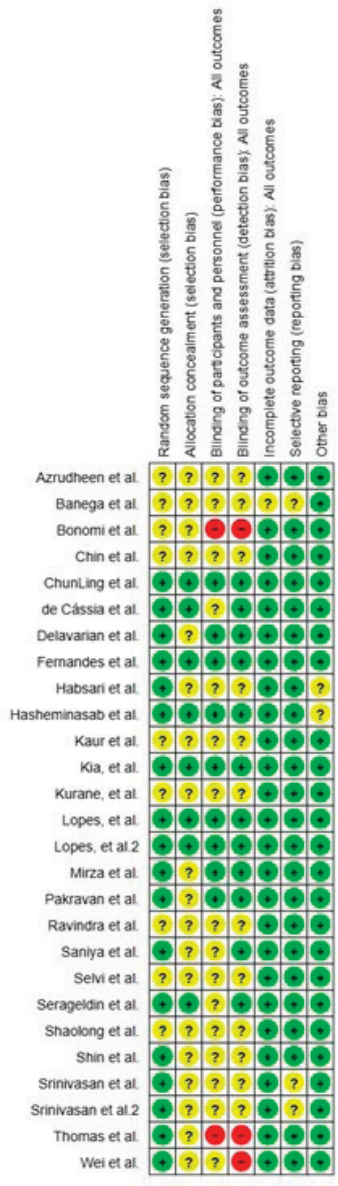


Figure 2. Risk of bias. Cochrane Risk of Bias 1.0 tool for randomized trials (+ = low; – = high; ? = unclear).
Slika 2. Rizik od pristranosti. Cochrane alat Rizik od pristranosti 1.0 za randomizirana ispitivanja (+ = nisko; – = visoko; ? = nejasno).

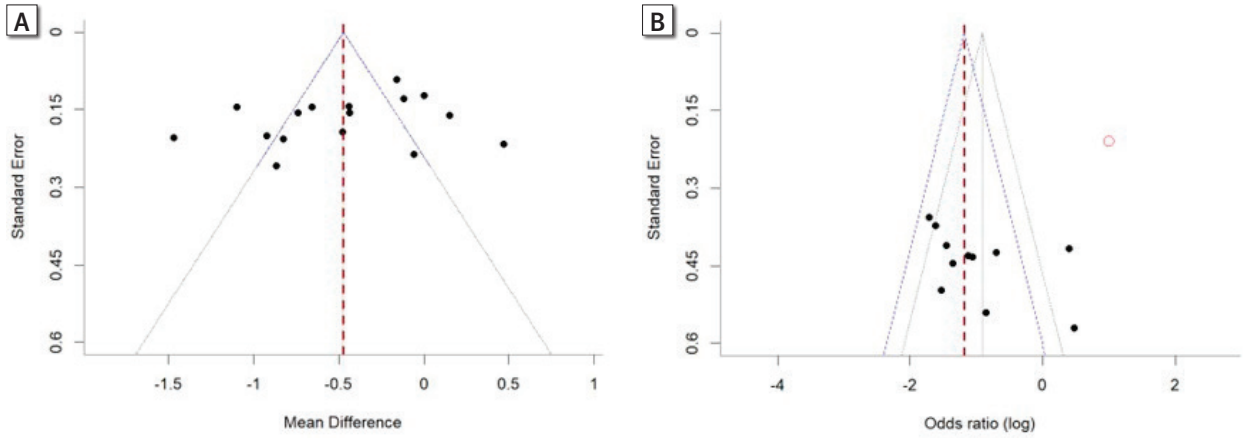
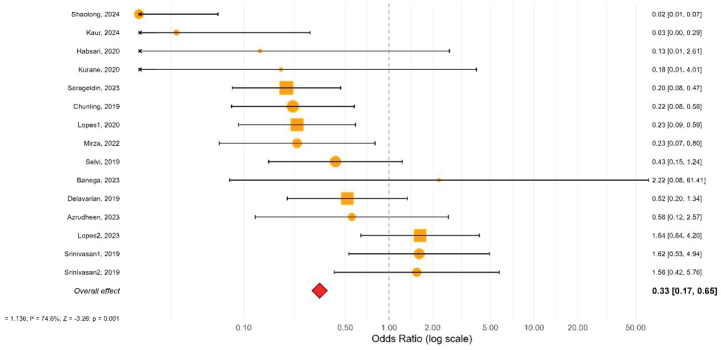


Figure 3. Funnel plot of included studies evaluating the effect by: (A) MD and (B) OR.
Slika 3. Dijagram uključenih studija koje procjenjuju učinak prema: (A) MD i (B) OR.



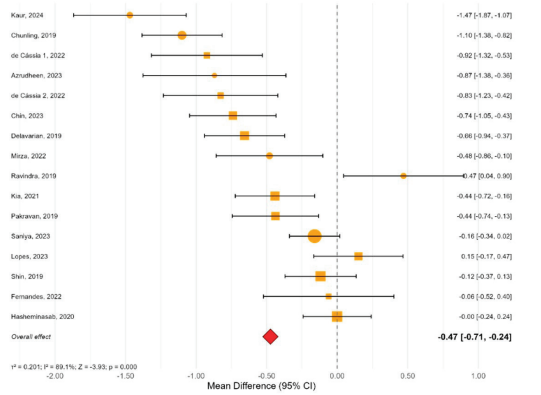


Figure 4. Forest plot of odds ratio and 95% confidence intervals for the effect of interventions groups on OM incidence without the high-risk studies, after RoB 1.0 analysis.
Slika 4. Dijagram omjera šansi i 95% intervala pouzdanosti za učinak intervencijskih skupina na incidenciju OM bez studija visokog rizika, nakon RoB 1.0 analize.

Figure 5. Forest plot of MD and 95% confidence intervals for the mucositis scale.
Slika 5. Dijagram MD i 95% intervala pouzdanosti za skalu mukozitisa.

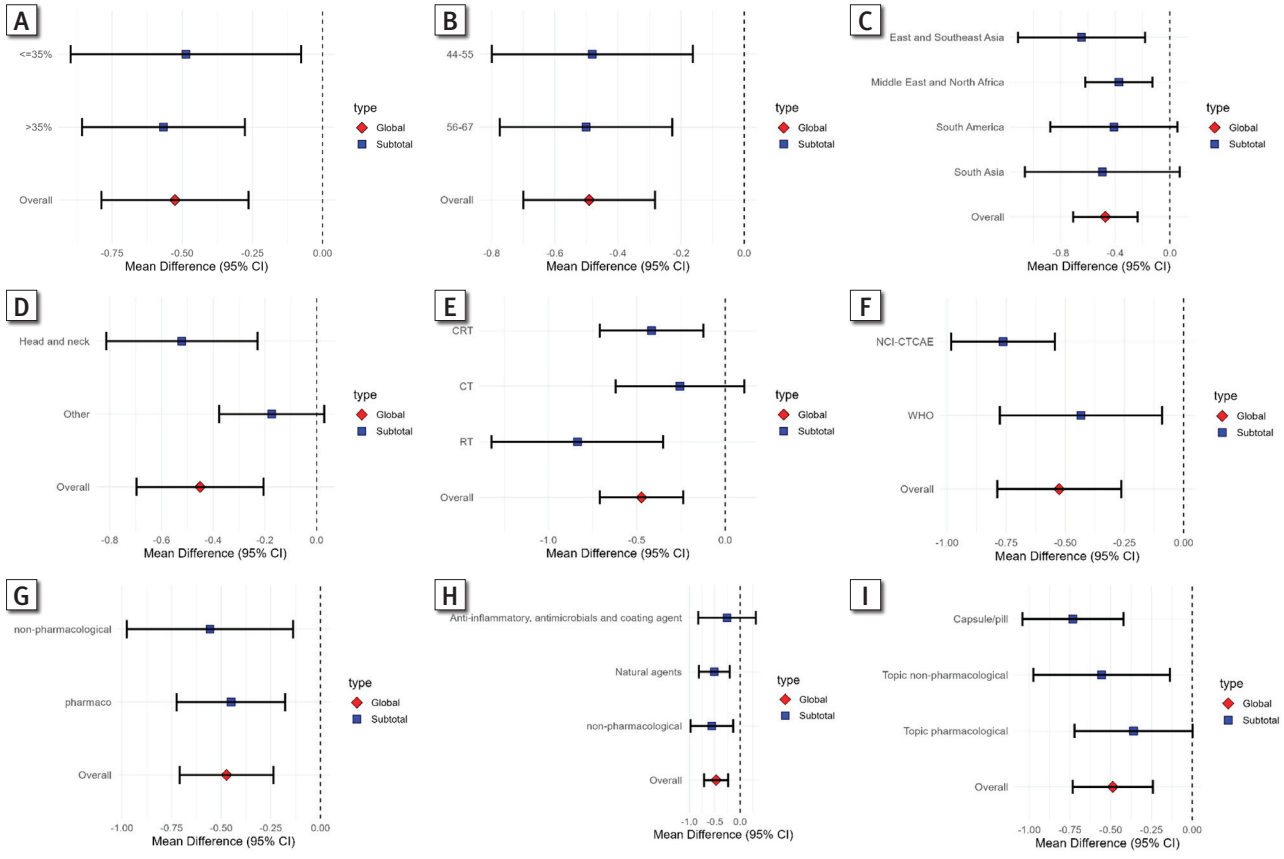


Figure 6. Subgroup analysis of oral mucositis assessed by mean differences: (A) Sex – 1. %Female ≤35%; 2. %Female > 35%; (B) Age; (C) Region; (D) Cancer; (E) Treatment Regimen; (F) Oral Mucositis scale; (G) Intervention type; (H) Intervention groups; (I) Delivery method.
Slika 6. Analiza podskupina oralnog mukozitisa procijenjena srednjim razlikama: (A) Spol – 1. %Žene ≤35%; 2. %Žene > 35%; (B) Dob; (C) Regija; (D) Rak; (E) Režim liječenja; (F) Skala oralnog mukozitisa; (G) Vrsta intervencije; (H) Intervencijske skupine; (I) Način provedbe.

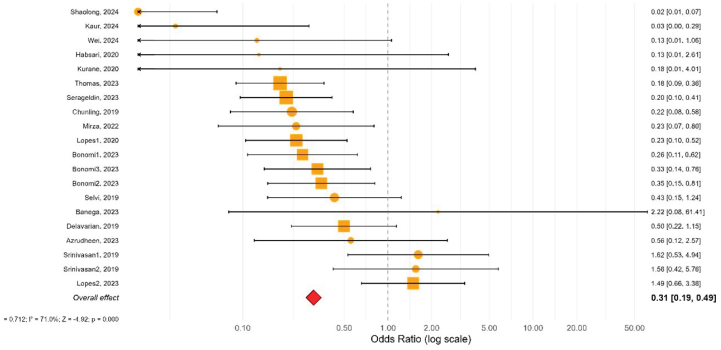


Figure 7. Forest plot of OR and 95% confidence intervals for the mucositis scale.
Slika 7. Dijagram OR-a i 95% intervali pouzdanosti za ljestvicu mukozitisa.

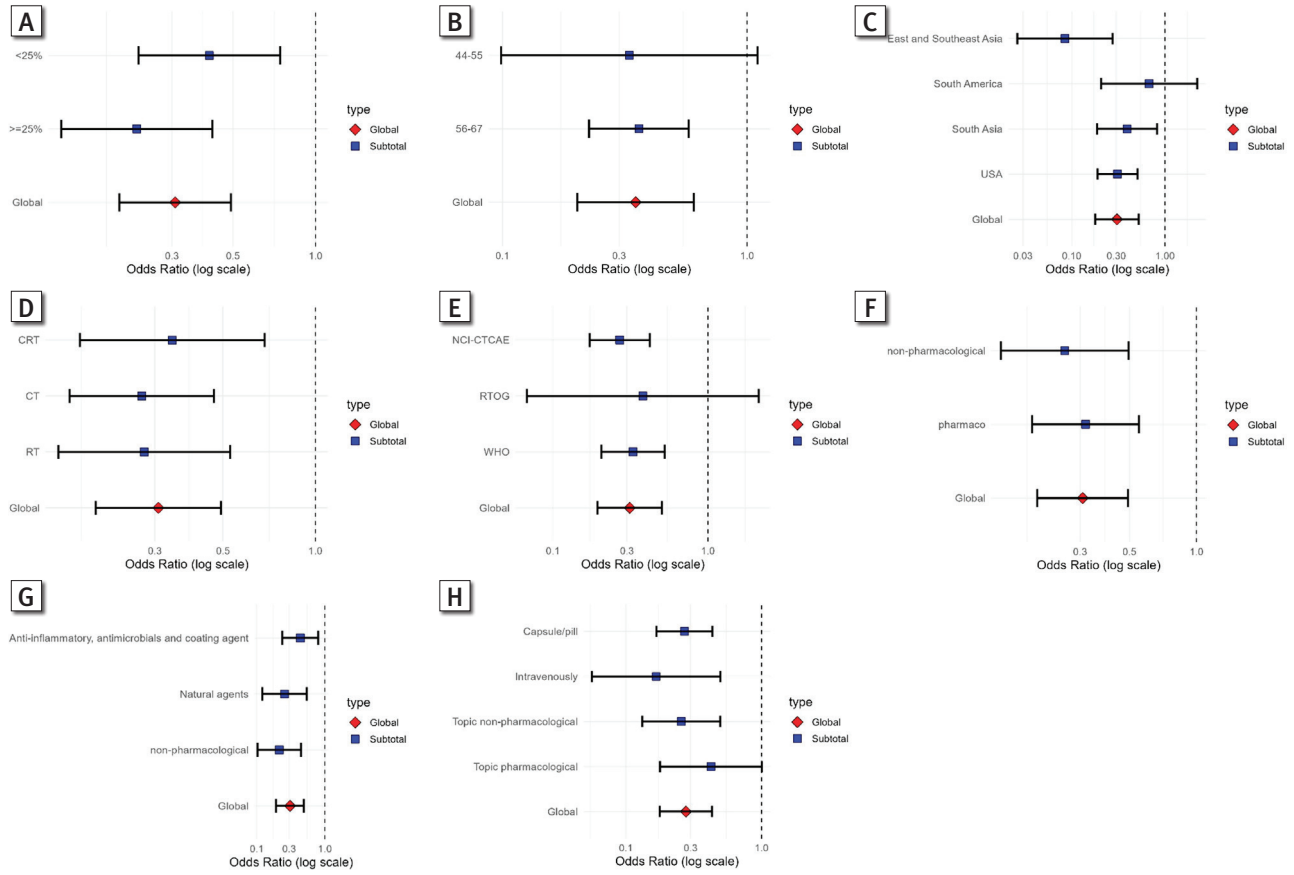


Figure 8. Subgroup analysis of oral mucositis assessed by odds ratio: (A) Sex – 1. %Female ≤35%; 2. %Female > 35%; (B) Age; (C) Region; (D) Treatment Regimen; (E) Oral Mucositis scale; (F) Intervention type; (G) Intervention groups; (H) Delivery method.
Slika 8. Analiza podskupina oralnog mukozitisa procijenjenog omjerom šansi: (A) Spol – 1. %Žene ≤35%; 2. %Žene > 35%; (B) Dob; (C) Regija; (D) Režim liječenja; (E) Ljestvica oralnog mukozitisa; (F) Vrsta intervencije; (G) Intervencijske skupine; (H) Način provedbe.

Table 2. Characteristics of the included studies. Abbreviations: CT – Chemotherapy; CRT – Chemoradiotherapy; RT – Radiotherapy.
Tablica 2. Karakteristike uključenih studija. Kratice: CT – Kemoterapija; CRT – Kemoradioterapija; RT – Radioterapija.

Study	Population characteristics			Intervention characteristics						
Author Year Country	Age Mean (years)	% Female	Cancer	Cancer treatment	Intervention (n of cases)	Intervention group	Control (n of controls)	Follow-up (n post-baseline)	Odds Ratio (95%-CI)	Mean Difference (95%-CI)
Azrudheen et al. 2023 India [67]	45.93	41.67		CT	Flavored with Honey and Tulsi Ice chips (30)	Natural agents	Placebo (30)	1	0.56 (0.12, 2.57)	
Banega et al. 2023 Argentina [68]	66.9	35	Head and neck	CRT	Green tea mouthwash (12)	Natural agents	Routine oral care (8)	1	2.22 (0.08, 61.41)	
Bonomi et al 1 2023 USA [69]	60	13	Head and neck	CRT	RRx-001 + Dexamethasone (12)	Anti-inflammatory, antimicrobials and coating agent	Routine oral care (10)	7	0.26 (0.11, 0.62)	
Bonomi et al 2 2023 USA [69]	60	13	Head and neck	CRT	RRx-001 + Dexamethasone (11)	Anti-inflammatory, antimicrobials and coating agent	Routine oral care (10)	7	0.35 (0.15, 0.81)	
Bonomi et al 3 2023 USA [69]	60	13	Head and neck	CRT	RRx-001 + Dexamethasone (13)	Anti-inflammatory, antimicrobials and coating agent	Routine oral care (10)	7	0.33 (0.14, 0.76)	
Chin et al 2023 Taiwan [70]	56.23	25	Head and neck	CRT	Polyacrylate silver salt oral gel (12)	Anti-inflammatory, antimicrobials and coating agent	Routine oral care (12)	4		-0.74 (-1.05,-0.43)
ChunLing et al 2019 China [71]	51.2	37.63	Head and neck	CRT	Probiotics (58)	Natural agents	Placebo (30)	1	0.22 (0.08, 0.58)	-1.10 (-0.38,-0,82)
de Cássia et al 1, 2022 Brazil [72]	59.3	16.67	Head and neck	CRT	Curcumin solution and blue diode light (10)	Natural agents	Nystatin (10)	4		-0.92 (-1.32,-0.53)
de Cássia et al 2, 2022 Brazil [72]	59.3	16.67	Head and neck	CRT	Photo-biomodulation (10)	Non-pharmacologic	Nystatin (10)	4		- 0.83 (-1.23,-0,42)
Delavarian et al, 2019 Iran [73]	59.03	40.63	Head and neck	RT	Curcumin (16)	Natural agents	Placebo (16)	6	0,50 (0.22, 1.15)	-0.66 (-0.94,-0.37)
Fernandes et al 2022 Brazil [74]	58.7	25	Head and neck	CRT	Brazilian Organic Propolis – Honey (32)	Natural agents	Placebo (28)	5		-0.06 (-0.52, 0.40)
Habsari et al 2020 Indonesia [75]		33	Non-Hodgkin lymphoma	CT	Vitamin E (31)	Natural agents	Placebo (31)	1	0.13 (0.01, 2.61)	
Hasheminasab et al 2020 Iran [76]	44,74	100	Breast cancer	CT	Plantago ovata-based herbal compound	Natural agents	Placebo (14)	2		-0.00 (-0.24, 0.24)
Kaur et al 2024 India [77]			Head and neck	RT	Honey(30)	Natural agents	No intervention (30)	1	0.03 (0.00, 0.29)	-1.47 (-1.87,-1.07)
Kia et al 2021 Iran [78]	55.96	44		CRT	Curcumin (25)	Natural agents	Placebo (25)	4		-0.44 (-0.72,-0.16)
Kurane et al 2020 India [79]		35		CT	Cryotherapy (20)	Non-pharmacological	Non intervention (20)	1	0.18 (0.01, 4.01)	
Lopes et al 1 2021 Brazil [80]	59.75	14.6	Head and neck	RT	Photo-biomodulation (25)	Non-pharmacological	Routine oral care (23)	4	0.23 (0.10, 0.52)	

Lopes et al 2 2023 Brazil [81]	57.08	14.6	Head and neck	CRT	Mucoadhesive phytomedicine - *Curcuma longa L.* and *Bidens pilosa L.* + Photo-biomodulation (25)	Natural agents	Routine oral care + Photo-biomodulation (27)	4	1.49 (0.66, 3.38)	0.15 (-0.17, 0.47)
Mirza et al 2022 India [82]	55	6.5	Head and neck	CRT	Probiotics – *Bacillus clausii UBBC-07* (23)	Natural agents	Distilled water (23)	1	0.23 (0.07, 0.80)	-0.48 (-0.86,-0.10)
Pakravan et al 2019 Iran [83]	57.5	41.67	Head and neck	RT	Triamcinolone acetonide (30)	Anti-inflammatory, antimicrobials and coating agent	Placebo (30)	4		-0.44 (-0.74,-0.13)
Ravindra et al 2019 India [84]		35	Head and neck	CRT	Chlorhexidine mouthwash (30)	Anti-inflammatory, antimicrobials and coating agent	KMnO4 mouthwash (30)	1		0.47 (0.04, 0.90)
Saniya et al 2023 India [85]			Head and neck	CRT	Ayurvedic mouthwash (30)	Natural agents	Saline mouthwash (30)	1		-0.16 (-0.34, 0.02)
Selvi et al 2019 Maldives [86]		66.7		CT	Saline mouthwash (30)	Natural agents	No intervention (30)	1	0.43 (0.15, 1.24)	
Serageldin et al 2023 Egypt [87]		100	Breast cancer	CT	Metformin oral (35)	Anti-inflammatory, antimicrobials and coating agent	No intervention (35)	16	0.20 (0.10, 0.41)	
Shaolong et al 2024 China [88]	46.67	27	Head and neck	CRT	Compound Kushen Injection(48)	Natural agents	No intervention (52)	1	0.02 (0.01, 0.07)	
Shin et al 2019 Korea [89]	45.76			CT	Cryotherapy (25)	Non-pharmacological	Routine oral care (25)	3		-0.12 (-0.37, 0.13)
Srinivasan et al 1 2019 India [90]	53.3	7.14	Head and neck	CRT	Clotrimazole lozenges and soda bicarbonate mouthwash (28)	Anti-inflammatory, antimicrobials and coating agent	Soda bicarbonate mouthwash (28)	1	1.62 (0.53, 4.94)	
Srinivasan et al 2 2019 India [91]	52	10	Head and neck	CRT	Benzydamine mouthwash and saline mouthwash (20)	Anti-inflammatory, antimicrobials and coating agent	Saline mouthwash (20)	1	1.56 (0.42, 5.76)	
Thomas et al 2023 India [92]	57.6	25	Head and neck	CRT	Turmeric Mouthwash (Curcumin) (46)	Natural agents	Benzy-damine mouthwash (46)	7	0.18 (0.09, 0.36)	
Wei et al 2024 China [93]	56.45	24	Head and neck	CRT	Early nutritional intervention (50)	Non-pharmacological	Late nutritional intervention (50)	1	0.13 (0.01, 1.06)	

Risk of bias in Included Studies

All included studies were randomized controlled trials. Overall, methodological quality was mixed: 5 studies were assessed as having low risk of bias, 19 as unclear risk, and 3 as high risk. The distribution of risk of bias assessments is shown in Figure 2. Funnel plots suggested minimal publication bias, with the trim-and-fill method estimating zero missing studies for mean difference analyses and one potentially missing study for odds ratio analyses (Figure 3). Figure 4 shows the forest plot of odds ratios and 95% confidence intervals for the effect of intervention groups on oral mucositis incidence, after excluding high-risk studies identified in the RoB 1.0 analysis.

Rizik od pristranosti u uključenim studijama

Sve uključene studije bile su randomizirana kontrolirana ispitivanja. Sveukupno, metodološka kvaliteta bila je mješovita: 5 je procijenjeno kao studije s niskim rizikom od pristranosti, 19 kao one s nejasnim rizikom i 3 s visokim rizikom. Raspodjela rizika od pristranosti prikazana je na slici 2. Ljevkasti dijagrami sugeriraju minimalnu pristranost objavljivanja, pri čemu se metodom obrezivanja i popunjavanja procjenjuje da nema nedostajućih studija za analize srednjih razlika i jednu potencijalno nedostajuću studiju za analize omjera mogućnosti (slika 3.). Na slici 4 šumski je dijagram omjera mogućnosti i 95 % intervala pouzdanosti za učinak intervencijskih skupina kad je riječ o incidenciji oralnoga mukoziti-

Meta-analysis

Primary Outcome – Mean difference (MD)

The pooled analysis demonstrated that interventions significantly reduced the severity of oral mucositis compared with controls. The overall MD was –0.47 (95% CI: –0.71 to –0.24, p < 0.001), indicating a moderate-to-large beneficial effect. Figure 5 presents the forest plot of MD and 95% confidence intervals for the mucositis scale. The red diamond represents the overall pooled effect. Negative values indicate a reduction in mucositis favoring the intervention group. Vertical dashed line indicates no effect (MD = 0).

Heterogeneity was high (I^2 = 89.1%). Subgroup analyses were conducted for sex, age, geographic region, cancer type, treatment regimen, mucositis scale, intervention type, intervention groups, and delivery method.

Subgroup analyses yielded the following key findings:

- By region: Significant effects were observed in East and South Asia (MD = –0.65, 95% CI: –1.11 to –0.18) and the Middle East/North Africa (MD = –0.37, 95% CI: –0.62 to –0.13).
- By cancer type: Only head and neck cancer studies showed a significant effect (MD = –0.52, 95% CI: –0.81 to –0.23).
- By treatment regimen: Significant effects were observed for CRT (MD = –0.42, 95% CI: –0.71 to –0.12) and RT (MD = –0.84, 95% CI: –1.32 to –0.35).
- By intervention category: Natural agents (MD = –0.51, 95% CI: –0.81 to –0.20) and non-pharmacological interventions (MD = –0.56, 95% CI: –0.98 to –0.14) demonstrated significant effects.
- By delivery method: Significant results were observed for capsule/pill administration (MD = –0.73, 95% CI: –1.04 to –0.42) and topical non-pharmacological approaches (MD = –0.56, 95% CI: –0.98 to –0.14).

However, no significant differences were found in the effect size across all subgroups considered (Table 3, Figure 6).

Primary Outcome – Odds ratio (OR)

When analyzed as a dichotomous outcome, interventions also significantly reduced the risk of oral mucositis compared with controls. The pooled OR was 0.31 (95% CI: 0.19–0.49, p < 0.001), confirming a robust beneficial effect. Figure 7 presents the forest plot of OR and 95% confidence intervals for the mucositis scale. The red diamond represents the overall pooled effect. Negative values indicate a reduction in mucositis favoring the intervention group. Vertical dashed line indicates no effect (OR = 1).

Heterogeneity among studies was very high (I^2 = 92,0%). This heterogeneity was explored through subgroup analysis (sex, age, region, cancer type, treatment regimen, oral mucositis scale, intervention type, intervention groups, and delivery method groups).

The treatment effect was statistically significant across the categories of sex, treatment regimen, intervention type (pharmacological vs. non-pharmacological), and intervensa, nakon isključivanja studija visokoga rizika identificiranih u analizi RoB 1.0.

Metaanaliza

Primarni ishod – srednja razlika (MD)

Sveukupna analiza pokazala je da su intervencije značajno smanjile težinu oralnoga mukozitisa u usporedbi s kontrolnom skupinom. Ukupni MD bio je -0,47 (95 % CI: –0,71 do -0,24, p < 0,001), što upućuje na umjeren do velik koristan učinak. Na slici 5. je šumski dijagram MD-a i 95 % intervala pouzdanosti za ljestvicu mukozitisa. Crveni romb pokazuje ukupni združeni učinak. Negativne vrijednosti upozoravaju na smanjenje mukozitisa u korist intervencijske skupine. Isprekidana okomita crta označava da nema učinka (MD = 0).

Heterogenost je bila visoka (I^2 = 89,1 %). Analize podskupina obavljene su prema spolu, dobi, zemljopisnoj regiji, vrsti raka, režimu liječenja, ljestvici mukozitisa, vrsti intervencije, intervencijskim skupinama i načinu primjene.

Analize podskupina dale su sljedeće ključne nalaze:

- Po regiji: značajni učinci uočeni su u istočnoj i južnoj Aziji (MD = –0,65, 95 % CI: –1,11 do –0,18) te na Bliskom istoku/u sjevernoj Africi (MD = –0,37, 95 % CI: –0,62 do –0,13).
- Prema vrsti raka: samo su studije raka glave i vrata pokazale značajan učinak (MD = –0,52, 95 % CI: –0,81 do –0,23).
- Prema režimu liječenja: značajni učinci uočeni su za CRT (MD = –0,42, 95 % CI: –0,71 do –0,12) i RT (MD = –0,84, 95 % CI: –1,32 do –0,35).
- Prema kategoriji intervencije: prirodni agensi (MD = –0,51, 95 % CI: –0,81 do –20) i nefarmakološke intervencije (MD = –0,56, 95 % CI: –0,98 do –0,14) pokazali su značajne učinke.
- Prema načinu primjene: značajni rezultati uočeni su pri primjeni kapsula/pilula (MD = –0,73, 95 % CI: –1,04 do –0,42) i lokalnih nefarmakoloških pristupa (MD = –0,56, 95 % CI: –0,98 do –0,14).

Nisu pronađene značajne razlike u veličini učinka u svim razmatranim podskupinama (tablica 3., slika 6.).

Primarni ishod – omjer mogućnosti (OR)

Kada se analiziraju kao dihotomni ishod, intervencije su također značajno smanjile rizik od oralnoga mukozitisa u usporedbi s kontrolnom skupinom. Združeni OR bio je 0,31 (95 % CI: 0,19 – 0,49, p < 0,001), što potvrđuje snažan i blagotvoran učinak. Na slici 7. je šumski dijagram OR-a i 95 % intervala pouzdanosti za ljestvicu mukozitisa. Crveni romb označava ukupni združeni učinak. Negativne vrijednosti upućuju na smanjenje mukozitisa u korist intervencijske skupine. Isprekidana okomita crta označava da nema učinka (OR = 1).

Heterogenost među studijama bila je vrlo visoka (I^2 = 92,0 %). Ta heterogenost istražena je analizom podskupina (spol, dob, regija, vrsta raka, režim liječenja, ljestvica oralnoga mukozitisa, vrsta intervencije, intervencijske skupine, skupine metoda primjene).

Učinak liječenja bio je statistički značajan u svim kategorijama spola, režima liječenja, vrste intervencije (farmakološ-

Table 3. Subgroup analysis for the oral mucositis assessed by mean difference in mucositis scale.
Tablica 3. Analiza podskupina za oralni mukozitis procijenjen srednjom razlikom na ljestvici mukozitisa.

	Number of studies		MD (95%-CI)	p-value
Sex				
%Female ≤35%	8	89.3	-0.49 (-0.90,-0.08)	0.75
%Female >35%	6	82.0	-0.57 (-0.86,-0.28)	
Age				
44-55	6	84.3	-0.48 (-0.80,-0.16)	0.93
56-67	7	77.9	-0.50 (-0.77,-0.23)	
Region				
East and South Asia	3	87.9	-0.65 (-1.11,-0.18)	0.88
Middle East and North Africa	4	68.1	-0.37 (-0.62,-0.13)	
South America	4	82.4	-0.41 (-0.88,0.06)	
South Asia	5	92.4	-0.49 (-1.06,0.07)	
Cancer type				
Head and Neck	12	89.9	-0.52 (-0.81,-0.23)	0.26
Other	3	46.2	-0.17 (-0.37,0.03)	
Treatment Regimen				
CT	3	75.7	-0.26 (-0.62,0.11)	0.29
RT	3	84.9	-0.84 (-1.32,-0.35)	
CRT	10	88.1	-0.42 (-0.71,-0.12)	
Oral Mucositis Scale				
WHO	10	89.4	-0.43 (-0.78,-0.09)	0.27
NCI-CTCAE	4	50.1	-0.76 (-0.98,-0.54)	
Intervention type				
Non-pharmacological	3	72.6	-0.56 (-0.98,-0.14)	0.68
Pharmacological	13	90.4	-0.45 (-0.72,-0.18)	
Interventions groups				
Anti-inflammatory, antimicrobials and coating agent	3	87.9	-0.26 (-0.82,0.31)	0.67
Natural agents	10	9.10	-0.51 (-0.81,-0.20)	
Non-pharmacological	3	72.6	-0.56 (-0.98,-0.14)	
Delivery method groups				
Capsule/pill	3	72.2	-0.73 (-1.04,-0.42)	0.44
Topic non-pharmacological	3	72.6	-0.56 (-0.98,-0.14)	
Topic pharmacological	8	91.0	-0.36 (-0.72,0.00)	

tion groups.

Subgroup analyses yielded the following key findings:

- By age: Significant effects were observed only in participants aged 56–67 years (OR = 0.36, 95% CI: 0.23–0.58).
- By region: Significant effects were reported in East and South Asia (OR = 0.08, 95% CI: 0.03–0.27), South Asia (OR = 0.39, 95% CI: 0.19–0.83), South America (OR = 0.39, 95% CI: 0.19–0.83), and the USA (OR = 0.31, 95% CI: 0.19–0.51).
- By treatment regimen: Statistically significant reductions were observed for CT (OR = 0.27, 95% CI: 0.16–0.47), RT (OR = 0.28, 95% CI: 0.15–0.53), and CRT (OR = 0.34, 95% CI: 0.17–0.68).
- By mucositis scale: Both WHO (OR = 0.33, 95% CI: 0.20–0.53) and NCI-CTCAE (OR = 0.27, 95% CI: 0.17–0.42) scales showed consistent beneficial effects.
- By intervention group: Natural agents (OR = 0.26, 95% CI: 0.12–0.54) and non-pharmacological interventions

ka vs. nefarmakološka) i intervencijskih skupina.

Analize podskupina dale su sljedeće ključne nalaze:

- Prema dobi: značajni učinci uočeni su samo kod sudionika u dobi od 56 do 67 godina (OR = 0,36, 95 % CI: 0,23 – 0,58).
- Prema regiji: značajni učinci zabilježeni su u istočnoj i južnoj Aziji (OR = 0,08, 95 % CI: 0,03 – 0,27), južnoj Aziji (OR = 0,39, 95 % CI: 0,19 – 0,83), južnoj Americi (OR = 0,39, 95 % CI: 0,19 – 0,83) i SAD-u (OR = 0,31, 95 % CI: 0,19 – 0,51).
- Prema režimu liječenja: statistički značajna smanjenja uočena su za CT (OR = 0,27, 95 % CI: 0,16 – 0,47), RT (OR = 0,28, 95 % CI: 0,15 – 0,53) i CRT (OR = 0,34, 95 % CI: 0,17 – 0,68).
- Prema ljestvici mukozitisa: i WHO (OR = 0,33, 95 % CI: 0,20 – 0,53) i NCI-CTCAE (OR = 0,27, 95 % CI: 0,17 – 0,42) ljestvica pokazale su dosljedne blagotvorne učinke.
- Prema intervencijskoj skupini: prirodni agensi (OR =

Table 4. Subgroup analysis for the oral mucositis assessed by OR.
Tablica 4. Analiza podskupina za oralni mukozitis procijenjen OR-om.

	Number of studies		OR (95%-CI)	p-value
Sex				
%Female <25%	10	67.4	0.41 (0.23, 0.74)	0.17
%Female ≥25%	10	63.3	0.22 (0.12, 0.42)	
Age				
44-55	6	83.1	0.33 (0,10, 1.10)	0.86
56-67	9	53.4	0,36 (0,23, 0,58)	
Region				
East and South Asia	4	53.4	0.08 (0.03, 0.27)	0.067
South America	3	67.3	0.68 (0.21, 2.22)	
South Asia	4	61.8	0.39 (0.19, 0.83)	
USA	3	0.00	0.31 (0.19, 0.51)	
Treatment Regimen				
CT	5	0.00	0.27 (0.16, 0.47)	0.80
RT	3	17.8	0.28 (0.15, 0.53)	
CRT	12	80.1	0.34 (0.17, 0.68)	
Oral Mucositis Scale				
WHO	10	52.7	0.33 (0.20, 0.53)	0.91
NCI-CTCAE	4	0.00	0.27 (0.17, 0.42)	
RTOG	5	83.1	0.38 (0.07, 2.13)	
Intervention type				
Non-pharmacological	4	0.00	0.26 (0.13, 0.50)	0.74
Pharmacological	16	77.0	0.32 (0.18, 0.55)	
Interventions groups				
Anti-inflammatory, antimicrobials and coating agent	6	61.5	0.44 (0.24, 0.80)	0.42
Natural agents	11	76.7	0.26 (0.12, 0.54)	
Non-pharmacological	3	0.00	0.21 (0.10, 0.45)	
Delivery method groups				
Capsule/pill	4	0.00	0.27 (0.17, 0.43)	0.48
Topic non-pharmacological	4	0.00	0.26 (0.13, 0.50)	
Topic pharmacological	7	68.5	0.42 (0.18, 1.01)	
Intravenously	4	81.6	0.17 (0.06, 0.50)	

(OR = 0.21, 95% CI: 0.10–0.45) demonstrated significant reductions.

- By delivery method: Significant results were observed for capsules/pills (OR = 0.27, 95% CI: 0.17–0.43), topical non-pharmacological approaches (OR = 0.26, 95% CI: 0.13–0.50), and intravenous administration (OR = 0.17, 95% CI: 0.06–0.50).

However, no significant differences were found in the effect size across all subgroups considered. (Table 4, Figure 8)

Discussion

High levels of heterogeneity among included studies limited the interpretation of the overall estimates. Nevertheless, the results of subgroup analysis provided a more structured aggregation of data, improving robustness and credibility of the significant effects observed.

Subgroup analyses are often underpowered when there are few studies or events per subgroup, and tests for subgroup differences typically have low power (94). In our review, sub-

0,26, 95 % CI: 0,12 – 0,54) i nefarmakološke intervencije (OR = 0,21, 95 % CI: 0,10 – 0,45) pokazali su značajna smanjenja.

- Prema metodi primjene: značajni rezultati uočeni su za kapsule/pilule (OR = 0,27, 95 % CI: 0,17 – 0,43), lokalne nefarmakološke pristupe (OR = 0,26, 95 % CI: 0,1 –0,50) i intravensku primjenu (OR = 0,17, 95 % CI: 0,06 – 0,50).

Nisu pronađene značajne razlike u veličini učinka među svim razmatranim podskupinama. (tablica 4., slika 8.)

Rasprava

Visoka heterogenost među uključenim studijama ograničila je interpretaciju ukupnih procjena. Ipak, poboljšavajući robusnost i vjerodostojnost uočenih značajnih učinaka, analiza podskupina omogućila je strukturiraniju agregaciju podataka.

Analize podskupina često su slabije snage kada postoji malo studija ili događaja po podskupini, a testovi za razlike među podskupinama obično imaju nisku snagu (94). U na-

group analyses were performed as planned, but we acknowledge that subgroups with a limited number of studies should be carefully interpreted. In addition, variability in how outcomes were defined, and evidence originated from specific geographic regions, could limit the generalizability of our findings to other settings.

The systematic review and meta-analysis suggest that variety of interventions, both pharmacological and non-pharmacological, demonstrated efficacy in the prevention and treatment of chemotherapy- and/or radiotherapy-induced OM. Notably, natural agents (OR = 0.26; 95% CI: 0.12, 0.54; MD = -0.51; 95% CI: -0.81, -0.20) and non-pharmacological interventions (OR = 0.21; 95% CI: 0.10, 0.45; MD = -0.56; 95% CI: -0.98, -0.14) showed statistically significant effects, supporting previous evidence of their beneficial role in OM management (12,17,95-98).

These findings are consistent with the 2020 guidelines of the MASCC/ISOO Mucositis Study Group, which recommend non-pharmacological therapies such as photobiomodulation (laser therapy) and cryotherapy, as well as natural products like honey and curcumin. In this review, honey and curcumin were evaluated in three and five studies, respectively, supporting their role as integral components in the management of OM (17, 67, 72-74, 77, 78, 81, 92). According to Zadik et al., photobiomodulation has demonstrated efficacy in preventing OM among patients with head and neck cancer, a finding also supported in this review (MD = -0.52; 95% CI: -0.81, -0.23), (99-102). This population is at particularly high risk of OM due to tumor location and localized effects of radiotherapy, which justifies the need for more specific therapeutic approaches (103). Similarly, the efficacy of cryotherapy, especially in the context of chemotherapy, is consistent with the results reported by Brown et al. and Riley et al (95, 96).

Regarding delivery methods, capsules or pills-based interventions demonstrated a significant protective effect (OR = 0.27; 95% CI: 0.17, 0.43; MD = -0.73; 95% CI: -1.04, -0.42).

In contrast, topical pharmacological interventions (e.g., mouthwashes containing green tea, curcumin, chlorhexidine, or honey) yielded less pronounced reductions in OM severity, with no significant impact overall. Previous studies suggested that topical approaches may be more effective if initiated early, but the current evidence base remains limited (12). Similarly, interventions involving anti-inflammatories, antimicrobials, and coating agents did not show significant reductions in OM severity. A small number of studies in these categories represents a limitation and highlights the need for further high-quality trials.

Geographical subgroup analyses revealed stronger effects in East and South Asia (OR = 0.08, 95% CI: 0.03–0.27; MD = –0.65, 95% CI: –1.11 to –0.18), the Middle East (MD = –0.37, 95% CI: –0.62 to –0.13), and South Asia (OR = 0.39, 95% CI: 0.19–0.83). These differences may be influenced by regional variations in clinical practices, healthcare infrastructure, dietary habits, or cultural use of herbal agents. Importantly, no statistically significant differences were found across subgroups overall, suggesting a consistent therapeutic

šem su pregledu analize podskupina provedene prema planu, ali priznajemo da podskupine s ograničenim brojem studija treba oprezno interpretirati. Osim toga, varijabilnost u načinu na koji su ishodi definirani i dokazi koji potječu iz određenih geografskih regija mogli bi ograničiti generalizaciju naših nalaza na druge postavke.

Sustavni pregled i metaanaliza sugeriraju da su razne intervencije, i farmakološke i nefarmakološke, pokazale učinkovitost u prevenciji i liječenju OM-a prouzročenog kemoterapijom i/ili radioterapijom. Značajno je da su prirodni agensi (OR = 0,26; 95 % CI: 0,12, 0,54; MD = –0,51; 95 % CI: –0,81, –0,20) i nefarmakološke intervencije (OR = 0,21; 95 % CI: 0,10, 0,45; MD = –0,56; 95 % CI: –0,98, –0,14) pokazali statistički značajne učinke, što podupire dosadašnje dokaze o njihovoj blagotvornoj ulozi u liječenju OM-a (12, 17, 95 – 98).

Ovi su nalazi u skladu sa smjernicama studijske skupine za mukozitis MASCC/ISOO iz 2020. godine koja preporučuje nefarmakološke terapije poput fotobiomodulacije (laserske terapije) i krioterapije te prirodne proizvode poput meda i kurkumina. U ovom pregledu su med i kurkumin procijenjeni u tri, odnosno pet studija, što podupire njihovu ulogu sastavnih komponenti u liječenju OM-a (17, 67, 72 –74, 77, 78, 81, 92). Prema Zadiku i suradnicima, fotobiomodulacija je pokazala učinkovitost u sprječavanju OM-a kod pacijenata s rakom glave i vrata, što je nalaz koji je također podržan u ovom pregledu (MD = -0,52; 95 % CI: -0,81, -0,23) (99 – 102). Ova populacija ima znatno veći rizik od OM-a zbog lokacije tumora i lokaliziranih učinaka radioterapije, što opravdava potrebu za specifičnijim terapijskim pristupima (103). Slično tomu, učinkovitost krioterapije, posebno u kontekstu kemoterapije, u skladu je s rezultatima o kojima su izvijestili Brown i suradnici te Riley i suradnici (95, 96).

Kad je riječ o metodama primjene, intervencije na bazi kapsula ili tableta pokazale su značajan zaštitni učinak (OR = 0,27; 95 % CI: 0,17, 0,43; MD = –0,73; 95 % CI: –1,04, –0,42).

Suprotno tomu, lokalne farmakološke intervencije (vodice za ispiranje usta koje sadržavaju zeleni čaj, kurkumin, klorheksidin ili med) manje su izraženo smanjile težinu OM-a, bez značajnoga ukupnog utjecaja. U dosadašnjim studijama sugeriralo se da lokalni pristupi mogu biti učinkovitiji ako se s njima počne rano, ali trenutačna baza dokaza ostaje ograničena (12). Slično tomu, intervencije koje uključuju protuupalne lijekove, antimikrobne lijekove i sredstva za oblaganje nisu značajno smanjile težinu OM-a. Svakako je ograničenje mali broj studija u tim kategorijama pa se ističe potreba za daljnjim visokokvalitetnim ispitivanjima.

Geografske analize podskupina otkrile su snažnije učinke u istočnoj i južnoj Aziji (OR = 0,08, 95 % CI: 0,03 – 0,27; MD = –0,65, 95 % CI: -1,11 do -0,18), Bliskom istoku (MD = -0,37, 95 % CI: -0,62 do -0,13) i južnoj Aziji (OR = 0,39, 95 % CI: 0,19 – 0,83). Na te razlike mogu utjecati regionalne varijacije u kliničkoj praksi, zdravstvenoj infrastrukturi, prehrambenim navikama ili kulturnoj upotrebi biljnih sredstava. Važno je da nisu pronađene statistički značajne razlike među podskupinama u cjelini, što sugerira dosljednu terapijsku korist od intervencija u različitim populacijama (1,

benefit of interventions across diverse populations (1, 2, 14).

The results of this meta-analysis, comprising 27 articles from 11 countries, highlighted favorable effects of non-pharmacological interventions (MD = -0.56; OR = 0.21) (such as cryotherapy and photobiomodulation) and natural agents (MD = -0.51; OR = 0.26) (such as honey, green tea and curcumin). These findings align with and reinforce recent international expert consensus published in 2025, such as that by Xia et al., which emphasized the integration of evidence-based natural and non-pharmacological approaches, while underscoring the need for therapeutic personalization (20,104).

Taken together, this review confirms the validity of the MASCC/ISOO 2020 recommendations, while simultaneously demonstrating the necessity of updating them in light of the growing body of evidence published in recent years. The convergence of our results with the 2025 expert consensus highlights the evolving therapeutic landscape and the importance of regularly re-evaluating guidelines to ensure optimal patient care.

Although the present review demonstrates the efficacy of several interventions, it also highlights gaps in the existing literature. Notably, most trials focused exclusively on clinical endpoints, while few included patient-centered outcomes such as pain, quality of life, or functional impact. This limitation in the primary evidence base restricts the ability to fully assess the patient experience of OM and emphasizes the importance of incorporating patient-reported outcomes in future clinical trials (105,106).

This systematic review and meta-analysis demonstrated that non-pharmacological interventions, particularly photobiomodulation and cryotherapy, as well as natural agents such as honey, curcumin, and green tea, are effective in reducing the severity of chemotherapy and/or radiotherapy induced oral mucositis. These findings provide strong support for their integration into supportive care protocols, in line with current MASCC/ISOO guidelines.

Nevertheless, the substantial methodological heterogeneity, variability in outcome assessment scales, and the limited reporting of patient-centered outcomes reduce the certainty of the evidence. Future research should prioritize high-quality randomized controlled trials that incorporate validated patient-reported outcomes such as pain, oral functionality, and quality of life, in order to complement clinical scales and better capture the full impact of oral mucositis (107,108).

The risk of bias was assessed using the RoB 1.0 tool, which has been widely applied in systematic reviews and meta-analyses. Its extensive use facilitates comparability with previous studies. Although a newer version is available, RoB 1.0 remains acceptable and ensures consistency with the existing literature. In addition, independent assessments by two reviewers with a high level of agreement further reinforce the robustness of our evaluation. We therefore consider that the use of RoB 1.0 does not compromise the validity of our conclusions, although future reviews may benefit from adopting RoB 2.0.

Previous reviews and existing guidelines have largely emphasized pharmacological or non-pharmacological interven-

2, 14).

Rezultati ove metaanalize koja obuhvaća 27 članaka iz 11 zemalja istaknuli su povoljne učinke nefarmakoloških intervencija (MD = -0,56; OR = 0,21) (krioterapija i fotobiomodulacija) i prirodnih agensa (MD = -0,51; OR = 0,26) (med, zeleni čaj i kurkumin). Ti nalazi usklađeni su s nedavnim međunarodnim stručnim konsenzusom objavljenim 2025. godine i pojačavaju ga, poput onoga Xia i suradnika koji su istaknuli integraciju prirodnih i nefarmakoloških pristupa utemeljenih na dokazima, a istodobno i potrebu za terapijskom personalizacijom (20, 104).

Uzevši sve u obzir, ovaj pregled potvrđuje valjanost preporuka MASCC/ISOO-a 2020. te istodobno pokazuje potrebu za njihovim ažuriranjem na temelju sve većeg broja dokaza objavljenih posljednjih godina. Konvergencija naših rezultata sa stručnim konsenzusom iz 2025. ističe razvoj terapijskog krajolika i važnost redovitoga ponovnog vrjednovanja smjernica kako bi se osigurala optimalna skrb za pacijente.

Iako ovaj pregled pokazuje učinkovitost nekoliko intervencija, on također ističe praznine u postojećoj literaturi. Značajno je da se većina ispitivanja usredotočila isključivo na krajnje kliničke točke, a malo njih uključivalo je ishode usmjerene na pacijenta poput boli, kvalitete života ili funkcionalnog utjecaja. Ovo ograničenje u primarnoj bazi dokaza ograničava mogućnost potpune procjene pacijentova iskustva s oralnim mukozitisom i ističe važnost uključivanja ishoda koje su prijavili pacijenti u buduća klinička ispitivanja (105, 106).

Ovaj sustavni pregled i metaanaliza pokazali su da su nefarmakološke intervencije, posebno fotobiomodulacija i krioterapija te prirodni agensi poput meda, kurkumina i zelenoga čaja, učinkoviti u smanjenju težine oralnoga mukozitisa prouzročenog kemoterapijom i/ili radioterapijom. Ovi nalazi pružaju snažnu potporu njihovoj integraciji u protokole potporne skrbi, u skladu s trenutačnim smjernicama MASCC/ISOO-a.

Ipak, velika metodološka heterogenost, varijabilnost u ljestvicama procjene ishoda i ograničeno izvještavanje o ishodima usmjerenima na pacijenta smanjuju sigurnost dokaza. Buduća istraživanja trebala bi dati prednost visokokvalitetnim randomiziranim kontroliranim ispitivanjima koja uključuju validirane ishode koje prijavljuju pacijenti poput boli, oralne funkcionalnosti i kvalitete života, kako bi se nadopunile kliničke ljestvice i bolje shvatio puni utjecaj oralnog mukozitisa (107, 108).

Rizik od pristranosti procijenjen je s pomoću alata RoB 1.0 koji se često primjenjuje u sustavnim pregledima i metaanalizama. Njegova opsežna upotreba olakšava uspoređivanje s dosadašnjim studijama. Iako je dostupna novija verzija RoB-a 1.0 ostaje prihvatljiv i osigurava dosljednost s postojećom literaturom. Uz to, neovisne procjene dvaju recenzenata s visokom razinom slaganja dodatno jačaju snagu naše evaluacije. Zato smatramo da korištenje RoB-a 1.0 ne ugrožava valjanost naših zaključaka, iako bi budući pregledi mogli imati koristi od usvajanja RoB-a 2.0.

Dosadašnji pregledi i postojeće smjernice uglavnom su isticali farmakološke ili nefarmakološke intervencije. Ovaj

tions. This review, by including the most recent studies and performing subgroup analyses by cancer type, delivery method, and geographic region, provides a more comprehensive synthesis. This focus fills an important gap by highlighting practical and applicable approaches and by framing the evidence within the context of the latest international expert consensus.

All told, our results reinforce the validity of the 2020 MASCC/ISOO recommendations, while also underscoring the need for an evidence-based update. However, the considerable methodological heterogeneity, the diversity of outcome scales employed, and the scarcity of patient-centered outcomes limit the robustness of our conclusions. This highlights the importance of future investigations that incorporate subjective variables such as pain, oral functionality, and quality of life. In light of recent expert consensus published in 2025, integrating both pharmacological and non-pharmacological strategies with a personalized approach should represent the next step in clinical management of oral mucositis.

Conclusion

This systematic review and meta-analysis provide robust evidence supporting the efficacy of both pharmacological and non-pharmacological interventions for the prevention and management of chemotherapy- and/or radiotherapy-induced oral mucositis. The analysis of 27 randomized controlled trials demonstrated that natural agents such as honey, curcumin, and green tea, as well as non-pharmacological approaches—particularly photobiomodulation and cryotherapy—significantly reduce the incidence and severity of mucositis, with moderate-to-large pooled effect sizes.

From a clinical standpoint, these findings reinforce the need for integrating evidence-based supportive care into oncology protocols, particularly for head and neck cancer patients, where mucositis prevalence and severity are highest. The results are in line with, and expand upon, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology 2020 recommendations, thus providing updated evidence aligned with the 2025 international expert consensus.

Despite methodological heterogeneity among studies, the consistency of beneficial effects across multiple subgroups—cancer type, treatment modality, and region—supports the external validity of these interventions. The inclusion of patient-reported outcomes in future trials is essential to better assess quality of life, functional impact, and pain management, thus ensuring that therapeutic strategies address both clinical and human dimensions of care.

Clinically, this synthesis confirms that photobiomodulation and cryotherapy should be prioritized as first-line non-pharmacological strategies, complemented by natural pharmacological agents as adjuvants. The adoption of these interventions in daily oncology practice may substantially reduce symptom burden, treatment interruptions, and overall healthcare costs, thus improving patient outcomes and adherence to cancer therapy.

pregled, uključivanjem najnovijih studija i provođenjem analiza podskupina prema vrsti raka, načinu primjene i zemljopisnoj regiji, pruža sveobuhvatniju sintezu. Ovaj fokus popunjava važnu prazninu te ističe praktične i primjenjive pristupe uokvirujući dokaze u kontekst najnovijega međunarodnoga stručnog konsenzusa.

Uzeti zajedno, naši rezultati jačaju valjanost preporuka MASCC/ISOO-a iz 2020., a istodobno ističu potrebu za ažuriranjem na temelju dokaza. Međutim, znatna metodološka heterogenost, raznolikost korištenih ljestvica ishoda i rijetkost ishoda usmjerenih na pacijenta ograničavaju snagu naših zaključaka. To ističe važnost budućih istraživanja koja bi trebala uključiti subjektivne varijable poput bola, oralne funkcionalnosti i kvalitete života. U svjetlu nedavnoga stručnog konsenzusa objavljenog 2025. godine, integriranje farmakoloških i nefarmakoloških strategija s personaliziranim pristupom trebalo bi biti sljedeći korak u kliničkom liječenju oralnoga mukozitisa.

Zaključak

Ovaj sustavni pregled i metaanaliza daju čvrste dokaze koji podupiru učinkovitost farmakoloških i nefarmakoloških intervencija u prevenciji i liječenju oralnoga mukozitisa prouzročenog kemoterapijom i/ili radioterapijom. Analiza 27 randomiziranih kontroliranih ispitivanja pokazala je da prirodni agensi poput meda, kurkumina i zelenoga čaja te nefarmakološki pristupi – posebno fotobiomodulacija i krioterapija – značajno smanjuju incidenciju i težinu mukozitisa s umjerenim do velikim združenim učinkom.

S kliničkog stajališta ti nalazi pojačavaju potrebu za integriranjem potporne skrbi na temelju dokaza u onkološke protokole, posebno za pacijente s rakom glave i vrata, u kojima su prevalencija i težina mukozitisa najveće. Rezultati su u skladu s preporukama studijske skupine za mukozitis Multinacionalnoga udruženja potporne skrbi kod raka i Međunarodnoga društva za oralnu onkologiju iz 2020. i proširuju ih, pružajući ažurirane dokaze usklađene s međunarodnim konsenzusom stručnjaka iz 2025. godine.

Unatoč metodološkoj heterogenosti među studijama, dosljednost korisnih učinaka u više podskupina – vrsta raka, načinu liječenja i regiji – podupire vanjsku valjanost ovih intervencija. Uključivanje ishoda koje su prijavili pacijenti u buduća ispitivanja ključno je za bolju procjenu kvalitete života, funkcionalnog utjecaja i upravljanja bolom, osiguravajući da terapijske strategije obuhvate i kliničku i ljudsku dimenziju skrbi.

Klinički, ova sinteza potvrđuje da fotobiomodulacija i krioterapija trebaju biti prioritet kao nefarmakološke strategije prve crte, nadopunjene prirodnim farmakološkim sredstvima kao adjuvansima. Primjena ovih intervencija u svakodnevnoj onkološkoj praksi može znatno smanjiti opterećenje simptomima, prekide liječenja i ukupne troškove zdravstvene zaštite, čime se poboljšavaju ishodi za pacijente i pridržavanje terapije raka.

Clinical Interpretation: The synthesis supports integration of non-pharmacological (laser, cryotherapy) and natural adjuvant agents (honey, curcumin) into standard supportive care protocols for oncology patients.

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Klinička interpretacija: Sinteza podupire integraciju nefarmakoloških (laser, krioterapija) i prirodnih pomoćnih sredstava (med, kurkumin) u standardne protokole potporne skrbi za onkološke pacijente.

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Sažetak

Uvod: Oralni mukozitis česta je nuspojava kemoterapije i radioterapije, a obilježavaju ga eritematozne lezije, edemi, ulceracija, atrofija ili čak krvarenje. Aktualni dokazi pokazuju složenost njegova liječenja i koliko je važno prilagoditi terapijski pristup individualnom profilu pacijenta kako bi se poboljšala kvaliteta života tijekom liječenja raka. **Svrha:** Procijeniti učinkovitost farmakoloških i nefarmakoloških intervencija za prevenciju i liječenje oralnoga mukozitisa prouzročenog kemoterapijom i/ili radioterapijom. **Materijali i metode:** Također je proveden sustavni pregled s metaanalizom 27 članaka objavljenih između 2019. i 2024. godine, sa svrhom karakterizacije i kontekstualizacije terapijskih intervencija za oralni mukozitis. **Rezultati i rasprava:** Ovaj sustavni pregled i metaanaliza sugeriraju da su različite nefarmakološke intervencije (krioterapija i fotobiomodulacija) i farmakološke intervencije, posebno prirodni agensi (med, kurkumin, zeleni čaj), učinkovite u prevenciji i liječenju oralnoga mukozitisa. **Zaključak:** Oralni mukozitis veoma je česta nuspojava kod pacijenata koji se podvrgavaju kemoterapiji i/ili radioterapiji, sa značajnim funkcionalnim i nutritivnim implikacijama i aspektima potpore liječenja. Sustavni pregled s metaanalizom pokazao je učinkovitost nefarmakoloških i prirodnih intervencija.

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