

Review Article

The Impact of Public Health on Oral Mucositis Caused by Cancer Treatment: A Narrative Review Study

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Abstract

Cancer and its treatment complications are among the major challenges for health systems. Oral mucositis (OM) is one of the most common complications of chemotherapy and radiotherapy, which, with inflammation and painful ulcers of the oral mucosa, leads to nutritional disorders, reduced quality of life (QoL), and even interruption of the treatment process. This narrative review study was conducted by searching PubMed and Google Scholar databases and evaluating studies related to effective interventions on OM (including non-pharmacological methods, natural compounds, nutritional interventions, and health care). The findings revealed that the most effective interventions simultaneously target multiple pathophysiological axes (oxidative stress, inflammation, cellular damage, and secondary infection). Low-level laser therapy and cryotherapy were identified as the safest and most effective non-pharmacological methods of prevention. Furthermore, natural compounds demonstrated significant anti-inflammatory and reparative effects. Moreover, nutritional interventions and physical protectors played an important supportive role in reducing the severity of complications while accelerating tissue regeneration. Optimal management of OM requires an integrated and multifaceted approach. It appears that a combination of preventive methods (laser therapy and cryotherapy), targeted therapies with natural compounds, and supportive care (oral hygiene and nutrition) can significantly decrease the incidence and severity of this condition.

Keywords: Public health, Mucositis, Cancer



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Introduction

Cancer is one of the most serious health and financial issues worldwide, affecting millions of people annually. In 2020, approximately 20 million people died from the disease. In addition, the incidence of cancer is increasing rapidly and is expected to reach nearly 35 million cases by 2050. Lung, breast, colorectal, and prostate cancer are the most common types of cancer that cause the highest incidence and mortality rates. Likewise, there are significant differences in the incidence and mortality rates of these types of cancer among developed and developing countries, indicating the need for prevention and treatment programs tailored to each region (1). Despite significant advances in anti-cancer treatments, especially chemotherapy, which has increased life expectancy, these treatments are frequently associated with serious side effects that can negatively impact patients' physical and mental health. Oral mucositis (OM) is one of the most prevalent complications, which manifests as inflammation and painful sores in the OM. This condition causes problems in feeding, swallowing, and

speaking, and sometimes requires interruption or reduction of chemotherapy doses, ultimately affecting the course of treatment. According to some studies, implementing regular oral hygiene protocols can significantly reduce the risk of mucositis and oral infections (2, 3).

There have been limited studies in this area so far. Thus, this review study aims to investigate the effect of oral health care on preventing the symptoms and complications of cancer treatments, especially OM, as well as its role in rehabilitation and improvement of the QoL of patients. A more detailed study of this relationship could help develop more effective methods to reduce the complications of OM while improving the well-being of patients.

Overall Study Process

Figure 1 shows the overall process of the study. PubMed and Google Scholar databases were searched for articles published from 2005 to 2025. After selecting the articles and extracting the data, topics were written in three axes: function, mechanism, and health processes.



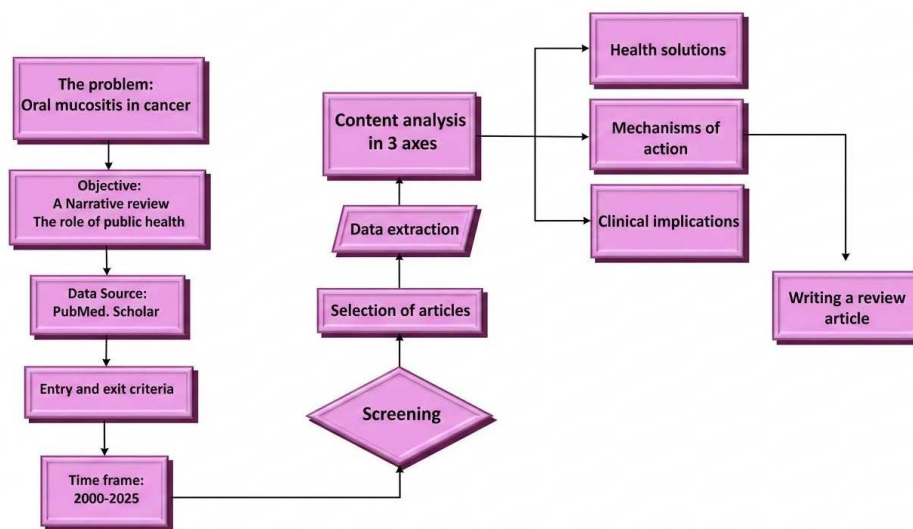


Figure 1. The Flowchart of the Process of This Study

Mucositis

OM, mainly characterized by symptoms such as erythema, atrophy, and ulceration of the OM, is a common side effect of anticancer treatments, including radiation therapy, chemotherapy, and immunotherapy. In addition, it occurs in 20–80% of chemotherapy patients and in almost all people receiving radiation therapy for head and neck tumors. Head and neck cancer is a broad term that includes epithelial malignancies of the paranasal sinuses, nasal cavity, oral cavity, pharynx, larynx, and salivary glands (4). In patients with head and neck cancer undergoing chemotherapy or radiotherapy, mucosal changes are usually observed after a cumulative dose of radiation, and ulcerative lesions frequently appear by the end of the third week of radiotherapy. This complication typically begins 4–5 days after drug injection and reaches its maximum severity about 5 days later (5).

Sufferers experience different symptoms, including severe pain, dehydration, dysphagia, dysgeusia, anorexia, weight loss, and increased susceptibility to secondary and systemic infections, which can interfere with treatment and reduce QoL. The severe pain associated with mucositis is primarily due to direct cytotoxic injury to the OM and subsequent activation of inflammatory pathways (6). This injury sensitizes peripheral neuroreceptors by releasing proinflammatory mediators, and cytokines and contributes to neuroplastic changes that perpetuate pain. Various methods have been proposed to manage this condition. Nonetheless, to the best of our knowledge, there is no definitive cure, and most treatments are palliative. However, severe mucositis may require treatment changes, including dose reduction or discontinuation of treatment, which can increase treatment costs, compromise the effectiveness of cancer treatment, and reduce overall survival (7).

Mouthwash

At the antioxidant level and regulation of the oral chemical environment, allopurinol blocks the endogenous source of reactive oxygen species (ROS) production in the irradiated tissue by directly neutralizing hydroxyl radicals and

inhibiting xanthine oxidase. Additionally, it delays the onset and severity of mucositis, especially in the middle weeks of radiation therapy, by reducing initial damage (8). Furthermore, sodium bicarbonate acts more as a physicochemical substrate for repair by alkalizing the environment, neutralizing the acidity resulting from cell breakdown and bacterial activity, reducing the irritation of sensitive nerves, and providing an unfavorable environment for the growth of *Candida* and other microorganisms. Moreover, it improves oral hygiene by gently washing away debris (9). In addition, zinc, as a cofactor for hundreds of enzymes, biochemically supports the healing process by facilitating DNA and RNA protein synthesis, accelerating epithelial cell division, enhancing the immune response, neutralizing ROS, and stabilizing the membrane. Similarly, the topical use of zinc chloride in mouthwashes focuses these effects directly on the wound site (10, 11). Finally, some compounds have a more prominent role in symptomatic and supportive control than in direct intervention in the pathobiological axis; by the non-competitive inhibition of N-methyl-D-aspartate receptor receptors, topical ketamine interrupts the pain cascade caused by glutamate release in the inflamed mucosa. Likewise, by local penetration into the injured tissue, it creates a limited sensory block that begins within 15 minutes and lasts for 1–3 hours, significantly reducing pain, rest, and odynophagia, without the need for high systemic doses and psychotropic side effects (7, 12). Although atorvastatin is primarily a lipid-lowering drug, it inhibits 3-hydroxy-3-methylglutaryl-coenzyme A reductase and the mevalonate and isoprenoid synthesis pathway and limits the activation of small G proteins (e.g., Ras and Rho), thereby attenuating inflammatory signaling pathways common to mucositis. Further, it has been shown to reduce chemotherapy-induced mucosal injury and inflammation in animal models, although clinical evidence remains more limited than for other interventions (13). Meanwhile, studies have investigated the effects of different solutions on OM. In opioid-based therapy, a morphine solution specifically designed for OM application was used

to deliver the drug directly to mucositis lesions and activate peripheral opioid receptors located in sensory nerve endings. This solution was 2 mg/mL, adjusted to a pH rate of about 6, preservative-free, and with artificial sweeteners for better acceptance. Then, it was sprayed onto the mucosa; a dose of about 50 µg/kg was administered every three hours, and the patient was asked to hold the solution in the mouth for a few seconds and then spit it out (14). The goal was to provide local relief with minimal systemic absorption and reduce the general side effects of morphine. Despite this design, the amount of morphine delivered via the pump was not substantially different between the solution and placebo groups, and the pain relief from the topical solution was not statistically greater than that from placebo. However, intravenous morphine produced stronger and more significant pain relief in the same patients. No serious complications were observed, and local mucosal irritation was similar in all groups, although slightly more irritation was reported in the group receiving morphine solution. These results suggest that, despite the presence of peripheral opioid receptors in the inflamed tissue, the relatively hydrophilic morphine was not sufficiently absorbed in the low pH and damaged OM and did not provide a clinically significant analgesic effect beyond placebo (15, 16). In the natural combination treatment, a syrup-like oral solution containing 300 g of natural honey and 20 g of instant coffee per 600 g of product was used for OM. Then, patients were asked to drink and swallow 10 mL of this solution dropwise every three hours in order to ensure prolonged contact with the mucous membranes of the mouth, pharynx, and esophagus. All three types of the applied solutions (honey and coffee combination, honey alone, and solution containing topical steroids) significantly reduced the severity of mucositis; however, the greatest reduction in lesion severity was observed in the group receiving the honey and coffee combination, followed by honey alone and steroids, respectively. These findings indicated that chemotherapy-induced OM can be successfully treated in a short period of time with a combination of honey and coffee, and that this combination is superior to topical steroids as a complementary, safe, acceptable, relatively inexpensive, and available method (17, 18). The therapeutic function of this combination is likely due to the synergistic effects of the active components in honey and coffee caffeine; honey accelerates the wound healing process by reducing ROS, inhibiting inflammation, having antibacterial properties, stimulating saliva secretion, moisturizing and cleansing the mouth, as well as stimulating epithelial cell proliferation and granulation tissue formation. On the other hand, caffeine, with its anti-inflammatory and antioxidant effects, enhances tissue protection and appears to create a new wound healing-accelerating property alongside honey (17-19). In another herbal treatment, the hydroalcoholic extract of wild pistachio leaves and anise fruits was topically applied to OM. Mucositis was experimentally induced in animals with cytotoxic drugs, and the animals were divided into several groups, including wild pistachio extract, anise

extract, a mixture of both, and control groups (20, 21). Mucosal sampling was performed on days 13, 15, and 17, followed by measuring malondialdehyde (MDA) indices as a marker of lipid peroxidation and oxidative stress (OS), superoxide dismutase (SOD) as an antioxidant defense enzyme, myeloperoxidase (MPO) as an indicator of neutrophil infiltration and activation, and interleukin-1-beta (IL-1β) as a key proinflammatory cytokine, along with epithelial volume density. In the group receiving the mixture of extracts, a significant decrease in MDA, MPO, and IL-1β levels and an increase in SOD activity were observed compared to other groups, and the density of the epithelium increased significantly. Nonetheless, there was no marked difference between the single-substance groups at some times (22, 23). These results revealed that the mixture of wild pistachio and anise can improve OM by reducing OS, inhibiting inflammatory responses, and accelerating epithelial regeneration, and its effect is stronger than that of either extract alone. The mechanism of this effect is multifaceted; both plants contain potent phenolic and antioxidant compounds, and wild pistachio leaves are rich in tocopherols and tocotrienols (forms of vitamin E) and sterols that inhibit free radicals and stabilize cell membranes. Further, the anise extract showed significant antioxidant activity in radical scavenging assays and contained terpenes, glycosides, and sterols with active anti-inflammatory effects. Likewise, the reduction in MDA and increase in SOD in the mixed group confirmed the decrease in free radical load and improved oxidant-antioxidant balance, while the decline in IL-1β and MPO indicated the inhibition of inflammatory pathways and the infiltration of inflammatory cells into the tissue. In addition, the increase in the volume density of the epithelium demonstrated an acceleration in the proliferation, differentiation, and repair of epithelial cells, which is probably due to the presence of tannins and other compounds that accelerate the healing process by inhibiting radicals, enhancing wound contraction, and stimulating angiogenesis and fibroblast activity (23, 24). The topical application of these extracts results in the high concentration of active ingredients at the lesion site, reduced systemic side effects, and relatively rapid onset of improvement in oxidative, inflammatory, and tissue indices within a few days of treatment initiation. In the physical barrier-based method, a special lipid solution was used for application in the oral cavity, which, upon contact with the inflamed mucosa and a small amount of saliva moisture, spontaneously organizes and forms an adhesive lipid layer with a liquid crystal structure on the mucosal surface. This formulation contains phospholipids and triglycerides that, after application in the mouth, disperse and undergo molecular self-assembly with a small amount of water on the mucosal surface, thereby forming a thin, transparent, elastic, and bioadhesive coating on the injured and painful areas (25). This layer acts like a “liquid bandage,” isolating the exposed nerve ending surface from direct contact with mechanical, chemical, and thermal stimuli (food, drink, teeth, tongue, and cheek movement), reducing friction and

abrasion, and helping to maintain local moisture (25, 26). Clinical evaluation revealed that both formulations, with or without the anti-inflammatory drug benzydamine, immediately caused a sharp reduction in pain intensity within a few minutes, and this effect remained stable for about 8 hours; the average pain reduction at 6 hours was about 40%, and no significant difference was found between the two pharmaceutical forms (27). Based on these findings, pain relief is primarily due to effective mechanical protection provided by the lipid barrier and that the addition of benzydamine had no remarkable effect on these specific circumstances. Both formulations were well tolerated and safe. Due to their non-pharmacological mechanism, they did not have the classic side effects of local anesthetics or anti-inflammatory drugs (28). In the mucosal cell protection approach, sucralfate was used as a topical mouthwash in order to prevent the occurrence and reduce the severity of mucositis. This compound is an aluminum salt of a sulfated, largely nonabsorbable disaccharide that, due to its positive charge, has a high affinity for binding to mucosal proteins, especially in damaged areas, and forms an adhesive gel-like layer on the mucosal surface. Moreover, this layer acts as a protective physical barrier, protecting inflamed and injured mucosa from direct contact with saliva, food, bacteria, and cytotoxic agents caused by chemotherapy and radiation therapy, and increases the possibility of natural tissue regeneration (29). In addition, sucralfate enhances mucosal innate defenses by increasing prostaglandin synthesis, mucus secretion, and local blood flow, possibly by concentrating growth factors (e.g., the epidermal growth factor) at the site of injury, which may accelerate the healing process. Similarly, some evidence suggests the inhibition of pathogen adhesion to mucosal surfaces or direct antibacterial effects that prevent secondary wound infection and reduce microbial burden. Comparative evaluation has shown that sucralfate mouthwash significantly reduces the incidence or severity of mucositis in patients undergoing cancer treatment and has one of the highest preventive effects among the studied topical agents, while its low cost, easy administration, good tolerability, and lack of association with significant side effects make it a highly promising option for widespread use in the supportive management of cancer treatments. Collectively, these interventions range from the most potent to the most supportive options based on their potency of action on the nuclear factor-kappa β (NF- κ β)–cytokine axis, antioxidant potency, role in tissue repair, and control of infection or pain. Additionally, their clinical selection can be tailored to the severity of mucositis, the primary goal (prevention, treatment, or pain relief), and the patient's condition (29, 30).

Topical Gel

In recent years, a wide range of natural products, mucoadhesive gels, and films, as well as novel drug delivery systems, have been investigated with the aim of preventing or reducing the severity of mucositis and relieving its pain. Most of them act on the axis of inhibiting inflammation,

reducing OS, protecting the epithelial barrier, and accelerating tissue repair (31–33). Meanwhile, olive oil and olive leaf extract, as available and low-cost natural interventions, inhibit inflammation and OS, and reduce dryness and mechanical irritation of the wound surface through oleic acid and polyphenols (e.g., oleuropein and hydroxytyrosol) by inhibiting tumor necrosis factor- α (TNF- α) and cyclooxygenase-2 (COX-2), increasing catalase and SOD activity, reducing ROS, and creating a protective and moisturizing layer on the mucosa (34, 35). Likewise, chamomile (Ad-Muc) considerably accelerates the mucosal repair process in animal models by neutralizing free radicals, having antimicrobial effects, and stimulating epithelialization and collagen synthesis, in addition to inhibiting inflammatory mediators and reducing neutrophil infiltration, with flavonoids, such as apigenin and quercetin, and terpenoids, including alpha-bisabolol (36, 37). Other interventions (e.g., curcumin, hufariqon, royal jelly, persimmon extract, and formulations containing zinc-aml-tulsi-curcumin) exert a range of anti-inflammatory, antioxidant, antimicrobial, and reparative effects simultaneously; Curcumin significantly reduces the severity of mucositis and pathological scores in 5-FU models by inhibiting NF- κ β , COX-2, and LOX and reducing TNF- α , IL-1, IL-6, and IL-8, and hufariqon by inhibiting COX-2 and inducible nitric oxide synthase, reducing MDA, and enhancing collagen synthesis and antibacterial effects, (38, 39). Royal jelly, with its specific fatty acid 10-HDA, proteins and active peptides, inhibits pro-inflammatory cytokines, stimulates epithelial cell proliferation and migration, and provides a combination of anti-inflammatory, antioxidant, antimicrobial and physical protective effects by creating an adhesive and micronutrient-rich layer on the mucosal surface (40, 41). At the molecular level, topical melatonin, focusing on the mitochondria-inflammation axis, inhibits radiation-induced mitochondrial OS, bioenergetic impairments, ROS release, NF- κ β and NLRP3-type inflammasome activation, and subsequent activation of the p53-Bax-caspase-3-dependent apoptosis pathway; melatonin gel prevents epithelial destruction, wound formation, and loss of progenitor stem cells by restoring tissue levels of melatonin, directly neutralizing ROS, structurally and functionally protecting mitochondria, and simultaneously inhibiting NF- κ β and NLRP3. It is proposed as a potent preventive option for radiation-induced mucositis (39, 42). In addition to this molecular approach, topical mucoadhesive systems, including triamcinolone film, gels containing indomethacin-PVA microparticles, chitosan-nystatin gel, omega-3 nanoemulsions and emulsions, and barrier gels (e.g., Gelclair), have significantly reduced pain, mucositis score, and treatment interruptions. These systems combine an anti-inflammatory or antifungal drug with a mucosal-adhesive carrier to provide controlled and sustained drug release at the lesion site, create a protective coating similar to a “liquid bandage”, reduce painful contact with stimuli, inhibit prostaglandins and cytokines, and, in some cases, regulate the oral microbiome

(36). Overall, the review of these studies demonstrated that the most successful approaches in the treatment and prevention of OM simultaneously target several key links in the pathophysiological cycle. Accordingly, as the complementary components of a multimodal protocol, natural compounds (e.g., olive oil and leaves, curcumin, omega-3, royal jelly, hufariqon, and persimmon), along with innovative topical drug delivery systems (mucoadhesive films and gels, platelet supernatant gel, Gelclair, and the like), can reduce the severity, duration, and pain of mucositis while substantially increasing the possibility of uninterrupted continuation of cancer treatment and improving the QoL of patients, especially children and head and neck patients.

Ointments

Some studies have attempted to reduce the severity and duration of mucositis using professional oral interventions, herbal compounds, antioxidant agents, and anti-inflammatory drugs (43). Professional oral care, which includes scaling, careful oral hygiene, and initial treatment of inflammation with steroid ointments, has been confirmed to diminish the incidence and severity of mucositis in patients treated with drugs such as everolimus and to aid tissue repair by reducing microbial load while improving mucosal health (44). In addition to these methods, the multicomponent herbal formulas of Kampo, which have been used in Japanese medicine for many years, with anti-inflammatory, antioxidant, analgesic and immunomodulatory effects, have shown promising results in recent studies and demonstrated that they can accelerate the healing process by inhibiting inflammatory pathways and reducing free radicals. Moreover, other compounds, such as polyperzinc, with sodium alginate have been able to accelerate the healing process by creating a physical protective layer on the mucosa and simultaneously reducing OS; while, in some animal models, the use of dexamethasone has worsened the condition due to immunosuppression. On the other hand, Indigo Naturalis ointment has been effective in patients with mild-to-moderate mucositis due to its increased IL-22 and enhanced mucosal defense, along with the inhibition of oxidation and inflammation (45). Unlike some chemotherapy conditions, the use of dexamethasone ointment in patients undergoing radiation therapy has been able to inhibit inflammation and prevent the progression of lesions, because in these conditions, there is no widespread immunosuppression and inflammation is reduced by inhibiting TNF- α and inflammatory cytokines (46). In other studies, green tea catechin could reduce oxidative damage caused by drugs such as 5-fluorouracil by activating the Nrf2 defense pathway and inhibiting the NF- κ B inflammatory pathway. Additionally, it has protected the mucosa from damage by increasing antioxidant enzymes. In addition to these methods, the use of honey, which has antibacterial, antioxidant, and restorative properties, has shown significant results in patients with grade 2 and 3 mucositis and has shortened the healing time (44). Although the HOPE combination, which includes honey,

olive oil-propolis, and beeswax, has different physical effects than honey. More precisely, it has shown acceptable performance in deep wounds and has been helpful by inhibiting bacteria, reducing inflammation, and enhancing mucosal repair. Likewise, in the case of triamcinolone, the analgesic and anti-inflammatory efficacy increases when the ointment has high persistence and adhesion on the mucosa; because this feature allows the drug to remain in place for a longer time and can inhibit inflammatory pathways (e.g., COX-2 and TNF- α) and reduce nerve sensitivity.

Cryotherapy

The available evidence presents a relatively consistent picture of the protective role of oral cryotherapy in preventing and reducing the severity of chemotherapy-induced mucositis, although the magnitude of this effect has been reported to vary somewhat depending on the type of cytotoxic drug, its plasma half-life and timing, the cryotherapy protocol, and the characteristics of the patient population (47, 48). It should be noted that the focus of all studies is the fundamental physiological mechanism of cryotherapy; in other words, a decrease in the temperature of the oral mucosa causes the rapid vasoconstriction of vessels and, consequently, a restriction of local blood flow during the period when the concentration of the chemotherapy drug in the blood is at its highest. This decline in blood supply sharply reduces the contact of oral epithelial cells with the cytotoxic drug and prevents or modulates the initial stage of injury, which is the starting point of the inflammatory cascade of mucositis (49, 50).

In drugs with short half-lives (e.g., 5-FU and melphalan), this mechanism operates almost optimally, as cooling occurs precisely at the time of high drug exposure in the circulation. Studies focusing on these drugs have reported significant reductions in the incidence, severity, and duration of mucositis, and this improvement has been achieved without marked adverse effects. In patients receiving melphalan, whether ice packs or oral cooling devices are used, the convergence of results suggests that the intervention is superior to standard care. The difference in the more stable temperature maintenance and greater tolerability of newer devices has occasionally led to more favorable clinical outcomes (51).

In pediatric studies, the combination of the cooling mechanism with the natural anti-inflammatory effects of chamomile significantly increased the protective power of the intervention. Chamomile ice cubes, in addition to reducing the blood supply of the drug to the mucosa, modulated inflammatory pathways by inhibiting COX-2 and reducing the production of prostaglandins, thereby accelerating mucosal healing. The result of this synergy was that in many cases, children had no active mucositis at the end of the evaluation period (5, 52).

Similarly, physiological studies have shown that cryotherapy reduces mucosal surface temperature by more than 10°C without remarkably increasing inflammatory markers, such as salivary IL-6. These findings demonstrate

that cold itself is not a pro-inflammatory agent, but rather that its primary mechanism is to limit drug exposure and prevent the initiation of the injury process. In addition, cellular and molecular studies indicate that cryotherapy inhibits local inflammation and accelerates the return of epithelial cells to their normal pattern by inhibiting the NF- κ B pathway and reducing the release of cytokines such as TNF- α , IL-1 β , and IL-6. Additionally, the reduced migration of inflammatory cells and reduced presence of opportunistic bacteria support faster and more efficient mucosal tissue regeneration (53, 54).

Laser Therapy

This type of therapy has received widespread attention over the past two decades as one of the most effective interventions in OM prevention and treatment in patients undergoing anticancer treatments, especially in children (55). Evidence from numerous studies shows that this method not only reduces the incidence and severity of mucositis, but also significantly alleviates pain, functional oral disorders, and nutritional problems associated with it, ultimately improving the QoL of patients (56). In addition, it is considered a multimodal and effective intervention since it acts simultaneously on different pathophysiological pathways affecting mucositis through a set of photobiological mechanisms (57). At the cellular level, the absorption of red or near-infrared light by cytochrome c oxidase in the mitochondrial respiratory chain activates a series of photophysical and biochemical reactions that result in increased electron transport, enhanced membrane proton gradient, and increased adenosine triphosphate production (58). This increase in cellular energy immediately leads to improved tissue repair capacity, stimulates the proliferation and differentiation of epithelial cells and fibroblasts, accelerates angiogenesis through increased expression of growth factors (e.g., vascular endothelial growth factor), and leads to more effective reconstruction of the oral mucosal structure (59). In addition to these regenerative effects, laser therapy can also modulate inflammation; the severity and extent of inflammation, which is a key step in the pathogenesis of mucositis, are reduced by decreasing the production of proinflammatory cytokines (e.g., TNF- α , IL-1, and IL-6), inhibiting NF- κ B-dependent pathways, and regulating the activity of enzymes such as matrix metalloproteinases (58). Furthermore, laser therapy, by modulating ROS, initially causes a short-term increase and then an adaptive decrease in OS, which is a process that prevents or limits DNA damage and cell death induced by chemotherapy and radiotherapy (60). The combination of these mechanisms has led to significant clinical results. In children with acute lymphoblastic leukemia treated with high-dose methotrexate, 60% of those receiving prophylactic laser treatment did not develop mucositis, compared with 25% in the group that received laser treatment only after the appearance of symptoms. Further, the severity of mucositis was significantly reduced, with zero grade 4 ulcers in the prophylactic group. The findings demonstrated that

initiating intervention before the onset of drug-induced mucosal destruction may yield the greatest benefit to the patient. Furthermore, the 660 nm red laser was slightly more effective than the 830 nm infrared laser, although the difference was not statistically significant. This pattern was observed in other studies, both in children and adults; regular use of low-level lasers, whether intraoral or superficial and extraoral, could substantially decrease the incidence of severe mucositis, the need to discontinue anticancer therapy, the severity of pain, and the time to healing of lesions (61, 62).

In adult patients with head and neck cancer undergoing radiotherapy with or without concomitant chemotherapy, the use of extraoral photobiomodulation (PBM) markedly reduced the incidence of grade 3 or higher mucositis, even though the oral mucosa received high doses of radiation (63). This is of particular importance, as head and neck patients typically suffer from the most severe types of mucositis due to the extensive involvement of salivary and epithelial tissues (64). Moreover, the mechanism of action of this method is similar to that of other PBM protocols, but its important advantage is that it avoids direct intraoral radiation, thus allowing for easier use in patients who cannot tolerate intraoral instruments (58). Additionally, this systemic approach has also been reflected in studies using “noninvasive laser blood irradiation” (NLBI) or intravascular laser blood irradiation. In children with cancer who received NLBI, no cases of OM were observed, and the phagocytic activity of leukocytes was significantly increased. Increased innate immunity, reduced OS, improved microcirculation, and stimulation of cellular metabolism are among the mechanisms that systemically protect the body from chemotherapy-induced mucosal damage (65). In addition to all this evidence, studies have shown that the successful laser management of mucositis indirectly improves the nutritional status of patients. In patients who developed mucositis during head and neck radiation therapy, the use of high-power class IV laser resulted in a significantly smaller decrease in body mass index. This is of considerable clinical importance, given the key role of nutrition in the tolerance of anticancer therapy and the prevention of long-term hospitalization. Pain reduction, reduced inflammation, accelerated wound healing, and improved swallowing and chewing function are factors that explain this favorable outcome (66, 67). Overall, low-level laser therapy, with its simultaneous effect on four key axes of mucositis pathogenesis, reducing OS, inhibiting inflammation, promoting tissue regeneration, and reducing pain, is a safe, effective, and multifaceted approach to the prevention and treatment of this condition. Likewise, the use of preventive protocols is most effective, especially in children or patients undergoing intensive courses of anticancer therapy. In addition, the use of extraoral or systemic approaches (e.g., superficial laser or NLBI) allows treatment in situations where the patient is not sufficiently cooperative or the mucosal damage is severe. The combination of these findings emphasizes that PBM should be considered an integral part of cancer

treatment support programs, as it not only reduces the severity of mucositis, but also has a direct and significant impact on nutritional outcomes, treatment tolerance, and QoL of patients.

Conclusion and Future Perspective

The findings of this narrative review emphasized that OM requires a comprehensive and multifaceted approach for effective management. Among them, low-level laser therapy and cryotherapy are recognized as the most effective and safest non-pharmacological methods that play a key role in prevention by reducing ROS and inflammation. Moreover, natural compounds (e.g., curcumin, honey, and propolis), by inhibiting the NF- κ B inflammatory axis, along with nutritional interventions and probiotics (as valuable complementary options), accelerate the process of mucosal repair. Ultimately, the most successful strategy is a combination of preventive interventions, molecularly targeted therapies, and supportive care (including oral hygiene) that is adjusted according to the patient's condition, severity of the condition, and type of cancer treatment to reduce complications, improve patients' QoL, and improve the continuation of the treatment process.

It is highly important to employ appropriate strategies for managing OM in patients. The use of health protocols, global health policies, and a combination of health strategies for managing OM in patients can help increase patient survival. It is noteworthy that implementing these strategies is extremely effective not only in improving patient treatment but also in reducing the incidence of OM in cancer patients.

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Competing Interests

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Consent for publication

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Data Availability Statement

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Ethical Approval

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