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The Effects of Herbal Medicines on Cancer Therapy-Induced Oral Mucositis: A Literature Review

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A B S T R A C T

Oral mucositis caused by cancer treatment is examined in this review along with the effects of herbal remedies for its treatment. A very frequent and excruciating side effect of chemotherapy and radiation, the paper reviews a range of therapeutic approaches, including pharmaceutical and non-pharmacological treatments such as caphosol, palifermin, cryotherapy, and photo biomodulation, by the combination of data provided from clinical trials, randomized controlled studies, and systematic reviews. Herbs like honey and botanical preparations are also under study to assess its potential. The results mainly center on how an early precaution with proper oral hygiene works in preventing severe mucositis. The research in turn shows that the treatment processes require further verification of herbal remedies in the treatment of OM, though some of them are good treatments for reducing symptoms such as cryotherapy and photo biomodulation. From all the above, it may be concluded that, in practice, the best management method for enhancing patients' quality of life after cancer treatment might be a multimodal approach of pharmaceutical and natural medicines.

INTRODUCTION

Oral mucositis is a very disabling side effect that can occur after radiation and chemotherapy. It is expected that 100% of chemotherapy patients will experience OM after oral cavity irradiation, however the actual incidence ranges from 40% to 80% [1]. It also occurs more frequently in individuals with head and neck cancer (HNC) who underwent radiation and chemotherapy at the same time. Varieties of tumors, nutritional status, oral hygiene, and age all have an impact on OM. Radiation, chemotherapy, or chemoradiotherapy in combination, dose, and administration all have an impact on OM [2]. It is usual for OM to appear on the floor of the mouth, the lips, the buccal mucosa, and the edges of the tongue. The intensity of adverse effects can be described using the 2013 Common Terminology Criteria for Adverse Events (CTCAE) v5.0 scale, regardless of whether they are related with a medical treatment or therapy. From completely absent symptoms to potentially fatal outcomes, the five-point scale covered it all [3]. Oral pain, swallowing difficulties, infectious diseases, a diminished quality of life, and the need to stop cancer therapy are all symptoms that patients may encounter as mucositis advances. Costs to patients may also be impacted by OM.

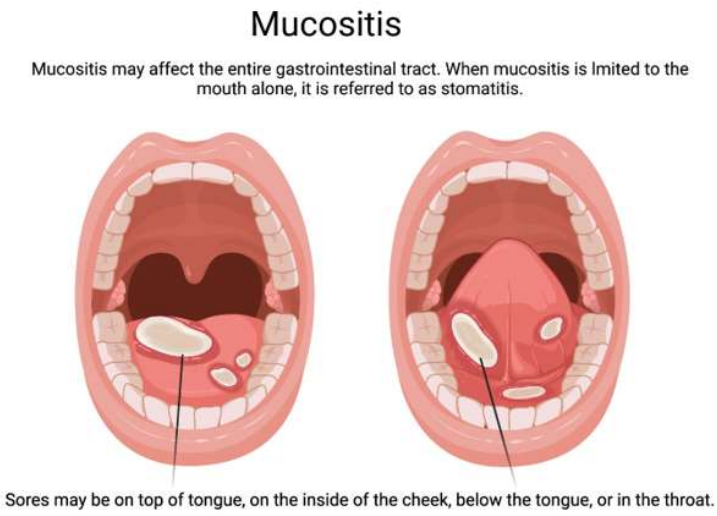

Figure 1: Mucositis [4]

Two forms of OM include erythema and inflammation-induced ulceration. Cell water becomes oxygen-free radicals when cells are exposed to radiation, which leads to OM. Owing to their reactivity, cells are damaged by oxygen-free radicals. Death, DNA damage, mitochondrial dysfunction, and lipid peroxidation are all possible outcomes. medication for OM centres on stopping the metabolic cascade early on since there is currently no recognized medication for the condition [5]. Good dental hygiene and inflammatory regulation can alleviate or postpone OM pain. To alleviate pain, lower bacterial burden, and hasten recovery, additional therapeutic options are required. In this case, anti-inflammatory, antimicrobial, and antioxidant medications might be helpful.

Mouthwashes powered by chemicals or herbs. The oral mucosa is vulnerable to damage from the chemicals found in many mouthwashes used to treat cancer. Researching infection-control products is something that the World Health Organization (WHO) suggests. There are numerous benefits to using herbal medicine instead of chemical treatments. These include the fact that it is all-natural, cheap, widely available, easy to get, and typically well-received by patients without any harmful side effects [6]. Medicinal herbs possess antioxidant, antiviral, antifungal, antibacterial, and anti-inflammatory properties. Herbal and medicinal plant treatments for oral and dental problems are considered safe according to traditional medicine. These medications are effective in preventing and treating periodontal diseases, gingivitis, and aphthous stomatitis, according to research by Li, C. L., Huang, Wang, and Hua (2016) [7]. A large body of research shows that medicinal herbs and nutraceuticals can mitigate some of the negative effects of cancer. Herbal remedies have anti-inflammatory

and antioxidant effects. No study has evaluated and summarized the effects of herbal drugs on OM caused by cancer therapy as far as the authors are aware. As a result, we looked at how OM responded to natural therapies.

1.1.Causes and Preventative Measures for Oral Mucositis

Oral mucositis develops after a lengthy series of steps, including start, damage response, signal amplification, ulceration, and healing. Damage to DNA hinders the growth of basal cells in the oral mucosa, which in turn causes the generation of reactive oxygen species (ROS), which has recently come to light as a key process in the development of oral mucositis. Matrix metalloproteinases, adhesion molecules, pro-inflammatory cytokines, and modulators are overexpressed as a result of transcription factor activation in the first damage response [8]. As a result, the oral mucosa is injured, cells die, and the integrity of the epithelium is compromised. As the tissues deteriorated due to the chemicals produced in earlier stages, signal amplification followed. The infiltration of ulcers by both gram-positive and gram-negative bacteria occurs during ulceration, the most symptomatic stage. The oral mucosa can be further damaged if this causes the bacteria to produce pro-inflammatory cytokines [9]. Biological processes beneath the skin's surface eventually repair ulcerative lesions caused by oral mucositis.

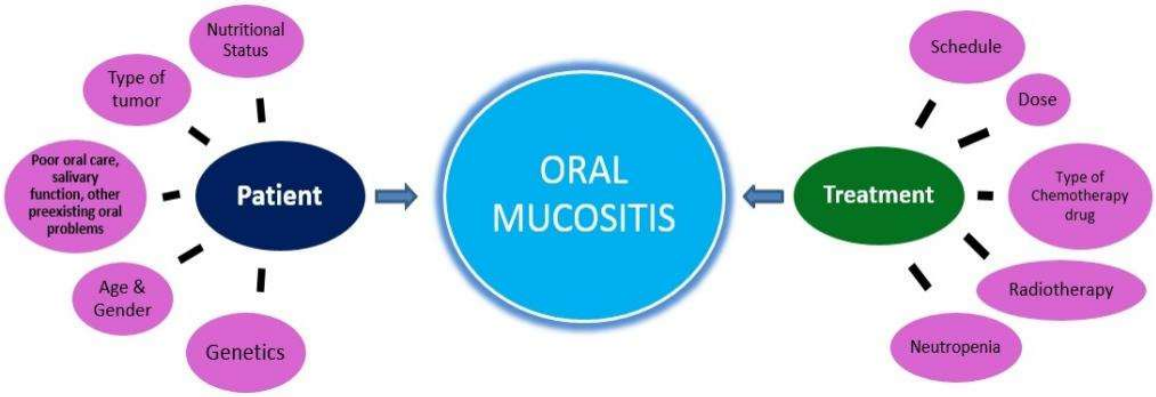

Figure 2: Oral Mucositis patient and treatment [10]

Risk factors for oral mucositis may be broadly categorized under two: those associated with the patient and those related to the treatment. The type of tumour itself plays an important role. The timing of chemotherapy or radiation therapy, the choice of drugs, and the use of adjuvant agents are all part of the treatment. Some of the patient characteristics determined include age, BMI, dental health, and genetic predispositions. Oral mucositis is prevalent in female patients who take drugs like 5-fluorouracil (5-FU) and methotrexate [11]. Chemotherapy-induced oral mucositis lasts shorter time and also milder symptoms in children aged less than ten years. Genetic considerations are also crucial because of the impact some genes have on enzymes that metabolize chemotherapy drugs. For example, the toxicity of 5-FU is positively correlated with the deficiency of dihydropyridine dehydrogenase. Although enzymatic deficiencies that lead to the predisposition of oral mucositis can be very subtle, they are unusual.

1.2.Objectives of the Study

- To determine whether or not herbal treatments can reduce the incidence and severity of oral mucositis in cancer patients undergoing radiation or chemotherapy.
- To determine how well honey, caphosol, palifermin, cryotherapy, and photo biomodulation work in alleviating oral mucositis symptoms.

- To evaluate how herbal remedies and good oral hygiene habits help prevent and treat oral mucositis during cancer treatment.

METHOD

Through a combination of clinical trials, randomized controlled studies, and systematic reviews, the research methodology for examining the management of oral mucositis entails a thorough evaluation of different therapeutic options and their efficacy. The method incorporates pharmaceutical and non-pharmacological treatments, including caphosol, palifermin, cryotherapy, and photo biomodulation. Studies that look at the effectiveness of topical medications, mouthwashes, and dietary changes are chosen because they are pertinent to the management of oral mucositis. Research on outcomes including treatment duration, symptom intensity, quality of life improvements, and RCTs, cohort studies, and meta-analyses is conducted. The study approach also considers patient groups receiving radiation or chemotherapy, with a focus on evaluating the degree and course of mucositis as well as its effects on day-to-day functioning. To evaluate the interventions' relative efficacy, both qualitative and quantitative data are analyzed, and the results are combined to draw conclusions about the most promising treatments for oral mucositis management.

RESULT

1.3.Oral Mucositis's Management

Efficient treatment of oral mucositis is essential for enhancing patients' quality of life and reducing hospital stays. Baseline oral hygiene is essential in preventing oral mucositis significantly as well as its severity. Removal of any possible precipitating factors of mucosal injury is very important before initiating chemotherapy and radiotherapy because these therapies may exacerbate and delay the onset of oral mucositis [12]. There must be a reduction in the use of dental prosthesis, removal of fixed orthodontic appliances from the mouth, and smoothing of sharp tooth edges. Even though the disease, oral mucositis, is non-infectious by itself, secondary colonization of ulcers may delay healing and must thereby also reduce the density of microorganisms in the oral cavity. As supragingival and subgingival dental plaque is the major source of bacteria in the oral cavity, periodontium is a probable cause for acute infections and, therefore, tooth plaque must be professionally controlled to minimize the risk of irritation. Good oral hygiene is very important after radiation therapy, especially when salivary flow is depressed. Oral hygiene instruction should be given to all patients. A healthy diet also helps to reduce symptoms of oral mucositis. Alcohol, tobacco, hot and acidic foods, and processed sugar-containing products are avoided [13]. A diet soft or liquid is often necessary due to the severity of the pain caused by oral mucositis, making eating impossible or very painful. The insertion of a gastrostomy tube can be preventive if the symptoms are likely to become severe. To alleviate symptoms, specific mouthwashes are applied having topical anesthetics, topical coating agents, antibiotics, antifungals, and steroids.

Topical anesthetics may possibly act locally to relieve pain; however, they generally should not be used frequently because of the possibility of systemic side effects such as altered taste. Coating agents may well diminish pain by creating a barrier of defense across ulcerated mucosa. For patients who experience serious mucositis, these drugs alone may be insufficient; they might require systemic analgesics, such as opioids [14]. Their anti-inflammatory properties make it possible that corticosteroids will also be prescribed. Benzylamine mouthwash is an excellent prophylactic treatment for oral mucositis due to its anti-inflammatory properties, which are shown to reduce the formation of TNFα and IL-1β. Topical anesthetics are widely applied in the prevention and treatment of oral mucositis, which can offer temporary relief, but further research is required regarding ideal dosages of substances such as topical morphine. Xerostomia and hyposalivation are relatively

common side effects of radiation therapy that may make chewing difficult and increase the risk of local infections. Patients should be encouraged to use artificial saliva or other supportive products and to sip water frequently. If these measures are insufficient, cholinergic medications may be necessary. Other supplements to be taken simultaneously with the treatment include vitamins A and E [15]. Vitamin E is known to possess antioxidant activity, which makes it soft the oxidative damage and also seen to minimize the severity of mucositis. Patients who have severe oral mucositis have been proven to be low in vitamin A as well since it minimizes inflammation. There is no guideline, and scanty scientific information exists to ensure if vitamins work in the treatment of oral mucositis.

Natural remedies include herbal preparations and honey. Honey contains antibacterial properties that may help avoid subsequent infections. Honey has been found to enhance the rate of wound healing when applied topically [16].

Patients receiving radiation or chemotherapy to the head and neck have been shown to see a decrease in oral mucositis when honey is applied topically or taken systemically, according to clinical evidence. Cryotherapy, photo biomodulation (PBM), palifermin, or caphosol, in addition to changes in dental hygiene, food, and topical medications, may be necessary for severe oral mucositis caused by radiation and chemotherapy. The mechanism of cryotherapy in reducing symptoms of oral mucositis in chemotherapy patients has been established through vasoconstriction and decreased blood flow. It has been suggested that the topical application of ice chips five minutes prior to chemotherapy reduces blood flow to the mouth mucosa and thereby diminishes delivery of the chemotherapy drugs [17]. Clinical studies have evidenced the fact that cryotherapy is effective in comparison to saline mouthwash in the reduction of the severity of mucositis.

Although there is a lack of data in patients undergoing chemotherapy and radiation to the head and neck, randomized trials demonstrate that the approach effectively prevents oral mucositis caused by allogeneic hematopoietic stem cell transplantation. Cryotherapy with the whole conditioning regimen was utilized to decrease the occurrence and severity of severe mucositis. Because of the risk of harm to the oral mucosa, it is not advised as a routine course of treatment. Cryotherapy did not reduce the incidence of severe oral mucositis in the children evaluated under the stem cell transplantation. Photo biomodulation, formerly known as low-level laser therapy, is another option for treating oral mucositis [18]. This has anti-inflammatory, analgesic, and wound-closure properties. A monochromatic, coherent light source is used topically to apply PBM, which has cytoprotective properties. Research has demonstrated its efficacy in preventing and alleviating oral mucositis symptoms.

Clinical trials on radiation-induced mucositis patients have demonstrated that PBM can reduce disease severity and analgesic usage. Patients' quality of life is improved since most trials found that PBM is beneficial in preventing and treating mucositis caused by radiation therapy and chemotherapy. To understand how PBM regulates inflammatory cytokines, more study is required to determine the mechanisms of action [19]. Pharmacologic treatments such as palifermin, a keratinocyte growth factor-1, have been shown to alleviate the severity and duration of oral mucositis. Patients' mucositis symptoms were considerably alleviated with palifermin, according to clinical investigations. In randomized, placebo-controlled trials, palifermin reduced the incidence of oral mucositis and the severity of adverse effects in chemotherapy patients. Patients who took palifermin had the same survival rate as those who took a placebo [20]. The prescription mouthwash Caphosol is another option; patients have reported no side effects from using it. Restoring the oral cavity's ionic balance is aided by this calcium phosphate solution, which promotes epithelial growth while alleviating irritation and inflammation. Clinical trials have shown that it lessens the severity and duration of oral mucositis. Cryotherapy, photo biomodulation (PBM), and the use of caphosol or palifermin are all included in the

randomized double-blind studies summarized in Table 1.

Table 1: Cryotherapy, photo biomodulation (PBM), and palifermin/caphosol use studies.

Author	Patient Count	Type of Study	Oral Mucositis Management and Treatment
Askarifar et al. (2016) [21]	29 patients	Randomized study	Cryotherapy
Lu et al. (2020) [22]	145 patients	Prospective randomized study	Cryotherapy
Kamsvåg T et al. (2020) [23]	49 patients	Randomized study	Cryotherapy
Oton-Leite et al. (2015) [24]	30 patients	Randomized study	PBM (Photo biomodulation)
Henke et al. (2011) [25]	186 patients	Randomized study	Palifermin
Raphael et al. (2014) [26]	29 patients	Randomized study	Caphosol

1.4.Herbal Solutions for Cancer-Induced Oral Mucositis

Curcumin

Curcumin, a polyphenol with impressive antioxidant, anti-inflammatory, anti-cancer, and anti-microbial capabilities, originates from the Zingiberaceae family of rhizomatous plants. Due to its potential as an orally active treatment for various chronic illnesses, such as pathological pain, curcumin has increasingly drawn attention since its long practice in Oriental medicine [27]. In the context of oral mucositis (OM), curcumin has established various palliative benefits. It's supposed to result in a decrease in inflammatory cytokines' activity from interfering with pathways such as NF-κB, mitogen-activated protein kinase signalling, and toll-like receptor 4 (TLR4).

Recent research has focused on investigating the potential role of curcumin in OM treatment for cancer patients receiving radiation and chemotherapy. According to a comprehensive literature review and meta-analysis of clinical investigations that comprised five trials, curcumin and turmeric considerably diminished the degree of pain, erythema, ulceration area, and the severity of OM [28]. The research also found that curcumin can postpone the beginning of mucositis, therefore it might be used as a chemo preventive medicine. Another meta-analysis of six RCTs found that curcumin may protect against treatment-induced OM, especially in HNC patients, and lessen weight loss that is related with OM.

Table 2: Summary of Studies on Curcumin and Other Treatments for Oral Mucositis in Cancer Patients [29]

Study	Number of Trials/Studies	Treatment Evaluated	Findings	Conclusion
Systematic Review and Meta-analysis of Clinical Trials	5 trials	Curcumin	Pain, redness, ulcer area, and severity all decreased. A possible protective measure is the postponement of mucositis symptoms.	Curcumin has the potential to alleviate oral mucositis symptoms and postpone their development.
Meta-analysis of RCTs	6 RCTs	Curcumin	No side effects and no risk of treatment-induced OM in patients with head	Curcumin is safe and effective in preventing

			and neck cancer. Weakened weight reduction caused by OM.	treatment-induced oral mucositis.
Network Meta-analysis of 28 RCTs	28 RCTs	Curcumin, Honey, Other Oral Care Solutions	When it comes to avoiding OM, curcumin is at the top of the list, followed by SUCRA-based honey.	Curcumin is the most recommended solution for prevention of OM in cancer patients.
Bayesian Network Analysis of RCTs	36 studies	Chamomile, Honey, Curcumin, Benzylamine (Mouthwashes)	There is little to no variation throughout the various mouthwashes. The compounds with the greatest therapeutic benefits for severe OM were chamomile, honey, curcumin, and benzydamine.	The most effective mouthwashes for severe OM include chamomile, honey, curcumin, and benzylamine.

Silymarin

The extract of silymarin is known in the milk thistle plant, Carduus marianum. It has nephroprotective and hepatoprotective benefits along with anti-inflammatory and antioxidant qualities. From both preclinical and clinical findings, silymarin helps shield cells from oxidative stress by increasing glutathione and superoxide dismutase, which in turn lowers lipid peroxidation. Silymarin modulated the immune system by affecting the NF-κB pathway, enhancing proliferation of lymphocytes, and raising cytokine production including IFN-γ, IL-4, and IL-10. It inhibited neutrophil migration, diminished the activation of T cells, and lowered prostaglandin and leukotriene synthesis, which are mechanisms that exert activity anti-inflammatory. These features position silymarin as a potentially useful therapy in OM [30]. A randomized controlled experiment was carried out to assess whether oral silymarin would prevent the development of radiotherapy-induced OM. As tested, utilizing the WHO and NCI-CTCAE scoring, silymarin was able to retard the onset and reduce the severity of radiation-induced mucositis.

Tea

Ten varieties of tea have been found to possess antiviral, antifungal, antimicrobial, antibacterial, and anti-inflammatory properties that may help cancer patients cope with OM during therapy. The use of these teas has been found to reduce stomatitis, oral candidiasis, and pharyngolaryngitis. The efficacy of a mouth rinse made with hydrosols of peppermint, sage, and tea tree on chemotherapy-induced OM was investigated in a pilot randomized controlled trial. This study randomly allocated 60 chemotherapy patients into two groups. To a group of patients, the herbal mouthwash was provided over and above the standard oral hygiene routine; however, in another group, patients only brushed twice daily as a part of their basic oral hygiene routine [31]. The mouthwash was utilized four times a day for 14 days. OM was assessed using the WHO scale on days 5 and 14. The results of this study demonstrated efficacy of sage tea, thyme, and peppermint hydrosol in the reduction of chemotherapy-induced OM severity and validated this compound as a highly effective, well-tolerated OM management agent in cancer patients.

Honey

It has been known for many decades that honey has positive effects on the healing of wounds, particularly in the treatment of burns and pressure wounds. Because of its properties to have protective effects, it was

researched as a potential method for the protection of cancer patients against OM. In four studies, it was assessed whether honey could protect head and neck cancer patients against mucositis [32]. Three of these studies examined both systemic and topical effects, while one looked at topical administration only. Largely, the results of these studies came positive, but there was insufficient information for giving explicit recommendations or coming to some sort of consensus on whether honey should be recommended for the prevention of OM.

Aloe-vera gel

Anecdotal evidence suggests that the aloevera is indeed effective as an agent in managing radiation dermatitis, and it has been used traditionally to help heal wounds. Recent randomized controlled trials have investigated the efficacy of aloevera gel as a mouthwash for the prevention of radiation-induced mucositis in patients with head and neck cancer [33]. Aloevera juice (94.5% concentration), concentrated pear juice (5%), lemon-lime flavour (0.4%), and citric acid (0.1%) made up the formulation. Due to the lack of evidence and the remedy's apparent ineffectiveness, no aloevera therapy for mucositis prophylaxis has been recommended.

Indigo wood Root

The antiviral and anti-inflammatory effects of the plant indigowood root have made it a staple in traditional Chinese medicine. Indigowood root's potential to avert oral mucositis in patients undergoing medium-dose radiation treatment (45 Gy) for head and neck cancer was the subject of this brief randomized controlled trial. A 30-milliliter solution of indigowood root was taken orally by trial participants once daily with meals after three minutes of gargling with the root. The results of the studies revealed that mucositis, anorexia, and dysphagia due to radiation therapy were decreased in extent. These findings were not supported by adequate data to establish recommendations for the use of indigowood root in preventing OM [34].

Oils of Manuka and Kanuka

The Māori and early European immigrants both relied on the therapeutic properties of the oils extracted from manuka (Leptospermum scoparium) and kanuka (Kunzea ericoides). The essential oils of manuka and kanuka have anti-inflammatory, antibacterial, antifungal, and analgesic properties. In a preliminary trial, irradiated patients with head and neck cancer used manuka-kanuka oil mouthwashes. A total of twelve patients were included in the study: six who received manuka-kanuka oil, six who received a water rinse, and seven who received standard care without any rinse [35]. Despite the fact that the study's small sample size was a disadvantage and that few clear recommendations could be made, the results did point to the possibility of using manuka-kanuka oils to prevent mucositis. An oral polyherbal gel wafer containing Glycyrrhizin, Centella asiatica, Polygonum cuspidatum, Angelica sp., Camellia sinensis, sorbitol, Cyamopsis tetragonolobus, stearic acid, magnesium stearate, aloe, and other extracts is what you'll find in Mucotrol medication.

Mucotrol has been hypothesized to have immunomodulatory, wound healing, local analgesic, and antioxidant properties, though the exact mechanism of action is unknown. The results of a pilot RCT on 11 patients with oropharyngeal and oral cancers under radiation therapy and chemotherapy with cisplatin were assessed [36]. According to the results, the WHO mucositis score was reported 34.63% lower in the treatment group compared to that of the placebo group. Whereas the guidelines on using mucotrol for preventing oral mucositis were not set, as the basis for it is insufficient.

DISCUSSION

Oral mucositis (OM) remains a significant complication for cancer patients undergoing radio-chemotherapy, particularly those with head and neck cancers. The pathophysiology of OM involves a complex interaction of oxidative stress, DNA damage, and inflammation, leading to epithelial cell death and ulceration. As treatment regimens involving radiation and chemotherapy are essential for cancer management, their toxic effects on the

oral mucosa can severely impact a patient's quality of life. The findings suggest that while OM can be triggered by both chemotherapy and radiotherapy, the severity varies depending on factors like the type of treatment, the radiation dose, and individual patient factors such as age, nutritional status, and genetic predisposition. This complexity necessitates more personalized approaches to prevention and treatment [37].

The review also highlights the potential of herbal remedies as alternative treatments for OM. Many studies suggest that herbs with anti-inflammatory, antibacterial, and antioxidant properties could help manage OM more effectively than traditional chemical mouthwashes, which often cause additional damage to the oral mucosa [38]. These herbal treatments offer a promising avenue due to their natural composition, accessibility, and relatively lower risk of adverse effects. However, the review identifies a critical gap in the research on herbal treatments specifically for cancer therapy-induced OM. While existing studies on the broader effects of medicinal herbs on oral health are promising, the direct evidence supporting their use in cancer treatment-induced OM is limited, signaling the need for more focused research in this area.
To bridge this gap, future research should aim at conducting well-designed clinical trials to evaluate the effectiveness of specific herbal remedies for OM in cancer patients. These studies should assess not only the clinical outcomes (e.g., reduction in pain, healing of lesions) but also the molecular mechanisms underlying their action, particularly their anti-inflammatory and antioxidant properties [39]. Additionally, comparative studies between herbal treatments and conventional therapeutic options, such as mouthwashes and pain management strategies, would provide valuable insights into their relative efficacy [40]. It is also essential to explore the feasibility of integrating herbal remedies into standard clinical protocols, considering the variability in treatment responses due to patient-specific factors like genetics and overall health status.

CONCLUSION

For cancer patients undergoing radio-chemotherapy, oral mucositis (OM) remains an important complication that affects their quality of life and makes treatment challenging. Oxidative stress, inflammation, and cellular damage are closely interlinked in the pathophysiology of OM. Present methods of therapy focus on symptom relief but more effective treatments need to be devised. This analysis points out that herbal medicines can serve as the alternative for using chemical treatments, since their antioxidant, antibacterial, and anti-inflammatory properties are promising in the treatment of OM. However, further clinical studies are necessary to affirm the safety and efficacy of herbal medicines in treating OM caused by anticancer drugs. More studies are still recommended to focus on comparative analyses, clinical trials, and biological mechanisms to prove that these medicines from nature are one of the effective ways to manage OM in patients with cancer and add a comprehensive treatment approach.

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