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The Use of Photobiomodulation in The Prevention and Treatment of Chemotherapy-Induced Oral Mucositis

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REVIEW

The Use of Photobiomodulation in the Prevention and Treatment of Chemotherapy-induced Oral Mucositis

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Abstract

Oral mucositis (OM) is a severe and common complication in cancer patients, characterized by erosive and ulcerative lesions on the oral mucosa. The primary cause of OM is the destruction of oral mucosal epithelial cells and growth suppression resulting from cancer treatments, such as chemotherapy or radiotherapy. The first clinical signs of OM include thinning of the oral tissues, followed by erythema and ulceration, which can lead to several adverse effects, including pain, increased risk of infections, bleeding, difficulty swallowing, and dehydration. These issues can result in impaired nutritional status, delayed treatment sessions, and prolonged hospitalization. Thus, preventing and managing OM is crucial for maintaining the quality of life for cancer patients. Several approaches are available for preventing and managing OM, such as patient education, saline mouth rinses, pain relievers, and photobiomodulation using low-level laser therapy. This literature review aims to provide an update on the use of low-level laser therapy or photobiomodulation for preventing and treating chemotherapy-induced OM.

Keywords: Cancer chemotherapy, Low-level laser therapy, Mucositis, Photobiomodulation

1. Introduction

One of the extreme disadvantages of chemotherapy is that it is an unspecific treatment for cancerous tissues, it acts by the growth inhibition of quickly dividing cells, interfering cellular division [1]. Thus, prevents the differentiation of cells to the neoplastic cells. In cells with high proliferation rates, like cells of the oral mucosa this provokes several side effects [2]. In Addition, the oral cavity shelters countless amount of bacteria, The entry of numerous infectious microorganisms can be facilitated by anything that compromises the integrity of the oral mucosa, which can lead to serious infections and eventually death [3].

Several variables affect the frequency at which patients receiving chemotherapy experience oral problems. These variables can be categorized into two groups: those related to the patient and those related to the treatment. Patient-related factors may include age, diagnosis, pre- and during-therapy oral health level, and systemic condition. On the other hand, treatment-related variables comprise the chemotherapeutic agent, and dosage frequency and the administration of the medication [4].

Depending on where they originate, cancer chemotherapy's oral side effects can be categorized into two broad groups: those caused by the drug's direct action on the oral tissues, or direct stomatotoxicity. Alternatively, difficulties brought on by the alteration of other tissues, like bone marrow (BM), are known as indirect stomatotoxicity. For cancer patients, direct somatotoxicity is a major concern. Oral mucositis (OM) is the most typical type of direct stomatotoxicity [5].

There is currently no accepted method or standard therapy for the prevention or treatment of OM, despite years of intensive research. Numerous prospective therapies for preventing mucositis have been identified by systematic reviews and recent clinical studies; however, the quality of the evidence supporting these interventions varies, and it is still unknown if they will be beneficial for individuals

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with different forms of cancer. There is still inadequate data supporting it [2].

Because the prevention and treatment of OM are still unacknowledged this limits the effectiveness of antineoplastic therapy and negatively impacts patient quality of life [5]. Many approaches have been studied to effectively prevent and treat OM. Of which low-level laser therapy (LLLT), also referred to as Photobiomodulation (PBM), has become increasingly popular and has demonstrated beneficial results [6].

The purpose of this review of the literature is to provide up-to-date information regarding the use of low-level laser power densities for the treatment and prevention of OM in patients receiving chemotherapy or preparing for hematopoietic stem cell transplantation.

2. Search strategy

The search strategy used in the review was shown in Table 1.

3. Background

3.1. Etiology and pathophysiology of chemotherapy-induced oral mucositis

Chemotherapy-induced oral mucositis (CIM) is defined as a complex and multifactorial condition that arises from the toxic effects of chemotherapeutic agents on the rapidly dividing cells of the oral mucosa. Etiology and pathophysiology involve a cascade of events that result in mucosal injury and inflammation [7].

Chemotherapeutic drugs' have adverse impacts that affect the rapidly dividing cells of the oral mucosa. This results in a complicated and multifactorial illness known as CIM. Mucosal damage and inflammation are the results of a series of events that are part of the etiology and pathophysiology of CIM. The primary factor contributing to the etiology of CIM is cellular toxicity, which is brought on by chemotherapy medications, especially cytotoxic ones since they target rapidly dividing cells, both malignant and healthy cells [5].

Chemotherapy can have cytotoxic effects on the oral mucosa due to its high rate of cell turnover. OM is also a result of several chemotherapeutic medication types, including taxanes, alkylating agents, and antimetabolites. The kind, amount, and length of chemotherapy all have an impact on how severe and at what point mucositis develops for the first time [8].

Patients are susceptible to OM caused by chemotherapy for a variety of reasons, such as age, dietary status, general health, and genetic predisposition. The first pathophysiology of CIM is Cell Cycle Disruption, where chemotherapy interferes with normal cell division and proliferation, impairing oral mucosal cell differentiation and proliferation. The integrity of the mucosa is weakened because of this disruption [7].

The oral mucosal epithelium is damaged by chemotherapy, exposing the underlying connective tissue and causing vulnerable spots. Regrettably, this deterioration causes erosions and ulcers to develop [9]. An inflammatory response is then triggered by the release of pro-inflammatory cytokines such interleukin-1 beta and tumor necrosis factor-alpha. Inflammation slows the healing process and adds to tissue damage [10].

Microbial colonization is the end outcome of this sequence of events. The likelihood of microbial colonization and infection in the oral cavity is increased when the mucosal barrier breaks compromised. The symptoms of mucositis can be made worse and more complicated by bacterial, viral, or fungal diseases. Ultimately, pain and discomfort arise because exposed oral mucosa nerve endings contribute to the pain and discomfort that people with CIM feel. One major obstacle to treating OM is pain. This will ultimately result in less food intake, which will worsen the overall patient's health [11].

3.2. The incidence and prevalence of chemotherapy induced oral mucositis

The most frequent and severely incapacitating side effect of cancer treatment is OM brought on by chemotherapy. A risk of 60–100% is related with myeloablative (BM-suppressing) chemotherapy, and an almost 100% risk is associated with the combination of chemotherapy and radiotherapy [12].

Cancer patients may experience different rates and prevalence of CIM depending on several variables, such as the type of cancer, the particular chemotherapy regimen used, and the unique characteristics of each patient.

3.2.1. High-risk populations

These individuals are linked to an increased incidence of CIM. They include people undergoing particular cancer treatments, such as high-dose chemotherapy or hematopoietic stem cell transplantation [13].

3.2.2. Chemotherapy agents

Certain medications, such as anthracyclines, 5-fluorouracil, and methotrexate, have a higher mucotoxic potential [13].

Table 1. The search strategy used in the review.

Stage	Activity	Details
1. Define Scope	Identify research question and inclusion criteria	1. Research Question: How does PBM impact the prevention and treatment of chemotherapy-induced OM? 2. Inclusion Criteria: Population: Studies involving human subjects undergoing chemotherapy. Interventions: Research focused on PBM interventions, including various devices, wavelengths, and treatment protocols. Outcomes: Studies reporting outcomes related to the prevention and treatment of OM, such as reduction in severity, pain relief, and healing. 3. Exclusion Criteria: Studies not related to the use of PBM in OM. Animal studies, reviews, and non-English language publications. Studies with insufficient data or unclear methodologies.
2. Search Strategy	Developing effective search strings and utilizing appropriate keywords is essential for conducting a comprehensive literature search.	This literature review evaluated the last 5 years (from 2019 to the present) for pertinent papers that had been published, as part of our literature review. MeSH terms ('Stomatitis, 'Mucositis', 'Phototherapy', 'LLLT', 'Lasers', 'Laser Therapy', 'Photochemotherapy', 'Antineoplastic Combined Chemotherapy Protocols', 'Antineoplastic Agents', 'Cancer Chemotherapy', 'Hematopoietic Stem Cell Transplantation', and other keywords related to PBM and chemotherapy-induced OM in children ('OM', 'CIM', 'LLLT', 'PBM', 'LLLT', 'Chemotherapy', 'Acute Lymphoblastic Leukaemia', 'BM Transplantation', 'Paediatric Oncology', 'Childhood Cancer'). Retrospective research and paediatric clinical trials were our inclusion criteria. Only English-language literature was included in the search, and participants' ages were restricted to either 19–24 years old (young adults) or 0–18 years old (children and adolescents). In addition to the database search, a manual search was conducted to find the most recent systematic reviews and meta-analyses in our area of interest. As a result, we were able to filter the references of these reviews to find further papers that the initial search had not turned up.
3. Screening	Initial screening of titles and abstracts Exclude irrelevant papers based on title and abstract Apply inclusion and exclusion criteria	1. Initial Screening of Titles and Abstracts. 2. Applying Inclusion and Exclusion Criteria. 3. Full-Text Evaluation. 4. Managing Discrepancies. 5. Data Extraction for Included Studies. 6. Transparent Reporting. 7. Continuous Monitoring.
4. Data Extraction	Extract relevant information from selected papers	1. Basic Study Information. 2. Study Design. 3. Participants. 4. Intervention. 5. Comparator (if applicable). 6. Outcomes 7. Results 8. Quality Assessment 9. Conclusions and Implications Process: Use the extraction template consistently for each selected study. Extract information directly relevant to your research question and objectives. Document any notable limitations or challenges encountered during the extraction process. Verification: Consider having a second reviewer independently extract data from a subset of the studies to ensure inter-rater reliability. Resolve any discrepancies through discussion or consultation with a third party.
5. Quality Assessment	Assess the quality of included studies	1. Define Criteria for High-Quality Studies. 2. Apply the Quality Assessment Tool. 3. Consider Transparency and Reporting. 4. Resolve Discrepancies. 5. Sensitivity Analysis. 6. Interpretation of Results. 8. Reporting. 9. Consider Publication Bias. 10. Utilize Available Guidelines.
6. Synthesis	Summarize findings and identify patterns	Synthesize data to address the research question. Identify gaps and areas for future research.
7. Reporting	Write the literature review	

3.2.3. Frequency of treatment

Patients who get chemotherapy often or for extended periods are at a higher risk of developing CIM [13].

3.3. The prevalence of chemo-therapy induced oral mucositis

There can be differences in the frequency of CIM among different cancer types. For example, OM

may be more common in patients with hematologic malignancies or head and neck cancers [14]. Additionally, it might change as the cancer treatment progresses. The incidence of OM peaks in the first few weeks of treatment and is frequently more severe during the active phase of chemotherapy. Lastly, individual differences in sensitivity to CIM can be attributed to a variety of factors, including age, overall health, and dietary status [15].

3.4. Impact of oral mucositis on quality of life, treatment adherence, and overall outcomes

The fact that CIM impairs the patient's general quality of life is one of the key reasons it is such a severe and crippling condition. This is a result of, among other things, the patient's inability to eat, speak, and practice good oral hygiene due to severe pain and suffering. As a result of this discomfort, eating will be decreased, which will cause malnutrition and weight loss. Fatigue, weakness, and a general decline in well-being can all be further exacerbated by poor diet. Apart from the psychological effects, the physical difficulties associated with chronic illness management (CIM) and the emotional strain of cancer therapy may exacerbate stress, worry, and a diminished sense of overall well-being [16].

Severe CIM may result in dosage reductions or delays in chemotherapy treatment, which will therefore have an impact on the patient's treatment plan. The effectiveness of treatment may be compromised in patients with severe mucositis if they are unable to endure the entire term of their recommended medication. Therefore, it might interfere with the scheduled chemotherapy, influencing the length and timing of treatment cycles. The best possible care for the underlying malignancy may be hampered by this disturbance. Finally, if patients expect their mucositis to worsen, they could be reluctant to go through more rounds of chemotherapy [15].

The overall course of this illness will increase the need for further medical treatments, such as hospital stays or supportive care plans, which will raise the cost and use of healthcare services. Additionally, the risk of bacterial, viral, and fungal infections is raised by oral mucosal ulcerations. Infections can worsen the symptoms of mucositis and cause systemic problems, which can impact the effectiveness of treatment as a whole. Ultimately, to lessen these side effects and enhance the overall experience for those receiving chemotherapy, efficient management and preventative measures for CIM are crucial [3].

4. Photobiomodulation or low-level laser therapy

PBM is a non-invasive treatment strategy that uses low-level light or laser to stimulate cellular processes and alter biological responses. It is often referred to as cold laser therapy or LLLT. The concept of 'biomodulation' refers to light's capacity to alter and optimize a range of biological processes without generating heat damage [17].

PBM makes use of particular light wavelengths, usually in the near-infrared or red range. It has been discovered that these wavelengths cause photophysical and photochemical reactions as well as interact with biological components. Cellular chromophores, such as cytochrome c oxidase and porphyrins, which are involved in cellular respiration and energy production, absorb light at particular wavelengths. These chromophores absorb light, which sets off a cascade of biological reactions [18].

It is believed that the absorbed light energy improves mitochondrial activity, increases adenosine triphosphate (ATP) synthesis, and regulates reactive oxygen species levels to improve cellular performance. These outcomes support greater cellular resiliency and energy. PBM has also shown anti-inflammatory properties through cytokine production modulation and inflammation reduction. This may be especially important in situations when inflammation is involved, like in tissue damage or specific medical problems [3].

It has been demonstrated that PBM speeds up the healing process by encouraging tissue regeneration, cell migration, and proliferation. This is particularly helpful for ailments when tissue repair and wound healing are involved. Furthermore, it demonstrates a potent analgesic action that aids in easing pain and suffering. This is explained by how it affects endorphin release and nerve conduction [17].

One of PBM's many benefits is that it is nonthermal, which means it does not generate a lot of heat, and noninvasive, which means there is not much risk to the tissues being treated. This makes it a therapeutic method that is both safe and well-tolerated [].

PBM's effects are dose-dependent, which means that different elements, including light intensity, treatment duration, and specific parameters, can have different impacts. For the intended therapeutic benefits to be achieved, optimal dosimetry is essential [18].

PBM has been explored in various medical and dental applications, including wound healing, pain management, neurological conditions, and, as mentioned in previous discussions, as a potential

preventive and treatment modality for conditions like CIM [19].

4.1. The mechanism of action of pbm in response to chemotherapy induced oral mucositis

When it comes to OM, PBM works by way of a sequence of cellular reactions to low-light exposure. Even though the study into the precise pathways is still underway, several crucial processes have been identified:

4.1.1. Mitochondrial activation

It is thought that PBM interacts with the mitochondria, most especially with cytochrome c oxidase, to affect cellular activity. The electron transport chain is strengthened by this contact, which increases the synthesis of ATP. Increased cellular energy and metabolism, which support cellular viability and resistance, are facilitated by elevated ATP levels [].

4.1.2. Anti-inflammatory effects

PBM reduces the synthesis of pro-inflammatory cytokines such interleukin-1 beta and tumour necrosis factor-alpha. The inflammatory response linked to OM can be lessened by reducing pro-inflammatory cytokines [].

4.1.3. Cell proliferation and migration

PBM encourages the advancement of the cell cycle and DNA synthesis, which in turn promotes cell proliferation. Increased cell division promotes the regeneration of injured tissues and speeds up the healing process [].

4.1.4. Oxidative stress mitigation

Research has demonstrated that PBM lowers reactive oxygen species levels, which helps to mitigate oxidative stress. Reducing oxidative stress aids in cellular defense and might shield oral mucosal cells from additional harm [].

4.1.5. Angiogenesis promotion

PBM contains angiogenesis-promoting properties that encourage the growth of new blood vessels in the tissues it affects. Increased blood flow promotes tissue oxygenation and nutrition delivery, which helps the oral mucosa heal and regenerate [].

4.1.6. Neuroprotection

By regulating neuronal activity and lowering oxidative stress in nerve cells, PBM may have neuroprotective effects. This may help to lessen the discomfort and anguish brought on OM [20].

4.1.7. Immunomodulation

By affecting immune cell activity, PBM can regulate the immunological response. Immunomodulation may enhance tissue healing and the resolution of inflammation by preserving a balanced immunological environment [3].

4.1.8. Analgesic properties

PBM may have analgesic effects by releasing endorphins when it interacts with nerve cells. Discomfort relief is very important when it comes to OM because discomfort can be a serious symptom [17].

These processes can be illustrated in the following Diagram (Fig. 1) [21].

The combined effect of these pathways implies that PBM may contribute to the improvement of oral mucosal tissues' resilience, the reduction of inflammation, and the encouragement of injured cell regeneration and repair. PBM has the potential to be a useful treatment and preventative strategy

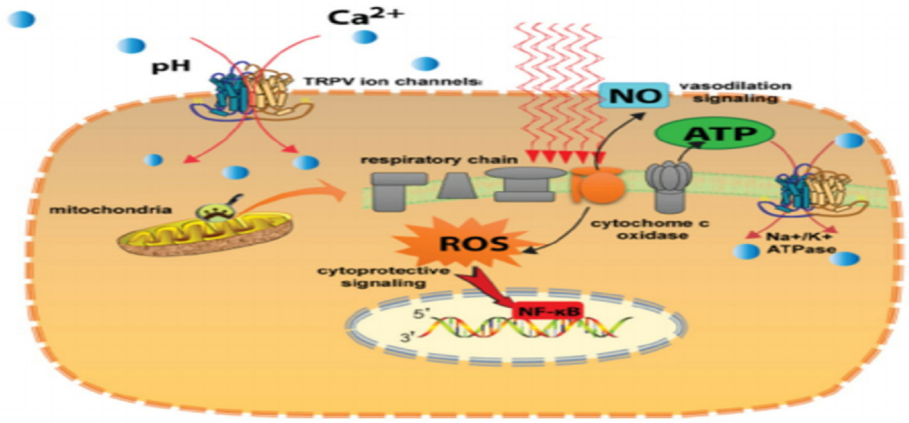

Fig. 1. The mechanism of action of photobiomodulation in response to chemotherapy induced oral mucositis'.

for chemotherapy-induced oral mucositis because of these effects [22].

Photobiomodulation, also known as PBM, has been researched and used in many different medical domains. It has shown promise in treating several therapeutic areas, including wound healing, pain management, neurological disorders, skin conditions like dermatitis, acne, and psoriasis, and musculoskeletal disorders like osteoarthritis and tendinopathies [23].

PBM has been studied in dentistry about oral health in an attempt to treat ailments like temporomandibular joint abnormalities, promote wound healing following oral procedures, and reduce inflammation [24].

5. Rationale for exploring PBM in the prevention and treatment of CIM

(i) Inflammation mitigation: CIM causes the oral mucosa to become inflamed. Due to PBM's anti-inflammatory properties, the inflammatory cascade linked to mucositis may be lessened [1].

(ii) Promotion of tissue repair: Research has demonstrated that PBM promotes cell proliferation and speeds up tissue repair. This may lessen the severity of mucositis and hasten the healing of oral mucosal lesions in the setting of CIM [1].

  (a) Analgesic properties: One of the main signs and symptoms of CIM is pain. The analgesic properties of PBM may assist chemotherapy patients feel less uncomfortable overall and with pain management [14].

(iii) Minimization of treatment disruptions: PBM may help to preserve treatment adherence and minimize chemotherapy schedule disruptions by perhaps lessening the severity of OM [1].

(iv) Noninvasive nature: PBM is a viable supplementary therapy in the all-encompassing care of cancer patients since it is noninvasive and well-tolerated. It is a desirable alternative for supportive care due to its low negative effects [1].

(v) Clinical safety profile: PBM has a good safety record with few side effects in most cases. Because of this, it is a good fit to be incorporated into multimodal CIM management strategies [25].

Because PBM has a proven track record of effectiveness in several medical sectors and can target important parts of the pathophysiology of mucositis, it is being investigated as a potential therapeutic option for CIM [26].

Promising outcomes have been shown in recent research and randomized clinical trials examining the effectiveness of PBM in the prevention and treatment of CIM [19,27,28]. A prospective randomized control trial was carried out by F. Marin *et al*. to evaluate the efficacy of PBM in reducing CIM in patients with head and neck malignancies. In this study one hundred and one children with WHO grade greater than 2 chemotherapy-induced OM were enrolled. Patients were then randomized to either PBM or sham treatment for four consecutive days (days +1 to +4). On days +4, +7, and +11, OM grade, pain (following a 0–10 numeric pain rating scale, NRS), and the need for analgesics were evaluated by an operator blinded to treatment [19].

The results of this study revealed that there was a significant reduction of pain on day +7 in the PBM versus sham group. Reduced use of analgesics was also reported in the PBM group. No significant adverse events attributable to treatment were recorded. Thus, it was concluded that BM is a safe, feasible, and effective treatment for children affected by chemotherapy-induced OM, as it accelerates mucosal recovery and reduces pain [19].

In addition, a retrospective study was conducted by Lilian D. *et al*. to evaluate the impact of LLLT. In this study, a regression model tested the association between OM with prophylactic Photobiomodulation Therapy (PBMT) and antineoplastic therapy. A total of 148 individuals who had undergone 358 chemotherapy cycles were analyzed. It was concluded that PBMT prevented chemotherapy-induced OM. Individuals who used Methotrexate (MTX) and did not undergo prophylactic PBMT were at increased risk of OM [23].

And Beatriz C. *et al*., used a 660 nm wavelength diode laser to evaluate the effectiveness of PBM in the prevention of OM brought on by chemotherapy and radiation therapy. Laser therapy was applied at a frequency of 660 nm, with a dose of 2 J/cm^2, for the prevention of OM induced by chemotherapy specifically for nonhematological tumors. Epidemiological data, total neutrophils, general side effects, development of OM and degree, and the performance of low-power laser therapy to prevent OM were collected. This study concluded that LLLT in the proposed protocol is efficient in reducing the development of OM [28].

Lastly, Alaba and colleagues reviewed numerous preclinical studies on various laser parameters used in CIM treatment and prevention. After reviewing 51 articles it was concluded that; The efficacy of

PBM is a promising strategy in preventing Chemotherapy-induced OM [29].

Based on numerous research and conclusions, PBM can be a successful therapy to reduce the incidence and severity of OM after cancer treatment when used with precise technique and settings [19,23,28,29].

Examining PBM characteristics, such as dosage and wavelength, is essential to comprehend how they affect the prevention of oral mucositis (CIM) caused by chemotherapy. These parameters have been the subject of numerous investigations aimed at optimizing PBM procedures for preventive efficacy [22,29].

Researchers looked into how different light wavelengths affected the prevention of CIM. PBM was used in certain investigations with wavelengths between 600 and 970 nm. The findings showed that some of this range's wavelengths were superior to others in terms of lowering the frequency and severity of OM. This result emphasizes how crucial it is to choose the right frequency for the best preventive results [20,30,31].

Together, these studies highlight how important it is to adjust PBM parameters like dosage and wavelength to improve its ability to prevent CIM. A deeper comprehension of the ideal PBM regimens will result from further research into these aspects, and this will help design focused and efficient preventive measures for OM in cancer patients receiving chemotherapy [29].

When delivering PBM, healthcare providers must adhere to established safety protocols and be cognizant of the patient's medical history, including any drugs and pre-existing diseases. Patients should also let their healthcare professionals know about any strange or uncomfortable feelings they have during or after PBM treatment [32].

Even though side effects are uncommon, continued study and clinical observation advance our knowledge of PBM safety. To stay up to date on documented side effects linked to PBM, it is advised to review the most recent guidelines and literature [32].

While adverse effects are rare, ongoing research and clinical monitoring contribute to the understanding of PBM safety. It's recommended to consult the latest literature and guidelines for the most current information on reported adverse effects associated with PBM [32].

In conclusion, research and clinical trials have continuously shown beneficial results, such as a decrease in the frequency and intensity of CIM, a reduction in pain and discomfort, and a faster pace of tissue healing. Important factors including dosage and wavelength have been carefully examined to maximize the therapeutic impact of PBM treatments. The mechanisms of action that have been reported include improved cellular proliferation, neuroprotection, anti-inflammatory effects, and mitochondrial activation. Even while PBM is usually thought to be safe and has few side effects, research is still being done to improve treatment protocols and account for patient differences in response to treatment [18].

The literature studies yielded positive results, which have various implications for future research and clinical practice. First, given the variability in cancer patients and chemotherapy regimens, further research is necessary to develop standardized protocols, including the best wavelengths and dosages. We can gain a deeper grasp of PBM's applicability by comparing research that examine its efficacy in various cancer kinds and stages [33].

Long-term follow-up studies that evaluate PBM's long-term advantages and possible drawbacks are also necessary to determine the treatment's place in CIM management. Healthcare professionals should think about incorporating PBM into multimodal strategies for CIM prevention and treatment in clinical practice, particularly for high-risk patients. Ensuring safe and successful implementation of evidence-based guidelines and building collaborative guidelines among oncologists, dentists, and PBM specialists is imperative [33].

5.1. Conclusion

With a large amount of research indicating its potential advantages, the present state of evidence on PBM for CIM prevention and treatment is encouraging. In conclusion, PBM is a safe, and well-tolerated in the prevention and treatment of CIM. Even though the results are promising, more research is still needed to improve protocols, handle individual differences, and investigate the wider application of this technology in other therapeutic contexts. To maximize its usefulness and improve patient outcomes, PBM integration into routine clinical practice for CIM management has a great need for constant cooperation, instructions, and research [32].

5.2. Recommendations

Given the current state of research, it is advisable to conduct additional studies on the effectiveness of PBM in preventing and treating OM caused by chemotherapy. Future investigations should prioritize larger sample sizes long-term outcomes and more clinical trials to provide a more

comprehensive understanding of its potential advantages. And to reach the optimum parameters needed for the prevention and management of CIM.

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Biographical information

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Conflict of interest

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