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Review Article

ANTI-INFLAMMATORY POTENTIAL OF *ALOE VERA* IN ORAL MUCOSITIS THERAPY: SYSTEMATIC REVIEW

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ABSTRACT

This review aims to analyse the potency of *Aloe vera* for Oral Mucositis (OM) therapy. Articles searched using the keywords "Oral Mucositis" AND "*Aloe vera*", conducted through PubMed, ScienceDirect, and Cochrane Library databases, and adapted to the PICO (Population, Intervention, Comparison, Outcome) framework. The inclusion criteria for articles were: Randomized Controlled Trial (RCT) study design; in English; full paper available; published in the range between 2011-2021 and with low risk of bias. RoB-tools JADAD Oxford Quality Scoring System was used. This paper writing refers to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. A total of 5 (five) articles met the criteria for a qualitative review and all showed a high range of quality articles. It was found that both *Aloe vera* solution 70% and *Aloe vera* gel 10% showed a reduction of radiotherapy or chemotherapy-induced oral mucositis grade. *Aloe vera* mouthwash has an equal anti-inflammation effect compare to benzydamine on the patient with radiotherapy-induced oral mucositis, whereas the use of other formula containing *Aloe vera* with other herbal materials did not show an anti-inflammatory effect. Drug formulation containing *Aloe vera* can be used as an alternative therapy in the management of Oral Mucositis (OM) with anti-inflammatory potency that can reduce pain and the severity of oral mucositis.

Keywords: *Aloe vera*, Anti-inflammation, Oral mucositis

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INTRODUCTION

Oral Mucositis (OM) is a toxic side effect of chemotherapy and/or radiotherapy treatment for malignancy/cancer [1]. The clinical feature of OM in the form of erosion and ulceration lesions on the oral mucosa that are usually widespread and painful, thus causing problems related to basic psychological needs such as chewing and swallowing food and can directly or indirectly affect a person quality of life [1]. OM involves a variety of complex biological interactions, such as: changes in tissue structure, infiltration of inflammatory cells, and oral microbiome [2]. It is estimated that 40-70% of patients who are undergoing chemotherapy and/or radiotherapy will experience OM with varying levels accompanied by clinical features that also varies [3, 4]. OM can also cause complications such as dysphagia, changes in taste, weight loss, and the appearance of secondary infections [5]. These complications can disrupt the schedule of cancer treatment so inadequate and complicate or extend the treatment time for malignancy conditions/cancer suffered [5].

Based on these problems, the therapy recommended according to the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) for OM is currently in the form of basic oral care. Therapies that use growth factors and cytokines, cryotherapy, photobiomodulation, anti-inflammatory drugs, anti-microbial drugs, coating agents, anesthetics, analgesics, and various natural ingredients are some of the basic oral care [6]. Steroids are also one of the drugs used as therapies for OM, but their use has several side effects [7]. This causes the scientist to look for steroid replacement alternatives with other drugs with equivalent but more potential, few or no side effects [7]. Currently, herbal products are being widely researched and used with therapeutic purposes because they are considered more economical, relatively safe, and generally have low toxicity [8]; however, the effectiveness and safety of these herbal medicines still need to be scientifically proven before they can be used to prevent or treat disease [9, 10].

Among these herbal products is *Aloe vera* (Aloe barbadensis miller) which is a shrub-like plant, can survive for years, xerophyte, succulent, and green in colour. *Aloe vera* belongs to the family Asphodelaceae (Liliaceae) [11]. All types of *Aloe vera* (AV) contain gels that have more than 70 biological compounds with various properties such as anti-inflammatory, antimicrobial, antioxidant, antidiabetic, wound healing, immune system enhancer [12], antiviral, and anticancer [13]. This plant includes types of plants that are easy to grow and do not require special care. AV can grow in areas at altitudes of 0-1500 meters above sea level, air temperatures range from 16 °C–33 °C, and rainfall of 1000-3000 mm per year [14].

Until now, there have been several clinical trials on the use of *Aloe vera* as an OM therapy [15–20], as well as the writing of systematic review published in 2016, on the clinical effectiveness of *Aloe vera* in the management of oral mucosal disease [21] and systematic review published in 2021 on the effectiveness and safety of herbal plants for oral mucositis therapy [22], but the two did not discuss specifics regarding *Aloe vera* therapy for OM. Based on this, the writing of this review is intended to specifically discuss the potential and therapeutic response of using *Aloe vera* as an OM therapy so that it can be the basis of treatment (evidenced-based) for OM therapy scientifically.

MATERIALS AND METHODS

This article is a systematic review compiled following the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [23]. Research questions are determined according to the purpose of writing, guided by the PICO (Population, Intervention, Comparison, and Outcome) [24] framework as follows: (1) Population: patients with Oral Mucositis (OM) diagnosis; (2) Intervention: *Aloe vera*; (3) Comparison: placebo and conventional therapy; (4) Outcome: (a) Subjective parameters of assessing pain; (b) Objective assessment parameters using the World Health Organization-Oral Mucositis (WHO-OM) grading system; (c) Complication parameters: dysphagia, nasogastric tube placement, intravenous hydration, need of supportive drugs, weight loss, and interruption of radiotherapy; (d) Side effects. The search method for research questions was conducted using the keywords "Oral Mucositis" AND "*Aloe vera*" Filters: Full text, Randomized Controlled Trial, in the last 10 y, Humans, English. The digital data bases used are: PubMed, Science Direct, and Cochrane Library. Additional article searches are also done manually by checking the list of article references that have been obtained, will be used if relevant to the research topic and have good article quality.

The inclusion criteria in this study are articles discussing the use of *Aloe vera* for oral mucositis (OM) therapy, is a clinical trial study with the design randomized controlled trial (RCT), in English, the full text is accessible, the subject of human research, published in the last 10 y (2011-2021), and has a low risk of bias (RoB) or good article quality. The article's screening and eligibility test are conducted by VCC and ISW. Articles resulting from the screening process using the inclusion criteria are assessed using the RoB-tools JADAD Oxford Quality Scoring System [25]. Oxford Quality Scoring System consists of five question points as stated in table 1. The maximum number of points is 5 and the minimum number of point's is-2. The number of points≥ 3 shows articles with a high range of quality, while when the number of points≤ 2 shows articles with a low range of quality [22, 25–27]. If there is a disagreement, a joint consensus will be made to determine the use of related articles.

Data extraction according to the expected outcome is carried out on all selected articles. Articles are analysed using qualitative thematic analysis. The analysis is done by identifying, grouping, and analysing data from articles based on the similarity of themes found [28].

RESULTS

A total of 6 articles were filtered through searches in the PubMed database (identified 35 articles), 28 articles in the Science Direct database (identified 194 articles), and 21 articles in the Cochrane library database (identified 24 articles). A total of 2 additional articles were manually identified from the selected article bibliography, bringing the total of 57 filtered articles. Furthermore, a total of 51 articles have been excluded because they are not in accordance with the purpose of the study, so as many as 6 articles were tested using the JADAD Oxford Quality Scoring System. A total of 5 articles in the high range of quality and can be reviewed qualitatively, and 1 article is excluded because it is in the low range of quality. Fig. 1 show a flow chart of search results and article selection in this study.

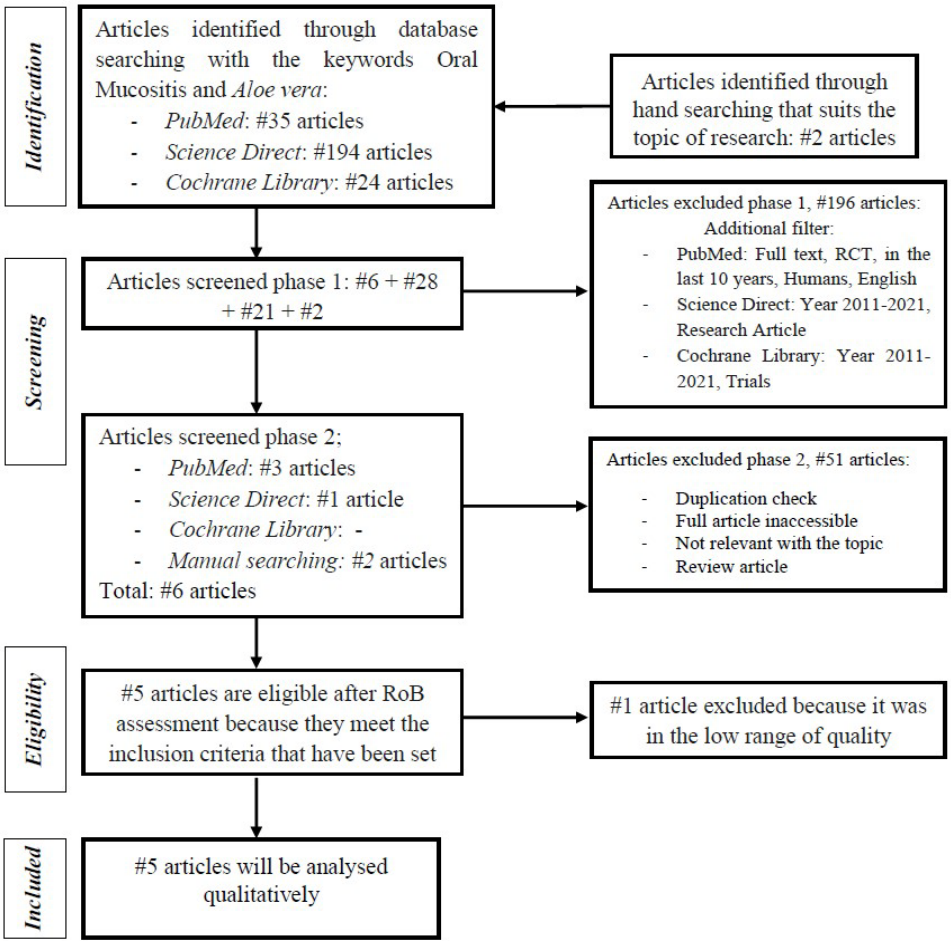

Fig. 1: PRISMA flowchart of this systematic review

Table 1: Assessment of the risk of bias using the oxford quality scoring system

Reference	Question No.					Result
	(1)	(2)	(3)	(4)	(5)	
(Alkhouli, Laflouf and Alhaddad,2021) [15]	1	1	1	1	1	*High range of quality*
(Alkhouli, Laflouf and Comisi,2021) [16]	1	1	1	1	1	*High range of quality*
(Sahebjamee *et al.*, 2015) [17]	1	1	1	1	1	*High range of quality*
(Mansouri *et al.*, 2016) [18]	1	1	0	-1	1	*Low range of quality*
(Marucci *et al.*, 2017) [19]	1	1	1	1	1	*High range of quality*
(Lakhani *et al.*, 2017) [20]	1	1	1	1	1	*High range of quality*

Note: Question No. 1. Was the study described as random? (Yes = 1, No = 0); 2. Was the randomization scheme described and appropriate? (Yes = 1, No =-1); 3. Was the study described as double-blind? (Yes = 1, No = 0); 4. Was the method of double-blinding appropriate? (Yes = 1, No =-1); 5. Was there a description of dropouts and withdrawals? (Yes = 1, No = 0)

Table 2: General summary of reviewed articles

No	Title	Reference	Country	Subject of research	Drug formula
1	Efficacy of Aloe-Vera Use for Prevention of Chemotherapy Induced Oral Mucositis in Children with Acute Lymphoblastic Leukemia: A Randomized Controlled Clinical Trial	(Alkhouli, Laflouf and Alhaddad, 2021) [15]	Syria	26 patient: - 13 patient intervention group - 13 patient control group	*Solution*
2	Assessing the topical application efficiency of two biological agents in managing chemotherapy-induced oral mucositis in children: A randomized clinical trial	(Alkhouli, Laflouf and Comisi,2021) [16]	Syria	36 patient: - 24 patient intervention group (12 patient of *Aloe vera* group, 12 patient of Olive oil group) - 12 patient control group	*Solution*
3	Comparative Efficacy of *Aloe vera* and Benzydamine Mouthwashes on Radiation-induced Oral Mucositis: A Triple-blind, Randomized, Controlled Clinical Trial	(Sahebjamee *et al.*, 2015) [17]	Iran	26 patient: - 13 patient intervention group - 13 patient control group	*Mouthwash*
4	Double-blind randomized phase III study comparing a mixture of natural agents versus placebo in the prevention of acute mucositis during chemoradiotherapy for head and neck cancer	(Marucci *et al.*, 2017) [19]	Italy	104 patient: - 53 patient intervention group - 51 patient control group	*Mouthwash*
5	Efficacy of *Aloe vera* gel topical application on Radiation Induced Mucositis in Head and Neck Malignancy: A Double-blind, Randomized Clinical trial	(Lakhani *et al.,* 2017) [20]	India	100 patient: - 51 patient intervention group - 49 patient control group	*Gel*

Table 3: Result and outcome

No	Reference	Population	Intervention	*Parameter outcome*	Result
1	(Alkhouli, Laflouf and Alhaddad, 2021) [15]	Chemotherapy Induced Oral Mucositis (CIOM)	70% *Aloe vera* solution+potassium sorbate 0.1% preservatives and sodium meta-bisulfate 0.01%. Comparison: Sodium bicarbonate Intervention: Topical application of 5 ml, 2x a day on the tongue, the base of the mouth, buccal and labial mucosa, and lips	1. Subjective 2. Objective	1. *Aloe vera* solution 70% decreasing stomatitis intensity and pain. 2. *Aloe vera* solution 70% was better at lowering the severity of OM compared to the sodium bicarbonate group in the 2nd, 3rd, 4th, and 7th weeks. 3. *Aloe vera* solution 70% slows down OM better compared to sodium bicarbonate significantly
2	(Alkhouli, Laflouf and Comisi,2021) [16]	Chemotherapy Induced Oral Mucositis (CIOM)	70% *Aloe vera* solution+potassium sorbate 0.1% preservatives and sodium meta-bisulfate 0.01%, Comparison: Olive oil and Sodium bicarbonate Intervention: Topical application 4x a day on the tongue, the base of the mouth, buccal and labial mucosa, and lips	Objective	1. *Aloe vera* solution 70% lowers the OM grading from Grade 3 into Grade 2. 2. Olive oil lowers the OM grading from Grade 4 into Grade 0. 3. *Aloe vera* dan olive oil were effective in the management of OM than sodium bicarbonate. 4. Significant statistical differences in mucositis degree before and after the use of *Aloe vera* and olive oil compared to the sodium bicarbonate group.
3	(Sahebjamee *et al.*, 2015) [17]	Radiation Induced Oral Mucositis (RIOM)	*Aloe vera* mouthwash (Pure *Aloe vera* gel/Barij *Aloe vera* Syrup+0.0009% Brilliant Blue dye+0.0006% tartrazine yellow dye) Comparison: Benzydamine. Intervention: Gargle 5 ml, 3x a day	1. Objective 2. Side effect	1. Early signs of mucositis appear after 15.6 d (*Aloe vera* mouthwash) and after 15.7 (benzydamine). 2. Maximum mucositis grade occurrence was 23.3 d (*Aloe vera* mouthwash) and 23.5 d (benzydamine). 3. *Aloe vera* and benzydamine mouthwash decreased the onset of mucositis and the maximum onset of mucositis, but there was no significant statistical difference in the appearance of mucositis signs. 4. *Aloe vera* mouthwash caused nausea side effect in 2 patients (15.4%).
4	(Marucci *et al.*, 2017) [19]	Concomitant chemoradiotherapy	Faringel (*Propolis* powder extract 6% 8.7g, *Aloe vera* gel 30% 2.6g, *Calendula* powder extract 2% 12.0g, and *Chamomile* aqueous solution 0.3% 19.2g) Comparison: Placebo Intervention: Gargle 7 ml, 4x the day before meals and radiotherapy sessions	*1.* Subjective *2.* Objective *3.* Complication	1. Faringel cannot prevent severe or higher pain. 2. Faringel cannot prevent the development of grade 3 mucositis during chemoradiotherapy. 3. Faringel cannot prevent patients from using nasogastric feeding tube, intravenous hydration, and the occurrence of dysphagia
5	(Lakhani *et al.,* 2017) [20]	Radiation Induced Oral Mucositis (RIOM)	10% *Aloe vera* gel Comparison: Base gel Intervention: Topical application 3x a day	1. Subjective 2. Objective 3. Complication	1. *Aloe vera* gel can slow the progression of OM and reduce pain during radiotherapy. 2. *Aloe vera* gel can lower the severity of OM compared to the control group significantly. 3. *Aloe vera* gel reduces and slows the use of supportive drugs, reduced weight loss, reduced need of radiotherapy feeding, and improves quality of life.

Table 2 shows a general summary of the reviewed article. All articles have a Randomized Controlled Trial (RCT) study design. The study was conducted on Syria [15, 16], Iran [17], Italy [19], and India [20]. The number of study subjects consisted of 26 to 104 oral mucositis patients for each article with equal comparison control. *Aloe vera* preparations used in the study in the form of solution [15, 16], mouthwash [17, 19], and gel [20].

Table 3 shows the results of *Aloe vera* effectiveness in the management and prevention of oral mucositis induced by radiation [17, 20], chemotherapy [15, 16], or chemoradiotherapy [19]. The effectiveness of *Aloe vera* is determined based on several parameters and compares it with control groups such as conventionally used therapies such as sodium bicarbonate [15, 16] and benzydamine [17], placebo [19], and base gel [20]. Outcome parameters used to assess oral mucositis in the study were subjective, objective, complications, and side effects. Pain assessment parameters use Verbal Descriptor Scale (VDS) [19] and Visual Analogue Scale (VAS) [20].

DISCUSSION

Oral mucositis refers to a painful erythema and ulceration lesion in the oral mucosa of cancer patients undergoing chemotherapy and/or radiotherapy [29]. The acute mucosa inflammation begins as a reddish color and develops into ulceration and forms a pseudomembrane that acts as a temporary dividing wall until cellular tissue performs the wound healing process [30]. Damaged mucosa tissue often causes bacteria and fungi to multiply on the mucosa and causes secondary infection [30, 31].

Steroids are one of the drugs used as a therapy for various oral diseases today, but because of some of the side effects caused, herbal medicines began to be widely researched and considered as alternative therapies that can be used to prevent and treat diseases [7, 9, 10]. *Aloe vera* becomes one of the alternative therapies that can be used to treat various types of diseases because of its therapeutic potential as an immunostimulatory, anti-inflammatory, antioxidant, antibacterial, antifungal, radioprotective, and accelerate wound healing [32]. *Aloe vera* properties such as immunomodulators, anti-inflammatory, and antioxidants [12] can be used to treat local inflammation in the form of ulceration and antimicrobial, antiviral, and antifungal [32] properties can be used to treat secondary infections on the inflamed oral mucosa mainly caused by *Candida albicans* or *Herpes simplex* virus type 1 [33]. Oral Mucositis is usually followed by a bacterial or fungal infection of the oral cavity, so if herbal medicines have the same ability, then this is very useful for oral mucositis therapy.

Our review found that research related to *Aloe vera* as an anti-inflammatory for Oral Mucositis (OM) has been conducted in Asian countries and one Europe continent. A total of four articles state that *Aloe vera* is safe and effective in slowing and alleviating [17, 20], as well as preventing [15, 16] the development and severity of oral mucositis induced by radiotherapy and/or chemotherapy when compared to conventional therapy. The results from objective assessment of the severity of oral mucositis with WHO OM grading system conducted in four research articles showed a decrease in pain intensity and onset of mucositis. One research article found that *Aloe vera* formulations along with other herbal ingredients could not prevent oral mucositis when compared to placebo [19]. *Aloe vera* can prevent the severity of OM better than it does to prevent the appearance of OM. OM until now is still a side effect of chemotherapy and/or radiotherapy as a malignancy therapy/cancer that is difficult to avoid [34].

Most research articles mention *Aloe vera* as an empirical anti-inflammatory in traditional medicine and in *in vitro* studies are able to protect the skin and accelerate wound healing. *Aloe vera*'s active compounds aloesin, aloin, and emodin show their pharmacological effects through antioxidant and anti-inflammatory mechanisms [35]. Emodin is an inhibitor to the inflammatory response that causes decreased production of prostaglandins E2 (PGE2) and Cyclooxygenase-2 (COX-2) mRNA, known as biomarkers of inflammation [36]. Other active compounds contained in *Aloe vera* such as acemannan as a polysaccharide have the potential as immunostimulatory, anti-inflammatory, antioxidants, and accelerate wound healing [32]. Aloe polysaccharides can be a beneficial agent in wound healing and inflammatory activities as they can inhibit the production of TNF-α, IL-8, and IL-12, which are pro-inflammatory cytokines in human keratinocytes [35].

Aloe vera extract in *in vivo* research is often used in gel preparations. Topical application of *Aloe vera* can demonstrate wound healing effects in animals induced with skin incisions indicated by reduced inflammatory cell infiltration parameters, increased CD4+/CD8+lymphocyte ratio, and increased epidermis thickness as well as collagen deposition [35]. Wound healing mechanisms are associated with polysaccharide compounds contained in *Aloe vera*. Polysaccharides can increase the proliferation of fibroblast growth factors, collagen production and strengthen connections among collagen tissue structures at the site of the wound [37, 38]. Research on radiation-induced rat oral mucosal ulceration shows that the use of *Aloe vera* and silver nanoparticles (AgNPs) can improve ulceration healing by restoring epithelial tissue and decreasing inflammatory cell infiltration [39]. Mucoadhesive gel preparations are generally more effective for oral mucosal ulceration lesion therapy [40], but mostly in all the articles we reviewed *Aloe vera* was tested in the form of mouthwash or solution preparations. The use of mouthwash preparations for OM therapy will be more effective to cover a large area of lesions [41], while the gel will be more effective because it can be directly registered on localized lesions [42].

Administration of *Aloe vera* mouthwash can cause a decrease in the onset of oral mucositis, decrease in the maximum onset severity of oral mucositis although not significant [17], or a significant decrease in oral mucositis degrees [15]. Alkhouli *et al.,* research with *Aloe vera* solution preparations showed a decrease in the severity of mucositis from grade 3 to grade 2, while the administration of intervention using olive oil showed a better decrease in the degree of mucositis and significantly from grade 4 to grade 0 [16]. Two patients were found to have nausea as an intervention side effect in the group given *Aloe vera* [17].

Aloe vera gel research shows a slowing of oral mucositis progression and reduced pain during radiotherapy. The secondary assessment showed a positive correlation in the use of *Aloe vera,* which can improve the quality of life [20]. However, article that tested the administration of mouthwash preparations containing *Aloe vera* gel along with three other herbal components, namely *Propolis*, *Calendula*, and *Chamomile* (Faringel), it was reported that no preventive effect of the preparation was found on the development of oral mucositis during chemoradiotherapy. This is still unexplained the reason, but it is estimated that the dose of natural ingredient use, or the possibility of interference with the wound healing process in patients, and the drug interactions that occur may be the causative factors [19].

Aloe vera mouthwash has anti-inflammatory effects equivalent to benzydamine in patients with radiotherapy-induced oral mucositis [17]. *Aloe vera* solution 70% can improve the condition of oral mucositis induced by chemotherapy [15, 16] and *Aloe vera* gel 10% can improve oral mucositis induced by radiotherapy [20]. *Aloe vera* solution with a concentration of 70% and gel 10%, both of which can reduce oral mucositis score. This effective concentration difference may be related to differences in *Aloe vera* extraction techniques, or differences in dosage forms, namely solutions and gels, or also due to differences in cancer therapy interventions received by patients, as well as the possible quantity of active metabolite content in different plants because they are grown in different countries as well. Environmental differences based on climate, temperature, rainfall, fertility, and soil moisture can also create plant variations that can affect plant growth phases, nutrients, and the content of plant secondary metabolites [43, 44].

Based on a review of these articles, we found a fairly high potential of *Aloe vera* as an alternative therapy that can be used for oral management because it can overcome inflammatory reactions in oral mucositis. Our current review complements the information of two previously published review discussions on the clinical effectiveness of *Aloe vera* in the management of oral mucosal disease [21] and in terms of the effectiveness and safety of herbal plants for oral mucositis therapy [22]. Thus, drug formulation containing *Aloe vera* can be recommended in OM management, especially in terms of reducing pain and severity of OM.

Limited information regarding the specific condition of the oral mucosa, differences in dosage form, and the amount of *Aloe vera* used can be one of the obstacles in comparing the effectiveness of *Aloe vera* in a balanced manner among the articles we reviewed. In addition, this review does not cover all parts of the continent in the world and only covers the continent of Asia and one European country, so it can be further recommended to conduct further clinical trials of drug preparations containing *Aloe vera* with various doses in more homogeneous populations in countries on the continent that have not been reached in this review, to strengthen its evidence-based use in OM therapy.

The results of this writing are expected to be evidence-based that supports consideration of clinical applications of the use of *Aloe vera*-based drug preparations for patients experiencing oral mucositis, can also be the basis of further research related to the development of *Aloe vera* as an anti-inflammatory in other inflammatory diseases of the oral mucosa, as well as research on the development of drug formulations.

CONCLUSION

Drug formulation containing *Aloe vera* can be used as an alternative therapy in the management of Oral Mucositis (OM) with anti-inflammatory potency that can reduce pain and the severity of oral mucositis.

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AUTHORS CONTRIBUTION

All the author have contributed equally

CONFLICTS OF INTERESTS

There are no conflicts of interest.

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