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Review Article

MECHANISM OF ACTION, EFFICACY, AND SAFETY OF PROPOLIS FOR THE MANAGEMENT OF ORAL MUCOSITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Oral mucositis (OM) is an oral mucosal inflammation and complication of chemotherapy and/or radiotherapy. One of the natural agents that has been widely studied as an alternative therapy for OM was Propolis. This review aims to analyze the effectiveness and safety of propolis and its mechanism of action in preventing and treating OM through clinical study in human and animal models. Articles searched using the keywords "Oral Mucositis" AND "Propolis", conducted through PubMed, ScienceDirect, and Cochrane Library databases. The inclusion criteria were: Clinical Trial and Animal Study design; in English; full paper available; published between 2016-2021; and high range of quality and articles in line to the research topic. RoB-tools JADAD Oxford Quality Scoring System and SYRCLE's RoB tool was used for risk of bias determination. This paper writing refers to PRISMA guidelines. *In vivo* studies and clinical trials have shown that propolis can reduce OM Index scores in animals or OM grades in patients. Propolis can also reduce the symptoms of inflammation in OM and almost all articles stated that there were no side effects of propolis for oral mucositis. *In vivo* studies showed that propolis was able to inhibit pro-inflammatory markers, hypoxia markers, MPO serum levels, and TNF-alpha cytokines, but increased the expression of pS6, pAKT, NF-B, and GSH. Propolis is effective and safe to use in patients receiving chemotherapy/radiotherapy to prevent the severity and potential for OM therapy. The mechanism of action of propolis in overcoming clinical symptoms of OM is as an anti-inflammatory, antioxidant, and helps accelerate wound healing.

Keywords: Oral mucositis, Propolis, Chemotherapy, Radiotherapy

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INTRODUCTION

Oral mucositis is one of the complications of chemotherapy and/or radiotherapy, in the form of inflammation of the oral mucosa, commonly found in patients with head and neck cancer. The type and dose of chemotherapy or radiotherapy can affect the severity of oral mucositis [1]. About 30-40% of cancer patients undergo oral mucositis, and the percentage increases to 60-85% in Hematopoietic Steam Cell Transplantation (HSCT) patients, even in head and neck cancer patients receiving chemotherapy and radiotherapy, the percentage can reach 90% [2]. Oral mucositis can cause erythema and ulceration of non-keratin mucosa, causing pain, potentially leading to nutritional deficiencies, decreased endurance of the patient, and systemic infection in sufferers. These things can cause delays in treatment, impact optimal cancer treatment, and affect the cancer healing process [1].

Oral mucositis management aims to prevent or reduce the severity of cancer therapy agents' toxicity effects and manage the symptoms that appear. This is expected to support the success of cancer therapy to improve prognosis [3]. An evidence-based practice guidelines for oral mucositis has already published by the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO). There are seven groups of treatment method, one of them is natural agents utilization [4].

Conventional medical treatment has limited effectiveness for OM, therefore a growing number of malignancy patients in children are using CAM to reduce the side effects of conventional cancer therapy [5]. On the other hand, the use of CAM treatment is feared to cause toxicity and interaction with antineoplastic drugs as well as other supportive treatment agents used during chemotherapy [6]. One of the efforts included in CAM is the administration of herbal medicine. A review article writes that licorice root plant extract (*Glycyrrhiza glabra*) can be said to have better effectiveness compared to curcumin (*Curcuma longa*), *Aloe vera*, or black mulberry (*Morus nigra*), but there has been no mention of propolis potential for use in treating inflammation in oral mucositis [7].

Many complementary therapies (CAM) were used in conjunction with the prime therapies in cancer patients. As well as treatments already tested to treat OM, to decrease symptoms and increase quality of life, still none have been accepted and widely used. Therefore, a review is needed that can analyze the effectiveness and safety of any CAM therapy in oncology [6]. Propolis is one of the complementary therapies has reported in several scientific research articles [6, 8, 9]. Propolis is a resin collected by bees from plant exudates and used to build and protect the beehive [6]. Propolis has antibacterial, antiviral, anti-inflammatory, wound healing, anticancer, antiradical free, antifungal, antioxidant, and antiapoptosis properties [10–14]. There have been several clinical trials on the use of propolis for chemotherapy-induced oral mucositis therapy and/or radiotherapy [6, 15–20]. Previous systematic reviews discussing the effectiveness of propolis for oral mucositis therapy induced by chemotherapy and/or radiotherapy, [21] it was published before 2016 and has not discussed in detail the safety aspects of its use, only discusses the use of propolis in mouthwash preparations, and has not discussed the mechanism of action. This review is shown to update information on propolis for oral mucositis, safety data on its use, the effectiveness of propolis in various dosage forms, and *in vivo* studies in animal models are also included to obtain the mechanism of work of propolis in OM therapy. The results of this writing are expected to be the scientific basis and clinical recommendations for using propolis in oral mucositis.

MATERIALS AND METHODS

This article is a systematic review compiled following the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [22]. Research questions are determined according to the purpose of writing, guided by the PICO framework as follows: (1) population: patients with OM and animal models with OM; (2) intervention: propolis; (3) comparison: placebo or conventional therapy; (4) outcomes: Clinical effectiveness (improvement of oral mucosal conditions and decreased oral grade of mucositis), the safety of propolis (side effects and adverse effects), and biological parameters studied *in vivo* studies. The search method for research related articles was conducted using the keywords "Oral Mucositis" AND "Propolis". Filters: Full text, in the

last 5 y, English. The digital databases used were PubMed, Science Direct, and Cochrane Library. Additional article searches are also done manually by checking the list of article references that have been obtained and used if relevant to the research topic.

The inclusion criteria in this study are articles discussing the use of propolis for oral mucositis (OM) therapy, in clinical trial studies (human) and *in vivo* studies (animals), in English, full text accessible, research subjects in human/animal models, published in the last 5 y (2016-2021). Articles resulting from the screening process using inclusion criteria are assessed eligibility using RoB-tools JADAD Oxford Quality Scoring System and SYRCLE's RoB tool [23, 24]. Oxford Quality Scoring System/JADAD used in articles with clinical trial studies consisting of five question points as stated in table 1. A total overall score from the range 5 to (-2). For a total score of<3 shows of low quality, while a total score>3 indicates a high of quality [7, 23]. Articles with *in vivo* study design are assessed using SYRCLE's RoB tool [24]. SYRCLE's RoB tool consists of 10 domains listed in table 2 [24, 25]. For assessment of each domain, if "Yes" indicates a low risk of bias; "No" indicates a high risk of bias; and "unclear" indicates an unclear risk of bias. If one of the relevant questions is answered with a "No", this indicates a high risk of bias in a particular domain. The total score of the 10 domains/questions determines the quality of the article, with the following criteria: the total score>5 has a low risk of bias, while the total score of<5 has a high risk of bias [24]. Data extraction is carried out according to the outcome obtained from all selected articles. Data is analyzed qualitatively using thematic analysis according to the needs of researchers or research objectives. Thematic analysis is a method used to identify, analyze, and report a pattern (theme) in the form of data [26].

RESULTS

A total of 57 articles were identified through searches in the Pubmed database, 135 articles in the Science Direct database, and 28 articles in the Cochrane library database. A total of 1 additional article was manually identified from the selected article bibliography, so that the total number of articles included were as many as 110 articles. A further 101 not a purpose-related article have been excluded. In the end, there were 9 articles assessed using a risk of bias tools and in accordance with the topic, then reviewed qualitatively. The following in fig. 1, is a flowchart of search results and article selection in this study, while table 1 and table 2 are the results of the risk of bias assessment to determine the quality of the articles.

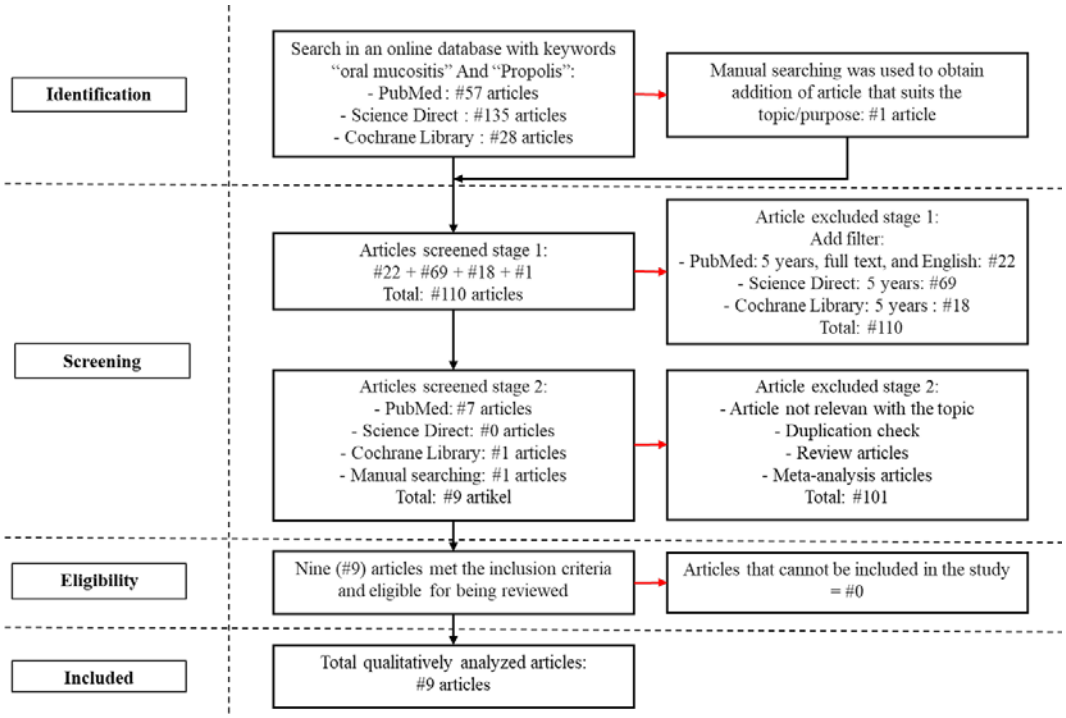

Fig. 1: PRISMA flowchart of this systematic review

Table 1: Assessment of RoB in clinical trial studies used oxford quality scoring system/JADAD

Reference	Questions					Total Score	Risk of Bias
	Was the study described as random?	Was the randomization scheme described and appropriate?	Was the study described as double-blind?	Was the method of double-blinding appropriate?	Was there a description of dropouts and withdrawals?		
[16]	1	1	1	1	1	5	Low risk of bias
[17]	1	1	1	1	1	5	Low risk of bias
[18]	1	1	1	1	1	5	Low risk of bias
[20]	1	1	1	1	1	5	Low risk of bias
[27]	1	1	1	1	1	5	Low risk of bias
[6]	1	1	0	-1	1	2	High risk of bias
[19]	1	1	0	-1	1	2	High risk of bias

Notes: JADAD = risk of bias on clinical trial article (Oxford Quality Scoring System); 1 = Yes; 0 = No; total score<3 = high risk of bias: total score>3 = low risk of bias [7, 23].

Table 2: Assessment of RoB in animal studies used SYRCLE's RoB tool

Reference	Sequence Generation	Baseline Characte-ristics	Allocation Conceal-ment	Random Housing	Blinding (Intervention)	Random Outcome Assessment	Blinding (outcome)	Incomplete Outcome Data	Selective outcome reporting	Other source of Bias	Total skor
[28]	+	+	-	-	-	-	+	+	+	+	6/10 (+)
[29]	+	+	-	-	-	+	+	+	+	+	7/10 (+)

Notes: SYRCLE's RoB tool = risk of bias tool for *in vivo*/animal study article; += low risk of bias; -= high risk of bias; total score<50% = high risk of bias; total score>50% = low risk of bias [24, 25].

Table 3: General summary of review articles

No	Reference	Country	Sample	Study design	Drug formulation
1	[16]	Iran	Control group = 24; Intervention group of propolis = 24; Hypozalix = 24. Total = 72.	RCT	Mouthwash
2	[17]	Iran	Control group = 15; Intervention group of propolis = 15. Total = 30.	RCT	Mouthwash/Solu-tion
3	[18]	Italy	Control group = 51; Intervention group of propolis = 53. Total = 104.	RCT	Solution
4	[20]	Iran	Control group = 25; Intervention group of propolis = 25. Total = 50.	RCT	Tablet
5	[27]	Iran	Control group = 20; Intervention group of propolis = 20. Total = 40.	RCT	Mouthwash
6	[6]	Italy	Control group = 30; Intervention group of propolis = 30. Total = 60.	RCT	Tablet
7	[19]	Brazil	Control group = 13; Intervention group of propolis = 13. Total = 26.	Preliminary study	Mucoadhesive Gel
8	[28]	Turkey	Control normal group = 7; Negative control = 10; Intervention group of propolis 100 gram = 10; Intervention group of propolis 200 gram = 10. Total = 37.	Studi *in vivo*	Solution
9	[29]	Brazil	Control group = 18; Intervention group of propolis = 18; Photobiomodulation therapy (PBMT) = 18; Royal Jelly (RJ) = 18. Total = 72.	Studi *in vivo*	Gel

Notes: RCT = Randomized Controlled Trial.

Table 4: Effectiveness and safety of propolis clinical trial studies for oral mucositis (low risk of bias articles)

No	Reference	Intervention and comparison	Effectiveness parameter	Safety parameter	Resume
1	[27]	Intervention: 5 ml Propolis mouthwash. Comparison: diluted water.	WHO scale and OMAS	No side effect	- Propolis mouthwash was better than diluted water to relieve mucositis, ulceration, and erythema. - On day 7, propolis group patients recovered by 65%. - Propolis is effective in relieving OM symptom compared to diluted water, and potentially as OM therapy.
2	[16]	Intervention: - Group 1 (CHX mouthwash and fluconazole+Hypozalix). - Group 2 (CHX mouthwash and fluconazole+propolis mouthwash). Comparison: CHX mouthwash and fluconazole.	WHO OM grading system	No mention	- CHX+Fluconazole+propolis mouthwash was better than CHX+Fluconazole+Hypozalix in terms of reduced the swallowing, increased sleep quality, reduced burning sensation, patient recovery rate 50%, and low number of OM grade 4 sufferers. - Propolis was effective in improving patient's quality of life and potentially preventing the severity and for therapy in OM.
3	[17]	Intervention: 20 ml propolis solution. Comparison: 20 ml placebo solution.	NCI-CTC and CTCAE	No side effect	- At week 3 and 4, propolis decreased the OM grade, there was 0% patients experienced with OM grade 3 in the propolis group. - Propolis solution was also more effective and faster in decreasing the grade of OM than the grade of dysphagia. - Propolis was effective in preventing the severity of OM and had protective effect better than placebo.
4	[18]	Intervention: Faringel (Chamomile, *Aloe vera*, Calendula, and Propolis) Comparison: placebo with honey and excipient.	CTCAE version 3.0	No adverse effect.	Faringel (Propolis powder extract 6%, g, *Aloe vera* gel 30%, g, Calendula powder extract 2%, g, Chamomile aqueous solution 0.3%, g) was not effective in preventing grade 3 acute OM.
5	[20]	Intervention: 50 mg propolis tablet. Comparison: placebo tablet.	WHO OM grading system	No side effect	- Propolis tablets 50 mg could prevent and treat OM in patients undergoing chemotherapy. - Propolis group might decrease the OM severity better than the placebo group in the 2nd and 3rd follow-up sessions.

Notes: OM = Oral mucositis; WHO OM = World Health Organization Oral Mucositis grading system; OMAS = The Oral Mucositis Assessment Scale; NCI-CTC = National Cancer Institute Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events.

Table 5: Effectiveness and safety of propolis clinical trial studies for oral mucositis (high risk of bias articles)

No	Reference	Intervention	Effectiveness parameter	Safety parameter	Resume
1	[6]	Intervention: Dry extract propolis with 8%–12% galangin, plus sodium bicarbonate mouthwash. Comparison: Sodium bicarbonate mouthwash.	NCI-CTCAE v4.0	Only 2 patients experienced with skin rash. After being stopped the rash immediately disappears. Propolis was considered to be safe.	- Propolis containing tablets were more effective and relatively safe to use along with sodium bicarbonate mouthwash, than bicarbonate used only to prevent oral mucositis. - In the propolis group, no one experienced OM grade>1, while in the bicarbonate group there were patients who experienced with OM grade>1.
2	[19]	Intervention: 5% of propolis mucoadhesive gel. Comparison: Benzydamine with fluconazole	WHO OM grading system	No side effect	5% of propolis mucoadhesive gel was better than benzydamine+fluconazole in maintaining low grades/decreased OM grade and speeding up patient recovery after 17 sessions of radiotherapy.

Notes: NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OM = Oral mucositis; WHO OM grading system = World Health Organization Oral Mucositis grading system.

Table 6: Effectiveness and safety of propolis *in vivo*/animal studies for oral mucositis (low risk of bias)

No	Reference	Intervention	Effectiveness parameter	Safety parameter	Resume
1	[28]	Intervention: - Group 2 = systemic administration of 100 mg/kg/ml of water soluble propolis; - Group 3 = systemic administration of 200 mg/kg/ml of water soluble propolis. Comparison: Group 1 = negative control (radiotherapy 15 Gray on the head and neck area).	Oral mucositis index (OMI)	No mention	- Systemic administration of water soluble propolis decreased OMI scores than the negative control. OMI scores, - Proinflammatory markers, hypoxia markers, serum myeloperoxidase (MPO) levels, and TNF-α showed improvement in the intervention groups.
2	[29]	Intervention: Propolis gel, Photobiomodulation therapy (PBMT, 6 J/cm^2), and Royal Jelly (RJ). Comparison: No intervention was given. Notes: All rats induced with 5-fluorouracil.	OM score	No mention	- Propolis, PBMT, and RJ were effective in the treatment of OM. - The OM score decreased, the expression of immune biomarkers (pS6, pAKT, and NF-κB), and levels of the antioxidant glutathione (GSH) increased in the propolis, PBMT, and RJ intervention groups.

Table 3 shows a general summary of the reviewed article. The article consists of several study designs namely Randomized Controlled Trial (RCT), Preliminary study and *in vivo* study. The study was conducted in Iran [16, 17, 20, 27] Italy, [6, 18] Brazil, [19, 29] and Turkey [28]. The number of study subjects consisted of 26 to 104 oral mucositis patients for each article with equal comparison control. Propolis preparations used in the study include mouthwash, [16, 17, 27] solution, [18, 28] tablets, [6, 20] and gel [19, 29].

Table 4, table 5, and table 6 show the results of propolis effectiveness and safety for oral mucositis-induced radiotherapy or chemotherapy. Several parameters were used to determine the effectiveness and safety of propolis, comparing it with control negative control or placebo, [17, 18, 20, 27] or commonly used conventional therapies CHX mouthwash and fluconazole, [16] benzydamine with fluconazole, [19] and sodium bicarbonate [6]. The effectiveness parameters used to assess oral mucositis in the study were the World Health Organization (WHO) OM grading system, the oral mucositis assessment scale (OMAS), National Cancer Institute Common Toxicity Criteria (NCI-CTC) Common Terminology Criteria for Adverse Events (CTCAE), and Oral mucositis index (OMI). The safety parameters in the form of no side effects and effects experienced by patients during the study.

In vivo study articles assess biomarkers as anti-inflammatory parameters: TNF-alpha, serum MPO, and IL-6 [28]. Antioxidants and anti-free radicals i.e., hypoxia markers consisting of [glucose transporter-1 (GLUT-1) and hypoxia inducible factor 1α (HIF-1α)], [28] and glutathione (GSH); [29] Wound healing accelerators are pS6, pAKT, and NF-B [29]. There was no information on the safety parameters of propolis administration in the *in vivo* study, but it was reported that no rats died or had systemic disorders due to propolis administration.

A total of six clinical trial research articles and two *in vivo* study articles stated that propolis effectively prevented, relieved, reduced the severity, and cured the oral mucositis induced by chemotherapy and/or radiotherapy compared to conventional therapy or placebo. In contrast, one clinical trial research article states that a mixture of natural agents and propolis is ineffective. Five clinical trial research articles reported that patients felt no side effects during propolis use interventions. In comparison, one article reported the presence of rashes on the skin as a mild side effect of propolis administration, and the other two articles did not assess safety parameters.

In table 4, as many as 5 clinical trial study articles reviewed have a low risk of bias quality, while table 5 shows 2 articles with a high risk of bias quality. However, both *in vivo* studies reviewed in this article show good quality, so the results of writing this review in general can be used as one of the guidelines for oral mucositis based on evidence-based medicine/dentistry.

DISCUSSION

Mucositis is a side effect associated with cancer therapy (chemotherapy and/or radiation therapy). It is characterized as the inflammation of the oral and/or gastrointestinal mucosa accompanied by numerous changes to the clinical appearance of the mucosa and complex submucosa [30]. OM can have varying degrees, for more severe OM can lead to mouth ulcers and painful dysphagia; therefore, it can result in decreased quality of life (QoL) and termination of treatment [31].

Conventional medical treatment has limitations in overcoming OM, so many patients use Complementary and Alternative Medicine (CAM) to reduce the side effects of conventional cancer therapy [5]. Propolis is one of the complementary therapies ever reported in

several scientific articles [6, 8, 9]. In general, propolis contains chemical components such as flavonoids and phenols, [32] both secondary metabolites are believed to have anti-inflammatory effects, in addition to antimicrobial, antitumor, antioxidant, immunomodulatory, and other effects [33]. The diversity of components contained in propolis depends on the timing of the intake of raw materials and geographical conditions [34].

Based on qualitative thematic analysis, it appears that some articles report that propolis use is more effective than placebo [6, 16, 17, 19, 20, 27] in lowering OM degrees, preventing the severity of OM grades, and reducing the occurrence of erythema and ulceration. The use of propolis is also reported to be more effective than the effects of using another herbal medicine (Hypozalix) [16]. An article even reported that propolis could cure 65% of patients who experienced OM on the 7th day, [27] or 50% of patients, [16] after regular use. However, an article also stated that propolis appeared ineffective in OM procedures compared to controls when joined in one preparation with other herbal ingredients [18].

The parameters of propolis use side effects in people with OM reportedly consist of dysphagia and skin rashes. The occurrence of dysphagia was reported less in the group that got propolis than the controls in an article, [17] but in other articles, severe dysphagia has been reported [18]. Rashes on the skin as a mild skin reaction have also been reported, [6] while complications of chemotherapy/radiotherapy are weight loss, the need for a nasogastric feeding tube, and intravenous hydration, which cannot be avoided during treatment despite propolis intervention [18]. However, in general, most articles state that there are no side effects of propolis use in OM procedures [16, 17, 19, 20, 27]. Weight loss, the need for nasogastric feeding tube use, and intravenous hydration are more part of chemotherapy/radiotherapy complications than as a side effects of propolis administration.

The success of propolis intervention in preventing the appearance of oral mucositis until now is still unclear. According to Su *et al.*, this can be due to radiation damage or chemotherapy in the superficial layer due to chemotherapy/radiotherapy exposing a large number of basal membranes and innervation of the mucosal epithelial mesenchyme tissue of the mouth. Healing of this type of damage relies heavily on basal membrane regeneration than inhibiting inflammatory mediators, making OM more easily preventable from becoming more severe, but it has not been successfully prevented from its appearance [35]. In addition, this healing disorder can also be caused by the inadequacies of the dose of the natural agent used or due to possible drug interactions, especially in the use of a combination of several natural ingredients. Other possibilities may also be affected by the content of secondary metabolites in plants, such as environmental factors, climate and seasonal variations, geographic region of growth, maturity level, planting practices, post-harvest treatment, processing, and active substance extraction techniques [18, 36].

Furthermore, in table 6, as many as 2 *in vivo* study articles are reviewed to have a low risk of bias quality. OMI scores and markers of pro-inflammatory mediator appeared to be highest in the group that received radiotherapy [28]. It was reported that systemic propolis administration in animals tried to show effectiveness in significantly lowering OMI scores in the group of rats who received radiotherapy, [28] speeding up tissue healing/repair, reducing inflammation, and wound closure in chemotherapy-induced cases of OM, [29] and may decrease the pro-inflammatory mediator TNF-α in the oral mucositis cycle [28]. It was also found that there was an increase in the activity of inflammatory process regulators, i.e., immunoexpression of pS6, pAKT, and NFkappaB in animals treated with propolis compared to the use of royal jelly and PBMT [29]. This is in line with research conducted by Tamfu *et al.*, which states that propolis can inhibit the formation of reactive oxygen species (ROS) because it has the potential as an anti-inflammatory drug agent and antioxidant [11]. The results of this *in vivo* study prove that in molecular biology, the administration of propolis is systemically able to inhibit pro-inflammatory mediators and stimulate anti-inflammatory mediators, thus supporting the speed of oral mucositis healing while also increasing anti-oxidant and wound healing mediators.

Our review complements the information in the review article that has been previously published, in terms of analysis of propolis safety studies and analysis on the results of *in vivo* studies that are the basis of understanding the mechanism of action of propolis as an anti-inflammatory, anti-oxidant, and wound healing accelerator. This review is in line with the previous review discussion on the efficacy of propolis mouthwash in patients who experience oral mucositis, the results of our review also showed that propolis is effective for oral mucositis treatment in both cancer patients receiving chemotherapy and radiotherapy [21]. The use of mouthwash remains more effective and relatively safe mainly due to the large number of evidence-based supports; therefore, the use of propolis mouthwash preparations may be recommended. Propolis in gel preparations still requires further research because there have not been enough clinical trials conducted in humans. In general, oral mucositis has lesions that extend to all parts of the oral cavity; therefore, the administration of gel formulations appears less effective in its clinical applications, although it has so far remained effective in terms of therapeutic efficacy. Propolis in tablet formulation also can not be recommended because side effects were reported in the form of skin rashes. Our review found that propolis is effective and relative safe to be used as an alternative therapy to prevent and treat oral mucositis, but its use should still be under the supervision of an oral medicine specialist. Propolis should not be given to individuals with a history of hypersensitivity.

CONCLUSION

Propolis is effective and safe to use in patients receiving chemotherapy/radiotherapy to prevent the severity and potential for oral mucositis therapy. The mechanism of action of propolis in overcoming clinical symptoms of OM is as an anti-inflammatory antioxidant, and helps accelerate wound healing.

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AUTHORS CONTRIBUTIONS

All the author have contributed well.

CONFLICTS OF INTERESTS

There is no conflict of interest from all the authors.

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