The Effectiveness of Oral Propolis on Mucosa Wound Healing after Removal Third Molars Surgery: A Systematic Review

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Abstract

Propolis in dentistry has been widely studied. Propolis is proven to be an herbal product used healing mucosal tissue after third molar extraction, reducing inflammation, and accelerating the healing of granulation tissue and epithelialization.

This systematic review was guided the Preferred Reporting Items for Systematic Review Method and Meta-Analyses (PRISMA) rules, using 5 electronic databases, namely PubMed, google scholar, science direct, Cochrane Library, and Willey Library. The keywords used were propolis, wound healing, and third molar surgery. The data search was carried out in April 2023. The data was compiled using the PICO (Population, Intervention, Comparison, and Outcome) framework. The population is postoperative third molar tooth extraction patients and interventions using propolis. The expected result is the effectiveness of propolis in healing third-molar extraction patients.

Identification of 2,665 articles was found, resulting in 4 filtered articles, considering the inclusion and exclusion criteria and meeting the eligibility criteria. Discussion: Propolis is capable of a barrier preventing bacterial colonization compared to conventional medicine, but it is more frequent. The antioxidant effect of propolis used in several studies could add a positive effect in preventing the infection from progressing.

Effectives propolis and safety parameter for patients after recovering from third molar tooth extraction to prevent the severity and help accelerate healing. The mechanism action of propolis clinical symptoms is an anti-inflammatory antioxidant and helps accelerate wound healing. Research is needed regarding the effectiveness of propolis in the field of oral surgery.

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Introduction

The third molars are the most commonly impacted teeth. In many cases, the presence of impacted third molars is associated with several problems such as pericoronitis, tumor development, cysts or reabsorption, and caries in adjacent molars.[1,2,3] The American Association of Oral and Maxillofacial Surgeons recommends asymptomatic extraction based on clinical studies investigating the occurrence and development of these lesions associated with impacted teeth. For this reason, lower extraction is one of the most common procedures in oral and maxillofacial surgery.[3,4]

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Conventional medical treatment for tissue healing after third molar extraction has broad effectiveness, then developed herbal therapy treatment to suppress side effects and support tissue repair.[5,6,7,8] One of the efforts included herbal medicine is feared to cause toxicity and interactions with antibiotics and other supportive treatment agents used during post-healing. A review article wrote that licorice root plant extract (Glycyrrhiza glabra) could 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 treating after minor surgery.[3,5,6]

The pharmacologically active molecules present in propolis are flavonoids and phenolic acids. Propolis has a degree of antimicrobial action against fungi such as Candida albicans and some bacteria, including various

microorganisms and viruses that can live in the oral cavity.[1,6,9] Propolis and its components have anti-inflammatory, immunomodulatory, and antitumor activities. Propolis is proven to be an herbal product used in post-operative wound healing, reducing inflammation and accelerating granulation tissue healing and epithelialization.[9,10] The cariostatic effect limits the number of microorganisms and slows down bacterial synthesis and glucosyltransferase activity. Antibacterial of propolis concerning reducing bacteria in the oral cavity and enhancing tissue healing processes.[10,11,12]

Dentistry research about propolis has been used in toothpaste as a storage medium for avulsed teeth in periodontal therapy.[7,8,13] Canal debridement for endodontic procedures has been explored. Due to its anti-infective solid activity, propolis is often called a "natural antibiotic." Many studies have shown its strong inhibitory effect on various pathogenic organisms.[14,15] This paper aims to assess the effectiveness of tissue healing in patients undergoing surgical extraction of third molars. Propolis has a promising role in future medicine and dentistry.

Materials and methods

The Preferred Reporting Items guided this systematic review for Systematic Reviewed Methods and Meta-Analyses (PRISMA),[16] they used 5 electronic databases : PubMed, google scholar, science direct, Cochrane Library, Cochrane, and Willey Library. The keywords used were propolis and third molar surgery. Manual searches were also conducted on topics related to the specified theme and based on selected article references. The data search was conducted in April 2023. The Systematic Literature Review (SLR) used the PICO (Population, Intervention, Comparison, and Outcome) framework following its objectives. The population was postoperative third-molar extraction patients. The intervention is the use of propolis. The expected outcome is the effectiveness of propolis on healing third molar extractions.

Inclusion criteria were analyzed based on the PICOS components: Postoperative third-molar and cell culture. The intervention carried out was surgical management; the result was the effect of the Propolis appliance, the dose given to cell culture. The research design is Prospective, retrospective, cohort study, cross-sectional, experimental, and RCT. Exclusion criteria were conference proceedings, studies not conducted on humans and cell culture, studies with insufficient follow-up time, and not published in English (table 1)

Population	Postoperative third-molar, cell culture
Intervention	Propolis appliance, dose given to cell culture
Ratio	No comparisons were made
Results	Effectiveness of propolis on healing third molar extractions and result dose to cell culture
Study design	Prospective, retrospective, cohort study, cross-sectional, experimental, RCT

Table 1. Table of descriptions of inclusion criteria based on PICOS criteria.

Qualitatively analyzed articles	Questions					Total score	Risk of bias
	Was the study describe as random?	Was the randomization sheme described and appropriate ?	Was the study describe as double-blind?	Was the methode of double-blinding appropriate?	Was there a description of dropounts and withdrawals?		
González-Serrano et al. 2021	1	1	1	1	1	5	Low risk of bias
Ali Khan et al. 2021	1	1	1	1	1	5	Low risk of bias
Lisbona-González et al. 2021	1	1	1	1	1	5	Low risk of bias
Mostafa et al. 2022	1	1	1	1	1	5	Low risk of bias

Table 2. Assessment of clinical trial studies used the oxford quality scoring system/JADAD.
Notes : JADAD = risk of bias on clinical trial article (Oxford Quality Sytem); 1 = Yes; 0 = No; total score <3 = high risk of bias : total score >3 = low risk of bias.

The eligibility criteria include inclusive criteria of English and Indonesian language journals, all study types, and articles published within the last 5 y (2018 - 2023). Articles were excluded if they were not relevant to the topic of third molar surgery, Propolis. The titles and abstracts of the articles to be reviewed were screened to check their relevance to the study objectives. Information related to population and problem (country, number of subjects), intervention (use of Propolis in wound healing after third molar extraction), comparison group, and outcome.

Risk of bias assessment and quality assessment studies were conducted for each selected article to determine the level of evidence-based medicine and the quality of articles to be reviewed. Articles were stratified according to their level of evidence, using the criteria JADAD = risk of bias on clinical trial

articles.[17] The Oxford Quality Scoring System consists of 5 questions, which can assess the randomization of research subjects, the blinding process during the study, the appropriateness of randomization and blinding methods, and any dropouts or withdrawals that occur. The conclusion of the risk of bias and article quality assessment refers to the total score of each article. The maximum score is 5, while the minimum score is <3 (high risk) and the maximum is >3 (low risk) (table 2).

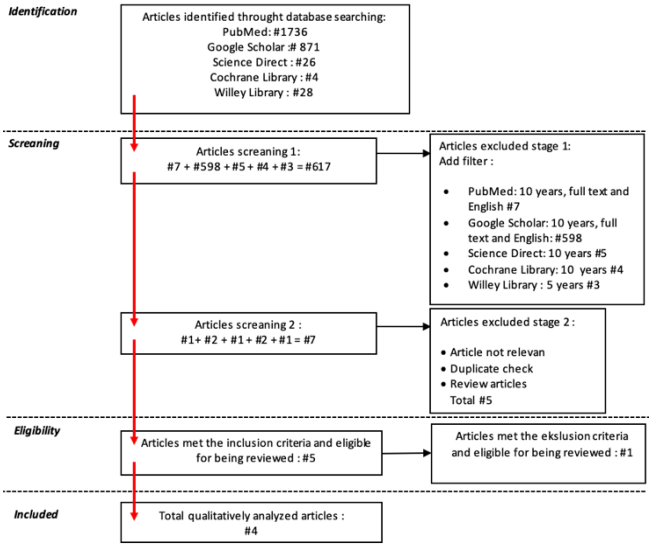

Figure 1. PRISMA flowchart of this systematic review.

Results

The article identification search process found 2665 articles derived from 5 databases with the order of the search through screening data in accordance with the exclusion criteria as much as and some assessment of articles that do not match the subject matter and obtained in accordance with the inclusion criteria resulted in a total of 4 articles that have been filtered by considering the objectives of the systematic review that will be made so that 4 articles that meet the eligibility criteria. Data and information from each article are presented and arranged in table 3. Presented are author name, year, country, study design, scopus index, population and sample, mean age, procedures used in the study, and important results.

Table 3 shows the results of the effectiveness and safety of propolis for wound healing after the third molar extraction. Several parameters were used to determine the effectiveness and safety of propolis, comparing it with negative control or placebo or conventional therapy commonly used chlorhexidine mouthwash and or the use of antibiotics to suppress bacterial virulence. Effectiveness parameters for assessing healing and pain suppression are VAS (Visual Analogue Scale), Friedman's test, and MTT assay on cell culture. Safety parameters include no side effects and effects experienced by patients during the study.

Randomized controlled trial														
REFERENCE	Sample Randomization	Group allocation	initial treatment	*Blind participants*	*Providing blind treatment*	*Blind outcome assessor*	Identical treatment	Complete follow	Analysis in randomized	Same	Measurement results	Precise statistical analysis	Design	Rating results (%)
González-serrano et al. 2021	+	+	+	-	-	-	+	+	+	+	+	+	+	76.9
Ali khan et al. 2021	+	+	+	-	-	-	+	+	+	+	+	+	+	76.9
Lisbona-gonzález et al. 2021	+	+	+	-	-	-	+	+	+	+	+	+	+	76.9

Table 4. RCT (Randomized Controlled Trials) bias risk assessment.

The article in vivo studies assessed biomarkers as anti-inflammatory parameters: TNF-alpha, serum MPO, and IL-6. Antioxidants and anti-free radicals are hypoxia markers consisting of [glucose transporter-1 (GLUT-1) and hypoxia-inducible factor 1α (HIF-1α)], and glutathione (GSH); Wound healing accelerators are pS6, pAKT, and NF-B. There is no information on the safety parameters of propolis administration in vivo studies, but it was reported that no mice died or developed systemic disorders due to propolis administration.[17,18]

Several clinical trials and in vivo research articles state that propolis is effective in preventing, relieving, reducing the severity, and healing wounds after third molar extraction compared to conventional therapy or placebo. The articles reviewed had a low risk of quality bias. This article showed good quality, so the results of writing this review can generally be used as one of the guidelines for wound healing after third molar extraction and wounds in the oral cavity based on evidence-based medicine/dentistry.

RCT (Randomized Controlled Trials) bias risk assessment is in the low category, namely 76.9% (> 70%) show in table 4, explained that the research had been assessed as feasible and was a low bias category.

Discussion

Propolis can act as a barrier to prevent bacterial colonization compared to chlorhexidine, but its use is more frequent. The antioxidant effect of propolis used in some studies could have an added positive effect in preventing infection from progressing.[5,9,10] *Tooth extraction* is a standard dental procedure that always precedes bone resorption and regeneration. Tooth extraction followed by socket healing usually leads to alveolar bone deformities, osteoblasts, and osteoclasts, with the result that receptor activators of both nuclear factor kappa-B (RANK) and nuclear factor kappa-B ligand (RANKL) proliferate.[17,18,19] The role of propolis in the oral cavity can also increase saliva production and suppress oxidative processes, benefits are believed to be antibacterial, lesion healing, anti-inflammatory, analgesic, or probiotic agents to treat lesions. The role of propolis in the oral cavity can also increase saliva production and suppress oxidative processes, so its benefits are believed to be antibacterial, lesion healing, anti-inflammatory, analgesic, or probiotic agents treat lesions.[6,7,18,19] Propolis has antimicrobial properties and anti-inflammatory properties. The caffeic acid and flavonoids present in the composition of propolis reduce the inflammatory response and, by inhibiting lipoxygenase and cyclooxygenase enzymes, prevent the conversion of arachidonic acid to prostaglandins and leukotriene and propolis, improve the function of the immune system because it induces phagocytosis and immune cell activity. Propolis properties are believed to improve the wound-healing process in the oral cavity.[12,13,14,15,20]

The results of these studies suggest that propolis can act as a barrier preventing bacterial colonization compared to chlorhexidine, but its use is more frequent. The antioxidant effect of propolis used in some studies could add a positive effect in preventing infection from continuing.[14] There are good results in the study of González-Serrano et el. 2021, which explained that the VAS results on day 7 were better after the third molar extraction compared to chlorhexidine.[4,5,21] The role of propolis in lesion healing has various practical and safe formulas, which do not address specific mucoadhesive processes. Many studies only explore herbs such as propolis but do not consider the role of mucoadhesive. The mucoadhesive ingredients in propolis are thought to be better at reducing pain and more effective at accelerating lesion healing.[1,7,8,9,10,22,23] This may explain why the different methods in some studies affect the results. Carvalho et al 2015, Magroet et al 2020, and Lisbona-González et al 2021 in their studies showed that mouthwashes containing propolis enhanced wound healing and exhibited anti-inflammatory and analgesic properties. Decades of studies examining propolis have shown no adverse effects.[4,7,10,24]

According to research by Mostafa et al 2022, The cytotoxic effect of a particular substance is evaluated by cell viability assay because it measures the behavior of the cell culture towards the tested substance. Different times were used to simulate the effect of irrigation immediately after contact with cells and the effect of the drug over time. Different propolis concentrations were used; 2% and 1% Propolis NanoParticles showed statistically significantly lower median values. This could be attributed to the increased concentration of propolis, resulting in increased cell proliferation and vitality. As a result, the biocompatibility of propolis was established.[17,18,21,24]

The herbal products are known for its high antimicrobial activity, biocompatibility, anti inflammatory, and anti oxidant properties.[25] Propolis as a herbal product which is a natural resin material produced by honeybees. Propolis has antioxidant properties, antibacterial, antifungal, antiviral, anti-inflammatory, anti-tumor, and has the ability to modulate the immune process.[26] Propolis in dentistry has been used especially in the field of oral surgery to treat wound tissue.

Conclusions

Propolis is effective and safe for patients after third molar tooth extraction to prevent the severity and help accelerate healing. The mechanism of action of propolis in overcoming clinical symptoms is an anti-inflammatory antioxidant and helps accelerate wound healing. More in-depth research is needed regarding the effectiveness of propolis in the field of oral surgery.

Declaration of Interest

The authors report no conflict of interest.

REFERENCE	SQOPUS	SAMPEL	DESAIN STUDY	INTERVENTION AND COMPARISON	PROPOLIS FORMULATION	PARAMETER	RESULTS	SAFETY PARAMETER
González-serrano et al. 2021	Q1	13 patient	RCT	2% propolis extract, 0.2% ascorbic acid and 0.2% tocopherol acetate	2 % - gel	The effect of propolis on postoperative pain according to VAS (visual analog scale) is lower than placebo.	Application of this gel may be effective in preventing alveolitis and thereby reducing postoperative pain following extraction of impacted third molars.	No side effect
Ali khan et al. 2021	Q1	Control = 30; intervensi propolis = 30; zinc oxide eugenol = 30; total = 90	RCT	Intervention = Al-Shifa 100% pure, certified by Saudi Arabian Standards Organization (SASO); zoe group = zinc oxide eugenol liquid; control = saline fluid	Al shifa, 100% pure - dressing	The effect of propolis on postoperative pain according to the vas (visual analog scale) was compared to the conditions before and after the intervention.	Implementing the intervention in the intervention group and the Zoe group significantly reduced pain scores and rapid healing.	No side effect
Lisbona-gonzález et al. 2021	Q1	40 mouthwash intervention patients; 60 patients with propolis paste intervention	RCT	Control mouthwash, 0.2% chlorhexidine mouthwash, 2% propolis mouthwash, and 2% propolis mouthwash + 0.2% chlorhexidine	2 % - mouthwash and pasta	The healing ratio for 7 days on the use of paste and crt ratio for mouthwash assessment after 48 hours of use.	Propolis mouthwash is considered effective in reducing bacterial proliferation. Propolis is a viable alternative for socket healing after tooth extraction and was more effective in controlling the inflammatory process during the trial period.	No side effect
Mostafa et al. 2022	Q2	culture cell	Experimental, RCT	Group I: 17% edta, group II: 1% propolis nanoparticles, group III: 2% propolis nanoparticles, group IV: 1% chitosan nanoparticles, group V: 2% chitosan nanoparticles, group VI: cell culture	1% dan 2% nanopartikel	*Friedman's test* and mtt assay	Cell culture with 2% propolis nanoparticles, comparable to 1%, appears to increase tissue healing ability.	-

Table 3. General summary of Effectiveness propolis and review articles.

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