# Role of Medicinal Herbs in Periodontal Therapy: A Systematic Review

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Aims and Objectives: The use of medicinal herbs to prevent gingival and periodontal diseases has become increasingly popular due to their antiinflammatory and antioxidant properties. This systematic review aims to provide the current literature to validate the traditional use of medicinal herbs in the management of gingival and periodontal diseases. Materials and Methods: An online literature search was conducted to identify research papers published from 2010 to 2022 in three major scientific databases, PubMed, Scopus, and Web of Science, in June 2022. Original research studies, case reports, and systematic reviews on medicinal plants' application in oral health care were selected to be included in this systematic review. Only high-quality articles identified in the quality assessment were included for evidence synthesis. Results: Initial keyword research yielded 726 free-text articles published between 2010 and 2022. Of these, 14 articles (8 research papers and 6 reviews) were included for evidence synthesis. The review's findings indicate that the antibacterial property of medicinal plants is due to their alkaline nature and prevents plaque and calculus formation by maintaining acid-alkali balance in saliva. Various parts of medicinal plants help maintain periodontal health. Glycyrrhiza glabra, Ficus religiosa, and Plantago *major* effectively inhibit primary plaque colonizers and periodontal pathogens. Medicago sativa, Aloe barbadensis Miller, and Trifolium pratense have excellent applications in treating periodontal diseases. Mangifera indica, Pongamia pinnata, the husk of Cocos nucifera, the root of G. glabra and Curcuma longa, leaves of Psidium guajava and Azadirachta indica, fruits of Citrus medica and Punica granatum, Ocimum Moringa oleifera extract, and pomegranate peel extract can serve as a promising alternative in managing chronic gingivitis. Conclusion: The anti-inflammatory, antioxidant, antibacterial, and astringent action of extracts obtained from various parts of medicinal plants make them effective in reducing gingival and periodontal diseases. Herbal medicine may be a viable alternative to contemporary pharmaceuticals as an adjuvant to scaling and root planning procedures.

**KEYWORDS:** *Herbs, medicinal plants, periodontal disease, phytomedicines, putative periodontal pathogens* 

# INTRODUCTION

The periodontal pathogens associated with gingival and periodontal diseases are predominantly Gramnegative anaerobic microorganisms which include Aggregatibacter actinomycetemcomitans, Porhyromonas

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gingivalis, Prevotella intermedia, Bacteroids forsythias, Fusobacterium nucleatum, Campylobacter rectus, Streptococcus intermedius, and Treponema species, etc.<sup>[1,2]</sup>

Gingival and periodontal disease develops when the bacterial balance shifts from Gram-positive aerobic to Gram-negative anaerobic microorganisms. Epidemiologic studies state that nonsurgical therapy and antimicrobial therapy as adjunct help in the reduction of total bacterial load.<sup>[3]</sup>

Patients in developing nations now prefer less intrusive, more effective, safe, practical, and affordable periodontal therapy that includes professional and patient-administered mechanical therapy and the utilization of complementary therapies, such as phytomedicine.<sup>[4,5]</sup>

The use of herbal medicines and products to treat gingivitis, periodontitis, and dental caries has recently gained popularity among dental patients and professionals. Herbal medicines include herbs, herbal materials, preparations, and products containing parts of plants or other plant materials as active ingredients.<sup>[6]</sup>

The principal phytochemical components are tannins, alkaloids, saponins, cardiac glycosides, steroids, terpenoids, flavonoids, phlobatannins, anthraquinones, and reducing sugars found in therapeutic plants. Phytochemicals are bioactive plant compounds with antimicrobial, antibacterial, and wound-healing properties to prevent inflammatory periodontal diseases.<sup>[6,7]</sup>

This review summarizes the most recent literature supporting the traditional use of medicinal herbs to prevent and treat periodontal and gingival disorders.

# **HISTORICAL ASPECTS**

Since ancient times, many herbal plants have been used to treat and prevent certain diseases due to their curative properties. Plant-origin drugs have been extracted from barks, seeds, fruits, stems, roots, and other medicinal plants.<sup>[5,6]</sup>

Phytotherapy or phytomedicine has been a part of medical traditions for treating certain diseases since 200 B.C. the first written evidence of medicinal plant use was found in a clay board in the Sumerian culture. In India, medicinal plants have been used to treat patients' illnesses since 800 A.C. in Ayurveda, a holistic system of medicine that evolved some 5000 years ago.<sup>[6]</sup>

Hippocrates, the father of Greek medicine, depended on "natural" medicines to treat any kind of illness.<sup>[7]</sup>

There are approximately 500,000 plant species worldwide, of which only more than 2,000 plants were thought to have curative properties from ancient times. With the help of advanced technology and the development of new ideas, there is great potential to discover newer phytochemicals of medical and dental use from the wide variety of plant species available worldwide.<sup>[8,9]</sup>

## METHODOLOGY

This review followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). The following research questions are based on the aim of this systematic review.

RQ1. What are the commonly used medicinal herbs in dentistry?

RQ2. To provide the current literature on the traditional use of medicinal herbs in the management of periodontal diseases.

Original research studies, case reports, and systematic reviews related to the use of medicinal herbs in the management of gingival and periodontal diseases were included. Research papers written in a language other than English were excluded. Also, editorial letters and opinions were not included.

The terms like medicinal plants, plant medicine, dental herbs, medical herbs, and phytomedicine were used in the initial search to identify research papers in databases such as PubMed, Scopus, and Web of Science. The terms used in the PubMed, Scopus, and Web of Science database were as follows:

"Herbs" [All Fields] OR ("medicinal plants in health profession" [All Fields] OR ("medicinal plants" [MeSH Terms] OR "dental herbs" [All Fields] AND ("dental herbs in health profession" [All Fields] OR " plant medicine" [MeSH Terms] OR "plants in dentistry" [MeSH Terms] AND ("herbs in dentistry "[MeSH Terms] OR " medicinal plants in dentistry "[All Fields] OR " phytomedicine "[All Fields] OR " phytomedicine "[MeSH Terms] OR " phytomedici "[All Fields]. AND (("2010/01/01" [PDAT]: "2020/12/31" [PDAT]) AND "humans" [MeSH terms] AND English[lang]).

After meeting this systematic review's objectives, all the articles identified were reviewed and checked for their inclusion based on above-mentioned criteria. Original research studies, case reports, and systematic reviews related to the use of medicinal plants in oral health care were selected to include in this systematic review [Figure 1].

10



Figure 1: Demonstrates flow diagram of the study selection process as indicated by the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis)

### **C**RITICAL APPRAISAL AND EVIDENCE SYNTHESIS

The risk of bias was assessed with the Cochrane collaboration tool. The percentage of each judgment was based on the different domains used for this systematic review. Approximately 75% of papers were at low risk, 16.6% unclear, and 8% were at high risk of bias [Figure 2]. We assessed each paper by reading the abstract, methodology, objectives, and results. Only the eligible publications of high quality were included in this present systematic review.

### RESULTS

An initial search with the keywords yielded a total of 726 free-text articles published from the year 2010 to 2022. In the initial search, 380 published articles were from PubMed, 220 were from Scopus, and 126 were from Web of Science databases.



**Figure 2:** Describes the assessment of the risk of bias with the Cochrane collaboration tool

Of those, 189 articles belonged to periodontal research and were screened for relevance. Once reviewed based on the objectives of the systematic review, only 74

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articles remained eligible after initial screening. Out of the eligible articles, 28 were in PubMed, 24 were from Scopus, and 22 were from Web of Science, in which papers related to medicinal plants' use in preventing gingival and periodontal diseases were included. The original research studies (48), case reports (12), and systematic reviews (14) were identified. A total of 14 articles (8 research papers and 6 reviews) were included and categorized based on the research objective and significance.

The review's findings indicate that herbal medicine may be a viable alternative to contemporary pharmaceuticals as an adjuvant to scaling and root planning procedures. The antibacterial property of medicinal plants is due to their alkaline nature. It helps prevent plaque and calculus formation by balancing the acid–alkaline nature in saliva. Most periodontal pathogens are

12)

resistant to antibiotics but not to the antibacterial effect of herbal medicine. Most medicinal herbs are not allergic to gingival tissues. Stems and leaves of various medicinal plants are used as toothbrushes and mouthwashes and help dental patients practice oral hygiene at more accessible and low costs in developing countries. Plant extract formulation can prevent and treat gingival and periodontal diseases.

The results suggest that *Glycyrrhiza glabra*, *Ficus religiosa*, and *Plantago* major effectively inhibit primary plaque colonizers and periodontal pathogens. *Medicago sativa*, *Aloe barbadensis* Miller (Aloe Vera), and *Trifolium pratense* (Red Clover) have excellent applications in treating various periodontal diseases and conditions. *Moringa oleifera* extract and pomegranate peel extract can be promising alternatives for managing chronic gingivitis.

Table 1: Commonly used medicinal plants for gingival and periodontal diseases				
Family and taxon	Part used	Periodontal use		
[Acoraceae] Acorus calamus	Rhizome	Paste of rhizome is applied on gums to relieve pain		
[Amaranthaceae] Achyranthes aspera	Bark	Treatment of gum disorders		
[Acanthaceae] Justicia adhatoda	Twigs	Twigs are used as toothpicks and to treat pyorrhea		
[Amaryllidaceae] Allium sativum	Bulb	Paste of the bulb is applied to the gums to treat infection		
[Anacardiaceae] Anacardium occientale	Twigs and leaves	Used for routine cleaning of teeth		
[Cashews] Mangifera indica	Twigs, leaves	Used for regular cleaning of teeth		
[Ginger family Curcuma longa	Rhizome	To treat pyorrhea and gum infections		
[Leguminosae] Acacia Arabica	Tender leaves, bark	Decoction of tender leaves is used as a mouthwash and to		
		treat spongy gums. Burnt bark used as tooth powder		
Acacia catechu [Legumes]	Seeds	Reduces bacterial load		
[Legumes] Glycyrrhiza glabra	Root	Effectively reduces plaque formation by its antibacterial effect		
Pongamia pinnata [Legumes]	Leaves	Used for routine cleaning of teeth		
[Mahogany] Azadirachta indica	Bark	To treat pyorrhea and gum infections		
[Mints] Vitex negundo	Leaves	Leaf decoction is used as a mouthwash		
[Mulberry family] Ficus bengalensis	Latex, twigs	To strengthen gums, slender twigs are used as a toothbrush		
[Myrtle family] Psidium guajava	Leaves	Used to treat swollen gums and oral ulcers		
[Palms] Areca catechu	Pericarp	Used for regular cleaning of teeth		
[Palms] Cocos nucifera	Husk	For regular cleaning of teeth		
[Phyllanthaceae] Emblic myrobalan	Fruit	General rebuilder of oral health		
[Piperaceae] Piper betle	Leaves	Used in the treatment of malodor		
[Piperaceae] Piper nigrum	Fruit	Treatment of oral infection		
[Punicaceae] Punica granatum	Fruit	Used to treat bleeding gums		
[Rose family] Crateagus oxycanthus	Fruit	Stabilizes collagen and strengthens the gingival tissues		
[Rutaceae] Citrus limonum Risso	Outer peel	For routine cleaning of teeth		
[Rutaceae] Citrus medica	Fruit	Used to treat bleeding gums		
[Sapindaceae] Sapindus mucorosai	Seed	Used in the treatment of gingival inflammation		
[Salvadoraceae] Salvadora persica	Stem	Used as a chewing stick for oral care		
[Sapotaceae] Mimusops elengi	Stem	To treat spongy gums and pyorrhea		
[Spurges] Jatropha curcas	Stem, leaves	Decoction of leaves used as a mouthwash and to cure bleed-		
		ing gums. The stem can be used as toothbrush		
[spurge family, Euphorbiaceae]	Twigs	Twigs can be used as toothbrush for routine cleaning		
Jatropha gossypifolia				
[Spurges] Ricinus communis	Root, Leaves	Roots are used as a toothbrush. Leaf juice is used as a mouth		
		wash		
[Walnut family] Juglens regi	Oils, fruit	Used to make tooth powder and to treat pyorrhea		

Table 2: Pharmacological actions of various medicinal plants used in periodontal therapy				
Generic name	Useful parts	Properties		
[Ginger family] Curcuma longa	Dried roots	Analgesic, anti-inflammatory		
[Heaths] Vaccinium macrocarpon	Fruits	Antioxidant		
[Legumes] Acacia arabica	Bark	Astringent		
[Legumes] Glycyrrhiza glabra	Root	Anti-inflammatory, antioxidant		
[Mahogany] Azadirachta indica	Leaves	Antioxidant, antibacterial, anti-inflammatory		
[Mints] Mentha piperita	Leaves	Analgesic, counterirritant		
[Mints] Ocimum sanctum	Leaves	Anti-inflammatory		
[Rose family] Rosa canina	Leaves, flower, hips	Astringent, antibacterial		
[Rose family] Rubus idaeus	Leaves	Anti-inflammatory, astringent		
[Salvadoraceae] Salvadora persica	Bark	Anti-inflammatory		

The most common medicinal herb and its part used in the treatment of gingival and periodontal diseases include the leaves and twigs of *Mangifera indica*, leaves of *Pongamia pinnata*, and husk of *Cocos nucifera* are used for regular cleaning of the teeth. The root of *G glabra* effectively reduces plaque formation through its antibacterial effect. The leaves of *Psidium guajava* and the fruits of *Citrus medica* and *Punica granatum* are used to treat gingivitis and oral ulcers. Dried roots of *Curcuma longa* and leaves of *Azadirachta indica* and *Ocimum sanctum* are most commonly used to treat gum infections because of their analgesic, anti-inflammatory, antibacterial, and antioxidant properties. A few of the commonly used medicinal plants for treating gingival and periodontal diseases are presented in Table 1.

### DISCUSSION

The key conclusions of this systematic review focus on the importance of various herbal medications in the treatment of gingival and periodontal disorders. Also, the most recent research supports the traditional use of medicinal herbs in the treatment of periodontal and gingival disorders.<sup>[10]</sup>

The anti-inflammatory, antioxidant, antibacterial, astringent, and other therapeutic qualities of medicinal plants make them effective in reducing gingival and periodontal diseases. The national toxicology program prepared herbal medicine according to a few rules. This aids in avoiding the undesirable side effects of the inappropriate use of herbal medicine. The rules followed are<sup>[5,6]</sup> determining the potential health risks of herbal drug contaminants, any negative effects when combined with conventional drugs, and stopping herbal drugs use 2–3 weeks before any dental surgical procedures or in case of any negative reaction.<sup>[11,12]</sup>

One of the main advantages of using medical herbs over chemotherapeutic medicines is that adverse reactions, like hypersensitivity and the development of bacterial resistance to standard drugs, are less likely. Chlorhexidine, a substance frequently applied topically as an antibacterial, has been reported to cause negative effects such as allergic contact dermatitis and anaphylaxis.<sup>[13,14]</sup>

The anti-inflammatory, antioxidant, antibacterial, astringent, and other therapeutic qualities of medicinal plants make them helpful in reducing gingival and periodontal disorders, which is one of the secondary outcome measures of utilizing medicinal herbs. A few of the pharmacological traits of some medicinal plants frequently used in periodontal research are presented in Table 2.<sup>[15,16]</sup>

A rich source of medicinal plants in India provides an opportunity to research the pharmacological properties of various parts of plants. Almost all medicinal plants, like leaves, seeds, fruits, bark, stems, and roots, have been used for research purposes.<sup>[17,18]</sup> Table 3 illustrates the conclusive research remarks published recently from 2010 to 2022.<sup>[7-19]</sup>

In a paper published in 2018, Sidhu *et al.* reviewed the effects of liquorice and its constituents on oral diseases such as dental caries, periodontitis, gingivitis, candidiasis, recurrent aphthous ulcer, and oral cancer, as well as its use as a root canal medicament. They also summarized the results of clinical trials that looked into the potential beneficial effects of liquorice and its constituents as a prevention and treatment modality in oral diseases.<sup>[18]</sup>

In a study published in 2020, Veloso *et al.* assessed the antibacterial and anti-halitosis effectiveness of medicinal plants against oral microorganisms. All of the medicinal plants studied demonstrated antibacterial capabilities and the capacity to lower the primary chemicals linked to oral halitosis.<sup>[19]</sup>

In 2017, Sahrakary *et al.* conducted a study in the rat periodontal model to see how administration of the MO extract affected gingival TNF- and IL1-levels. In a rat periodontal model, pre/post-treatment with

Table 3: Illustrate the conclusive research remarks which were published in the recent years from 2010 to 2022 <sup>[7-19]</sup>				
Reference Author Title of the study Conclusive Remarks				
7	Liu C, Cui Y, Pi F, Cheng Y, Guo Y, Qian H	Extraction, purification, structural characteristics, biological activities and pharmacological applications of acemannan, a polysaccharide from aloe vera: A review. Molecules 2019;24:1554	This review summarizes the extraction, purification, structural characteristics, biological activities and pharmacological applications of acemannan and provides information for the industrial production and possible applications in dentistry and wound healing	
8	Sinha DJ, Sinha AA	Natural medicaments in dentistry. Ayu 2014;35:113-8	This review focused on various natural drugs and products and their therapeutic applications when used as a phytomedicine in dentistry	
9	Kumar M, Prakash S, Radha, Kumari N, Pundir A, Punia S, Saurabh V, Choudhary P, Changan S, Dhumal S, Pradhan PC, Alajil O, Singh S, Sharma N, Ilakiya T, Singh S, Mekhemar M	Beneficial role of antioxidant secondary metabolites from medicinal plants in maintaining oral health. Antioxidants (Basel) 2021;10:1061	This literature review summarises secondary metabolites, more specifically Eos, from the 20 most commonly used medicinal plants and their applications in maintaining oral health	
10	Seal M, Rishi R, Satish G, Divya KT, Talukdar P, Maniyar R.	Herbal panacea: The need for today in dentistry. J Int Soc Prev Community Dent 2016;6:105-9	The search for alternative natural products continues. This review includes a few herbs which can be used in dentistry as alternatives to allopathic medicines	
11	Milutinovici RA, Chioran D, Buzatu R, Macasoi I, Razvan S, Chioibas R, Corlan IV, Tanase A, Horia C, Popovici RA, Dinu S, Dehelean C, Scurtu A, Pinzaru I, Soica C	Vegetal compounds as sources of prophylactic and therapeutic agents in dentistry. Plants. 2021;10:2148	This review focused on the most used plants in oral health care, especially on active phytocompounds, regarding chemical structure and mechanism of action	
12	Akkaoui S, Ennibi OK	Use of traditional plants in management of halitosis in a Moroccan population. J Intercult Ethnopharmacol. 2017;6(3):267-73	The data could be the basis for experimental and clinical studies to promote using natural agents in treating bad breath	
13	Abuzenada BM, Pullishery F, Elnawawy MSA, Alshehri SA, Alostath RMB, Bakhubira BM, Amerdash WF	Complementary and alternative medicines in oral health care: An integrative review. J Pharm Bioallied Sci. 2021;13(Suppl. 2):S892-7	Medicinal plants such as <i>Medicago sativa</i> , <i>Aloe barbadensis</i> Miller (Aloe Vera), and <i>Trifolium pratense</i> (Red Clover) have excellent applications in treating gum disorders, preventing tooth decay, and have demonstrated good antifungal activity in the oral cavity	
14	Ocheng F, Bwanga F, Almer Boström E, Joloba M, Borg-Karlson AK, Yucel-Lindberg T, Obua C, Gustafsson A	Essential oils from Ugandan medicinal plants: <i>In vitro</i> cytotoxicity and effects on IL-1β-induced proinflammatory mediators by human gingival fibroblasts. Evid Based Complement Alternat Med. 2016;2016:5357689	It may be suggested that essential oil from <i>O. gratissimum</i> , applied at subcytotoxicity concentrations, could reduce the participation of gingival fibroblasts in the gingival inflammation and tissue destruction associated with periodontitis	
15	Sharma H, Yunus GY, Mohapatra AK, Kulshrestha R, Agrawal R, Kalra M	Antimicrobial efficacy of three medicinal plants <i>Glycyrrhiza glabra</i> , <i>Ficus religiosa</i> , and <i>Plantago</i> major on inhibiting primary plaque colonizers and periodontal pathogens: An <i>in vitro</i> study. Indian J Dent Res. 2016;27:200-4	<i>G. glabra</i> and <i>F. religiosa</i> showed antibacterial activity against primary plaque colonizers and periodontal pathogens	

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	Table 3: Continued				
Reference	Author	Title of the study	Conclusive Remarks		
16	Ashu Agbor M, Naidoo S	Ethnomedicinal plants used by traditional healers to treat oral health problems in Cameroon. Evid Based Complement Alternat Med. 2015;2015:649832	This study provides comprehensive information on therapeutic methods employed by traditional healers to treat oral diseases		
17	Eltay EG, Gismalla BG, Mukhtar MM, Awadelkarim MOA	<i>Punica granatum</i> peel extract as adjunct irrigation to nonsurgical treatment of chronic gingivitis. Complement Ther Clin Pract. 2021;43:101383	Pomegranate peel extract can serve as a promising alternative in managing chronic gingivitis		
18	Sidhu P, Shankargouda S, Rath A, Hesarghatta Ramamurthy P, Fernandes B, Kumar Singh A	Therapeutic benefits of liquorice in dentistry. J Ayurveda Integr Med. 2020;11:82-8	The results of clinical trials that investigated the potential beneficial effects of liquorice and its constituents as a prevention and treatment modality in oral diseases were summarized		
19	Veloso DJ, Abrão F, Martins CHG, Bronzato JD, Gomes BPFA, Higino JS, Sampaio FC	Potential antibacterial and anti- halitosis activity of medicinal plants against oral bacteria. Arch Oral Biol 2020;110:104585	The extracts display antimicrobial activity against the tested microorganisms. The investigated plants can reduce the main substances related to halitosis of oral origin		
20	Sahrakary M, Nazemian V, Aghaloo M, Akbari A, Shadnoush M, Nasseri B, Zaringhalam J	Treatment by <i>Moringa oleifera</i> extract can reduce gingival inflammatory cytokines in the rat periodontal model. Physiol Pharmacol 2017;21:102-9	<i>Moringa oleifera</i> extracts directly affect pro- inflammatory cytokines inhibition and can alleviate inflammatory symptoms in a rat periodontal model		

MO extract can reduce inflammatory symptoms due to its direct action on inhibiting proinflammatory cytokines.<sup>[20]</sup>

Cruz Martínez *et al.* in a 2017 study found that the use of plants to treat oral problems or to add to the dental pharmacological arsenal should be based on experimental trials validating their suitability for dental treatments.<sup>[21]</sup>

Vo *et al.* in 2020 updated insights about the immunoinflammatory pathway regulated by oxidative stress in periodontal pathology. This work further presented the systemic knowledge of antioxidant phytochemicals, particularly the pharmacological activities, which can be utilized in the prevention and treatment of periodontal disease.<sup>[22]</sup>

Eid Abdelmagyd *et al.* in 2019 analyzed the literature published in the research related to herbal medicine as an adjunct in periodontal therapies. This review provided the current literature to validate the traditional use of medicinal plants in the management of periodontal diseases, which is in accordance with the results of our study.<sup>[23]</sup>

Cicalău *et al.* in 2021 reviewed on the therapeutic properties of these bioactive compounds, in the treatment of periodontitis and diabetes. The results showed that carvacrol and magnolol have anti-inflammatory, antioxidant, antimicrobial, antiosteoclastic, and antidiabetic properties that benefit both pathologies. The new treatment strategies followed in this study are in accordance with our study, which maximizes the potential benefits of these extracts in subjects suffering from periodontitis or diabetes.<sup>[24]</sup>

Mekhemar *et al.* in 2021 conducted a study to analyze the reported effects of *Salvadora persica* (SP) as a support to periodontal therapy to endorse regeneration and healing. In consort with clinical trials, *in vitro* investigations show the advantageous outcomes of SP adjunctive to periodontal treatment.<sup>[25,26]</sup> This review results are in accordance with our systematic review in which both the studies added current literature to validate the use of medicinal herbs in treating periodontal diseases.<sup>[27]</sup>

The present article reviews the various therapeutic effects of medicinal herbs on oral health, which will help elucidate the significance of treating periodontal diseases. The lack of evidence-based research on the use of herbal medicines and the sparse number of clinical trials to evaluate the efficacy and safety of conventional herbal treatments are the two limitations of the study.

### CONCLUSION

Plant extract formulation can prevent and treat gingival and periodontal diseases due to their analgesic, antiinflammatory, antibacterial, and antioxidant properties and may be a viable alternative to contemporary pharmaceuticals as an adjuvant to scaling and root planning procedures. More clinical trials are needed to prove that herbal medicine is a valid therapeutic strategy for periodontal treatments.

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### **CONFLICTS OF INTEREST**

There are no conflicts of interest.

### **AUTHORS CONTRIBUTIONS**

Not applicable.

**ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT** Not applicable.

### **PATIENT DECLARATION OF CONSENT**

Not applicable.

#### **DATA AVAILABILITY STATEMENT**

Not applicable.

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16)