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Review Article

Potential role of *Pistacia* species in management of oral and dental diseases: a scoping review

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Abstract

Objective: To review the research conducted on the effect of the pistachio family on oral and dental diseases.
Materials and Methods: In this study, electronic databases including “PubMed”, “Scopus” and “ScienceDirect” were investigated to obtain evidence regarding the effect of *Pistacia* species on oral conditions. Systematic search was performed following PRISMA-ScR guidelines. A comprehensive literature search was conducted on English articles published from 2000 until July 2025 using relevant keywords related to the purpose of this review. Finally, 28 studies met our inclusion/exclusion criteria and were included in this review.
Results: Among *Pistacia* species, three species including *P. lentiscus*, *P. atlantica* and *P. vera* have been evaluated in different fields of oral healthcare such as microbial infections, dental caries, periodontitis and oral cancers. Chewing plant gum and mouthwashes were two main forms utilized in the clinical trials. These plants contain phytochemicals like monoterpenes and phenolics with antibacterial, anti-inflammatory, and antioxidant properties, so they can improve oral and dental conditions.
Conclusion: *Pistacia* species have the potential to be used for oral and dental complications, especially periodontal diseases. However, further studies are needed to identify the responsible phytochemicals and their mechanism of action. Also, clinical trials with a larger number of samples and using a positive control group are suggested.

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Introduction

The oral health plays an important role in overall health of the body, as it affects the quality of life and essential functions like eating, breathing and speaking, as well as psychosocial aspects like self-confidence, and communication abilities (WHO Global strategy 2024).

Dental and oral diseases impose a heavy financial burden on people from an economic standpoint. (Hashim et al.2025). In addition, there is considerable relationship between oral health and cardiovascular diseases, diabetes, osteoporosis, rheumatism and pregnancy complications (El Chaar 2025).

While efforts have been made to improve oral health, oro-dental diseases remain a major global health problem. The worldwide prevalence of these diseases is around 45%, which is much higher than that of any other non-communicable disease (WHO Global strategy 2024). Adding dentifrices and mouthwashes to mechanical methods such as brushing and flossing is recommended to maintain oral health. Active ingredients like chlorhexidine, fluoride and essential oils, may be used in mouth rinses (McGrath et al. 2023). Although oral therapeutics show positive efficacy in prevention and treatment of oral diseases, there is serious concern about their adverse effects. Chlorhexidine (CHX), as one of the widely used oral antimicrobial agents, leads to an increase in the resistance of oral pathogens, including *Streptococcus mutans* (Brookes et al. 2020; Guan et al. 2020). Other CHX complications are burning sensation, enamel destruction, and oral ulcers (Ashrafi et al. 2019)

Besides conventional medications, health researchers always try to improve treatment by considering minimal side effects, maximum efficiency, low cost, availability and acceptability (Karimi et al. 2024).

Natural products have recently received a lot of attention, so a number of scientific studies have shown that herbs, natural products and phytochemicals are effective in a variety of oral health care applications (Chatzopoulos et al. 2022; Ege and Ege 2021; Morais et al. 2021; Niculescu and Grumezescu 2021; Pytko-Polończyk et al. 2021; Tafazoli Moghadam et al. 2020)

Pistacia plants have been used for oral and dental disorders by different communities since ancient times as natural substances (Bozorgi et al. 2013; Moeini et al. 2019; Rauf et al. 2017). Avicenna, one of the main Persian physicians, has mentioned the properties of *Pistacia* species in teeth and gum strengthening and mouth freshening (Avicenna AAH 2005) . The use of these species in different oral conditions has also been reported in ethnopharmacological studies from Turkey, Morocco, Italy, and Spain (Ahmed 2017; Ahmed et al. 2021; Milia et al. 2021). A recent review study also highlighted the positive effects of *Pistacia lentiscus* (Mastic) gum in the prevention and treatment of oral diseases (Alwadi et al. 2023).

Researchers have found that *Pistacia* species have a wide range of biological activities, including antioxidants, anti-inflammatory, antimicrobial, antiviral, antifungal, antipyretic, analgesic, and immunomodulatory properties (Adibifard et al. 2024; Bozorgi et al. 2024).

While there are many studies regarding the effects of *Pistacia* species on oral conditions, there has been a lack of a comprehensive review of their effects. Therefore, in this study, *in vivo* and *in vitro* studies as well as clinical trials were reviewed to highlight research gaps and provide complete background for future studies.

Materials and Methods

Search strategy

PRISMA-ScR was used to establish the search strategy of the present study. Electronic databases including “PubMed”, “Scopus” and “Science Direct” were searched to obtain *in vitro, in vivo* or clinical studies related to the purpose of this review. The following keywords were used: “*Pistacia atlantica*”, “*Pistacia vera*”, “*Pistacia lentiscus*”, “*Pistacia khinjuk*”, “*Pistacia integerrima*”, “*Pistacia chinensis*”, “*Pistacia terebinthus*”, “mastic”, “pistachio” or “Pistaca” in title/abstract and “oral disease”, “mouth disease” or “dental disease” in the whole text. English articles (research and review) were collected from 2000 until July 2025 as primary search results. References of the related reviews and final included articles were also checked for additional relevant studies. Clarivate Endnote 21 was used as a reference management software to remove duplicate articles. The full-text of retrieved articles were investigated and final included articles were selected to be summarized in a tabular form based on PRISMA flow diagrams (Tricco et al. 2018).

Study selection and quality assessment

Study selection was conducted by two investigators independently who screened titles, abstracts, and full texts according to these eligibility criteria:

Studies were included if they (i) reported *in vitro*, (ii) *in vivo* or (iii) clinical trial, (iv) were published as full-text, and (v) were written in English. Studies were excluded if (i) they were not specific to oral and dental disorders, (ii) plant material was not related to *Pistacia* species, (iii) plant material was a herbal mixture, or (iv) they were review articles. For quality assessment of *in vitro* studies, a modified version of the quality assessment tool for *in vitro* Studies (QUIN) was applied (Sheth et al. 2024)

Results

Search

The flow diagram of the study selection strategy is presented in Figure 1.

The initial searches as well as the additional records identified 749 papers. After removing duplicates, reviews and unrelated articles based on their title/abstract, 81 study remained. The selected articles were examined in full text to determine their eligibility. Reasons for exclusion were: no access to the full-text, being mixed with other herbs, not being specific to oral diseases and unrelated to *Pistacia* species. Finally, 28 remaining studies were included in this review.

In vitro studies

Several laboratory experiments have demonstrated significant antimicrobial activity of *Pistacia* species against various oral pathogens as shown in Table 1.

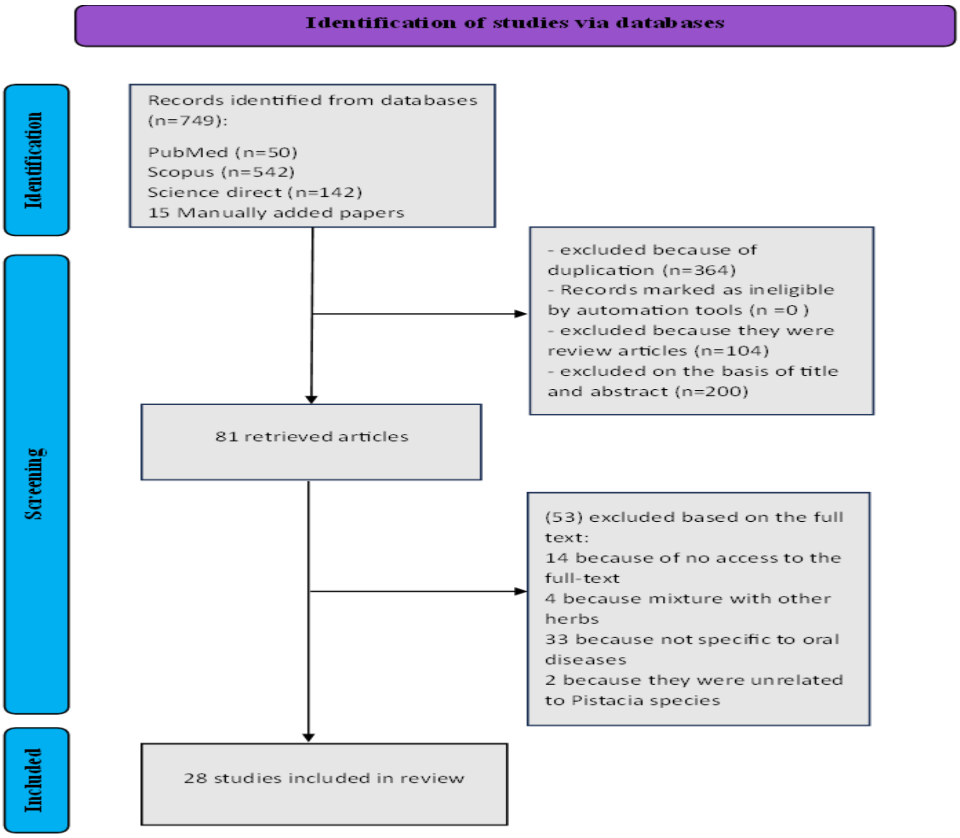

Figure 1. Flowchart of the selection process

Table 1. *In vitro* studies on the effect of *Pistacia* species on oral and dental disorders

***Pistacia* species**	**Plant part**	**Extract/ type of preparation/dosage**	**Tested oral microorganism**	**Study design**	**Outcome**	**Ref.**
	Gum	Chloroform, acetone, ethanol, petrolium ether extracts (20 and 50 mg/ml)	*S. mutans*	-Antibacterial effect disc (diffusion method) - Cytotoxicity on HEp-2 cells	Acetone extract (50 mg/ml) was the most effective (inhibition zone: 27.0 ±1.0 mm) - Concentrations up to 75 mg/ml showed no cytotoxic effect.	Aksoy et al., 2006
	Leaf	95% EtOH	*P. gingivalis*	- Growth inhibition assays	MIC:128– 256 (µg/ ml)	Carrol et al., 2020.
	Leaf	Aqueous extract			MIC: 64 (µg/ ml),	
	Woody part	95% EtOH			MIC: 32 (µg/ ml),	
	Fruit	95% EtOH			MIC: 8 (µg/ ml)	
	Gum	Ethanolic extract (0.5, 1, 2, 4% w/v)	*S. mutans, P. gingivalis, C. albicans*	Antimicrobial activities (agar diffusion test)	Dose-dependent antibacterial effect on all pathogens especially *P. gingivalis*	Sterer et al., 2008
	Gum	Methanolic extract (0.5%, 1%, 2%, 4%)	*P. gingivalis*	Antimicrobial activity (agar diffusion test)	- Inhibition zones:10.5-13.7 mm, without hemolysis. -Inhibition zone for chlorhexidine (0.2%): 33.5 with 17 mm hemolytic zone.	Sterer, 2006
	Gum	Ethyl acetate- methanol extract (1:3)	*S. mutans, S. sobrinus, S. oralis, E. faecalis, S. aureus, E. coli, P. gingivalis, P. intermedia, F. nucleatum, P. micra*	Determination of MIC MBC	MICs: 0.02 mg/ ml (P. gingivalis) to 10 mg/ ml; MBCs: 0.07 mg/ ml (P. gingivalis, P. micra) and 10.00 mg /ml (*S. mutans*, *S. sobrinus*, *E. faecalis*, *C. albicans*, and *E. coli*).	Karygianni et al., 2014
P. lentiscus	Gum	Ethanolic extract (concentrations of 1, 2, 3 % dissolved in 20, 25, 33, 38 % ethanol)	*P. gingivalis A. actinomycetemcomitans, P. intermedia, F. nucleatum, P. nigrescens, S. mutans, S. oralis*	-Antibacterial assay (Agar disc diffusion) - Cytotoxicity (XTT assay)	-Significant antibacterial effects toward all strains except *S. mutans;* Inhibition zones: 12 to 25 mm, the greatest inhibition zones by *P. gingivalis*. - Mastic extract was not harmful for the tested cell lines	Koychev et al., 2017
	Gum	Aqueous extract (5g / 50 ml)	*S. mutans*, *lactobacillus*, *A. viscosus*	Zone of inhibition (well diffusion method)	Significant antimicrobial properties.	Mahalakshmi et al., 2019
	Leaf	Essential Oil (EO) (1.0, 10, 25, 50, 75, and 100 µg/ml)	*S. gordonii, A. naeslundii, F. nucleatum, P. gingivalis, T. forsythia, C. albicans C. glabrata*	- MIC (microbroth dilution technique). -The anti-inflammatory activity: cyclooxygenase (COX-1/2) and lipoxygenase (LOX) inhibition - - GF (gingival fibroblasts) viability by the MTT assay. - The cytotoxicity toward four lines of oral cells (PDLF, GF, GK and DOK). (WST-1 assay)	-MIC (µg/mL): *P. gingivalis* (3.13), *F. nucleatumand* (6.25), *S. gordonii* (12.5). *C. glabrata* strains (6.25), *C. albicans* (12.5) -COX-1/2 and LOX inhibition: 80% and 20% with 100µg/mL of the oil, r. - - Significant increase in GF viability with 10, 25, 50 and 75 µg/mL of EO - No toxicity up to 100 µg/mL of the oil	Milia et al., 2020
	Gum	Hydroalcoholic extract (10-100%)	*S. mutans*	-Antibacterial activity (disc diffusion method) -The MIC (liquid serial dilution culture method)	- MIC range: 0.05-8.54 mg/mL bactericidal and bacteriostatic activity. The highest concentration has highest inhibiton - Reduction of total viable biofilms. -Inhibition of adherence to polystyrene surface	Hosseini et al., 2013
	Gum	10% alcoholic extract	-	- *In vitro* effect on remineralization of dentin layer was compared with sodium fluoride (NaF)	- After 14 days, the sealing of dentinal tubules in extract group was greater than NaF group	Valian et al., 2023

Table 1. Continued

	Gum	5~100 µg/ml	-	*In vitro* tests on oral squamous cell carcinoma cell line, YD-10B	Increase caspase-3 activity specially in low doses.	Li et al., 2011
	Gum	EO	*P. gingivalis*	MIC and MBC (serial dilution method)	MIC: 12.5 µl/ml equivalent to the MBC	Azeez and Gaphor, 2019
	Gum	Extraction with ethanol (70%) and DMSO, then paste was prepared by adding Tween 80 at 100 Cº,	*E. fecalis*	MIC, and MBC (disk diffusion, serial dilution method) - 45 extracted human teeth were examined in terms of CFU.	Dose-dependent zone inhibition; MIC: 0.5 µg/mL, MBC: 5µg/ml - CFU reduction: control (90×10-5 ±0.000), resin (6.667×10-5), CHX (10.87×10-5).	Barzinji and Dzaye, 2021
P. atlantica	Leaf	Aqueous extract (5,10,20,40,80, and 100%)	*S. mutans, S. mitis, S. salivarius*	- Disc diffusion and embedding sink diffusion methods, MIC and MBC Determination	- Disc diffusion technique: Significant inhibition on *S. mutans* and *S. mitis* (inhibition zones of 25 and 19 mm) at concentration of 100mg/ml -Embedding sink diffusion method: inhibition zones of 22 and 13 mm, respectively. -MIC and MBC for *S. mutans*: 60, 90 µg/ml and for *S. mitis*: 75, 115 µg/ml ($p<0.01$ significance), no significant effect on *S. salivarius*.	Roozegar et al., 2016
	Gum	EO, methanolic extract (ME) (60, 70, 80,90, and 100 %)	*S. mutans* and 3 strains isolated from caries	-Microdilution method -Anti-adherence properties (microplate adherence tests).	- Moderate anti-bacterial properties, growth reduction up to 47.1% (EO) and 39.1% (ME). -In all tested concentrations, EO showed a significantly stronger anti-adherence activity than ME.	Tahmourespour et al., 2022
	Leaf and Gum	Aqueous extract	*S. mutans*	-Growth inhibition zone (well-plate technique) -MIC (turbidity technique)	-No growth inhibition zones MICs (mg/ml): leaf extract and gum: 1.8 and 1.	Mokhtari et al., 2021
	Gum	Aqueous extract	*S. mutans*	Biofilm formation on the titanium dental implant discs	Significant antibacterial effect, comparable with CHX.	Salaie, 2023
P. vera	Fruits hull	Aqueous (2,6,10%), ethanolic (Eth), chloroformic extracts	*S. mutans, S. salivarious, S. sobrinus, S. sanguis*	-Antimicrobial activities (agar well diffusion method), MIC (liquid serial dilution culture method). -Determination of bactericidal activity -Salivary bacteria acid production (in vitro glycolytic assay) -Sucrose-dependent adherence of Strep. Sorbinus	-EtOH extract: the greatest inhibitory effect. The MIC values (mg/mL): Eth (1.25-2), chloroformic (3.25-3.75), aqueous (50-75) extracts - EtOH: bactericidal, chloroformic and aqueous extracts: bacteriostatic. -EtOH (6,10%): inhibition of acid-production of *S. mutans* - EtOH (10%): 75% adherence inhibition	Yari Kamrani et al., 2007
	Oleoresin	EO, neutral and acidic fractions (32,64,128,254 µg/ml), α-pinene and β-pinene	*S. anginosus, S. constellatus, S. intermedius, S. mutans, S. oralis, S. salivarius, S. sanguinis, S. vestibularis*	MIC and MBC, biofilm production, hemolytic activity inhibition	- MBCs(µg/mL): Oleoresin: ≥1024; Neutral and acidic fraction, α-pinene and β-pinene: 128 to 2048; EO: 256 to 2048 (bactericidal effect) - Significant biofilm reduction: *S. mutans* (up to 49.4%) and *S. sanguinis* (up to 71.2%). - Oleoresin showed Significant anti-hemolytic activity against *S. mutans* compared with other samples	Magi et al., 2018
	Seed	Hydroalcoholic extract (5%, 10%, and 20%)	*S. mutans, A. viscosus,* and *E. feacalis*	Agar diffusion method	Dose-dependent antibacterial activity	Salari Sedigh et al., 2021

***Pistacia lentiscus* (Mastic)**

The anti-cariogenic activity of *P. lentiscus* gum was assessed using the standard *Streptococcus mutans*. The gum was dissolved in chloroform, acetone, ethanol, and petroleum ether at two concentrations (20 and 50 mg/ml) and showed good dose-dependent activity compared with vancomycin. Most inhibitory effects were observed with the acetone extract of the gum (50 mg/ ml) (Aksoy et al. 2006).

An increase in the concentration of *P. lentiscus* gum hydroalcoholic extract decreased the minimum inhibitory concentration (MIC) (8.54 -0.05 mg/ml) and total viable *S. mutans* biofilms. The gum hydroalcoholic showed both bactericidal and bacteriostatic effect against this microorganism. Inhibiting plaque formation on teeth by inhibiting adherence to the surface was shown by the resin extract (Hosseini et al. 2013).

Testing *P. lentiscus* (gum) extract against oral bacterial strains causing dental caries revealed its antimicrobial activity against *Lactobacillus* and *Actinomycosis viscosus* strains, as well as *S. mutans* strains (Mahalakshmi et al. 2019).

The study of Koychev et al. found that mastic solutions had the least effect on *S. mutans* growth. However, in comparison to H2O2, mastic solutions demonstrated statistically significant antibacterial effects against other oral and periodontal pathogens namely *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Fusobacterium nucleatum, and Streptococcus oralis* but were less effective than chlorhexidine (CHX). *P. gingivalis* was mostly inhibited by mastic extracts (Koychev et al. 2017).

The bacterial growth inhibition effects of 109 extracts from 21 plant species on *Porphyromonas gingivalis* were evaluated. Among these, *P. lentiscus* fruits' ethanol extract had the lowest MIC (MIC: 8 µg/ml, IC50: 2 µg/ml). In addition, the MIC value for its woody part extract was 32 µg/ ml, for leaf extract was 64 µg/ ml and for leaf EtOH extract was 128– 256 µg/ ml (Carrol et al. 2020).

For evaluating the potential effect of mastic on oral malodor, mastic gum ethanolic extract activities against three known oral pathogens (*S. mutans, P. gingivalis* and *C. albicans*) were examined at varying concentrations (0.5, 1, 2, and 4% w/v) in an *in vitro* study. As results, a dose-dependent antibacterial effect was observed on all pathogens especially *P. gingivalis* (Sterer et al. 2008). Also, the methanolic extract of mastic gum (4% w/v) exhibited 40% of the antimicrobial effect of CHX against *P. gingivalis* without causing hemolysis (Sterer 2006).

Milia et al. conducted a study on the antibacterial, anti-inflammatory, antioxidant, and toxicity effects of *P. lentiscus* leaves essential oil (PLL-EO). PLL-EO exhibits a wide spectrum activity against reference and clinical strains of periodontal bacteria and *Candida* species including *P. gingivalis, Tannerella forsythia, Actinomyces naeslundii, F. nucleatum, Streptococcus gordonii, andida albicans and Nakaseomyces glabratus (Candida glabrata)*. 100µg/ml of the essential oil expressed anti-inflammatory effect by inhibiting Cyclooxygenase (COX)-1/2 and Lipoxygenase (LOX) enzymes about 80% and 20%, respectively. Moreover, it had no cytotoxicity against oral cells (Milia eta l. 2020).

The antimicrobial effect of total mastic extract was investigated against several Gram-positive and -negative bacterial species, including *S. mutans, Streptococcus sobrinus, S. oralis, Enterococcus faecalis, Staphylococcus aureus, and Escherichia coli* , *Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, and Parvimonas micra* . Additionally, the effect was tested against *C. albicans*. Although the MIC and minimum bactericidal concentration (MBC) values presented mastic effectiveness against all of them, Gram-negative oral microorganisms which are resistant to treatment showed higher sensitivity (Karygianni et al. 2014).

Effect of *P. lentiscus* extract on remineralization of dentin layer was compared with sodium fluoride and negative control. The mean microhardness of *P. lentiscus* group was not significant. However, sealing of dentinal tubules was greater in this group (Valian et al. 2023).

P. lentiscus or Chios mastic gum (CMG) extract showed *in vitro* anti-tumor effect on oral carcinoma. DNA fragmentation and western blot analysis demonstrated that the growth inhibitory effect of CMG extract could occur through apoptosis and caspase-3 activation. While, both CMG and Taxol inhibited the growth of YD-10B cells in a time- and dose-dependent manner, CMG extract showed a better effect at low concentrations (Li et al. 2011).

Pistacia atlantica

P. atlantica resin essential oil and methanolic extract had moderate growth reduction activity against *S. mutans* ATCC35668 and three isolated caries strains compared with CHX., In all tested concentrations the antibacterial and anti-adherence effects of the essential oil were significantly higher than those of the methanolic extract (Tahmourespour et al. 2022).

Roozegar et al. reported that *P. atlantica* leaf aqueous extract had a strong effect on *S. mitis* and *S. mutans* as evidenced by the MICs and MBCs. However, no significant effect was observed on *S. salivarius* (Roozegar et al. 2016).

Tar-like extracts of *P. atlantica* leaves and gum from the trunk of the tree failed to show strong antibacterial effects on *S. mutans*. The well-plate technique did not detect any growth inhibition zones surrounding these materials in comparison with CHX. Based on the MIC values, *P. atlantica* extracts were less effective than CHX (Mokhtari et al. 2021).

Barzinji et al. studied the antibacterial properties of *P. atlantica* gum against *E. fecalis* which appears to be the main cause of root canal failure. MIC and MBC results showed that the resin was bacteriostatic and increased zone inhibition diameter dose-dependently. In addition, similar to the effect of CHX 2% gel, the colony-forming unit (CFU) of microorganism was reduced in intracanal-resin-treated teeth (Barzinji and Dzaye 2021).

Essential oil from *P. atlantica* gum has been indicated to efficiently exert inhibitory and bactericidal activity against clinical strain of *P. gingivalis* isolated from periodontal pocket of patients (Azeez and Gaphor 2019).

Aqueous extract of *P. atlantica* gum showed significant effect against *S. mutans* biofilm formation on the titanium dental implant discs. Its effect was comparable with CHX (Salaie 2023).

Pistacia vera

The sensitivity of 4 species of *Streptococcus* (*Mutans*, *Salivarious*, *Sobrinus* and *Sanguis*) to the aqueous, chloroformic and ethanolic extracts of *P. vera* hull was evaluated in a microbial analysis. The result showed the stronger inhibitory effect of ethanolic extract compared to the other extracts as evidenced by the MIC values. Pistachio hull extract (10%) inhibited *S. sorbinus* adherence to glass surfaces about 75%, indicating that it prevents plaque formation on tooth surfaces (Yari Kamrani et al. 2007).

The oleoresin of *P. vera* shows moderate antimicrobial activity against various oral *Streptococci* species, whereas its acidic fraction demonstrates stronger effects. The essential oil and its main components (α-pinene and β-pinene) act bactericidally. In addition, the oleoresin and acidic fraction reduce key virulence factors like biofilm formation and hemolytic activity in certain strains, while the essential oil does not show significant anti-virulence effects (Magi et al. 2018).

There was a significant antibacterial effect of *P. vera* seed extract against *S. mutans*, *A. viscosus*, and *P. aeruginosa* in a concentration-dependent manner, but not for *E. faecalis* (Salari Sedigh et al. 2021).

In vivo studies and clinical trials

In addition to many *in vitro* studies on oral antimicrobial effects of *Pistacia* species, animal and human researches have been conducted (Tables 2 and 3).

Pistacia lentiscus (Mastic)

The total bacterial count of the aerobic oral bacteria (*Staphylococci*, *Neisseria* and oral *Streptococci*) after chewing *P. lentiscus* gum, was reduced to more than 5 grades (Al-Mofarji et al. 2013).

In 25 periodontally healthy volunteers, the inhibitory effect of 15-min chewing mastic gum against *S. mutans* in saliva was compared to a placebo gum. A significant reduction of the total number of bacterial colonies was found 15, 45, 75, 105 and 135 min after spitting the mastic gum (Aksoy et al. 2006).

In parallel, Aksoy et al. estimated the antibacterial effect of chewing mastic gum on *S. mutans, Lactobacilli*, and total viable cariogenic bacteria in patients with severe malocclusions, allocated for fixed orthodontic treatment. Results showed that in the first 15 min, there was a significant reduction in the *S. mutans* and total bacteria count but not in the amount of *Lactobacilli*. After 135 min, all of them decreased significantly (Aksoy et al. 2007).

Biria et al. in their single-blind, clinical trial assessed and compared the effects of three types of mastic gums (pure mastic gum, mastic gums enriched with xylitol or probiotics) on the number of *Mutans streptococci*, and *Lactobacilli* and the acidity of the saliva. *M. streptococci* amount decreased significantly in all three groups after three weeks. *Lactobacillus* count and pH of saliva increased in both pure and xylitol mastic gum groups, but decreased significantly in the probiotic gum group (Biria et al. 2014).

Pistacia atlantica

In a randomized, triple-blind controlled clinical trial, a mouthwash containing *P. atlantica* var. mutica essential oils was compared to a placebo and CHX. After 4 days, *P. atlantica* mouthwash and CHX showed a significant reduction in aerobic plaque bacteria compared to placebo (Arami et al. 2015).

As part of a single blind clinical study, salivary flow rate and pH were compared after chewing *P. atlantica* gum, parafilm, and sugar-free spearmint chewing gum to baseline. Sugar-free chewing gum and *P. atlantica* gum increased the flow rate significantly compared to parafilm. Contrary to *P. atlantica* gum, spearmint chewing gum did not significantly increase salivary pH compared to parafilm (Chamani et al. 2019).

A cross-over, single-blind, *in situ* study found that chewing *P. atlantica* gum or xylitol chewing gum resulted in a significantly reduced surface demineralization of caries-like lesions (Biria et al., 2009).

In a rat model of periodontitis, the gel form of *P. atlantica* gum essential oil, reduces the inflammatory cells, Interleukin-1 beta (IL-1β), the receptor activator of nuclear factor-κB ligand (RANKL) and osteoclast numbers. Accordingly, it has been shown to decrease alveolar bone resorption. Based on the histological assessment, the bone surface was regular and dense, the periodontal ligament space was uniformly thick with less organized proliferating periodontal ligament tissue attached to regular cementum surfaces, and the Periodontal Ligament (PDL) had significantly improved in thickness (Azeez et al., 2020).

Table 2. Clinical studies on the effect of *Pistacia* species on oral and dental disorders

Pistacia species	**Plant part**	**Study design**	**Outcome**	**Ref.**
	Gum	Chewing. crude gum (1.5 g), 45 minutes (n=10, 18-62 years). Total count of *Staphylococci*, *Neisseria* and *Streptococci* was evaluated.	Total bacterial count was reduced more than 5 grades (p<0.01)	Al-Mofarji et al., 2013
	Gum	Chewing the gum or placebo (paraffin) for 15 min (n=25 periodontally healthy volunteers) saliva sampling just before and after spitting the gum in different times.	Significantly fewer bacteria in gum group compared to placebo group (p < 0.001).	Aksoy et al., 2006
P. lentiscus	Gum	Chewing paraffin wax (placebo) in the first week, chewing mastic gum in the second week, in patients with fixed orthodontic appliances (n= 25).	Significant reductions of total bacteria, *S mutans*, and *lactobacilli* in the saliva of mastic group (p <0.001).	Aksoy et al., 2007
	Gum	Single blind, parallel-design clinical trial (n=42), 3 groups: mastic gum, xylitol mastic gum and probiotic mastic gum, 3 times/day, 5 min, for 3 weeks. *S. Mutans*, *Lactobacilli* and Salivary pH were assessed before and after the intervention.	Significant reduction in the level of *S. Mutans* in all three groups, Salivary pH and *Lactobacillus* count significantly decreased only in the probiotic gum group.	Biria et al., 2014
	Gum	Cross-over, single blinded, in situ study, investigating remineralization rate of caries-like lesions in enamel (n=50), 1.46 g *P. atlantica* gum or xylitol chewing gums: 5 times/day, 20 minutes after meals, 3 weeks.	Significant decrease in the demineralized surfaces, *P. atlantica*: 6.02%, xylitol gum: 8.86%.	Biria et al., 2009
P. atlantica	Gum	Single blind interventional clinical study (n=26), 3 groups: chewing parafilm, *P. atlantica* gum (1.5 g) or sugar-free spearmint chewing gum 70 times/minute and spitting the saliva every minute in a 15-minute interval.	*P. atlantica* gum and spearmint chewing gum significantly increased salivary flow rate compared to Parafilm (p = 0.001), *P. atlantica* increased pH more significantly than Parafilm (p = 0.031).	Chamani et al., 2019
	EO of the oleoresin	Prospective, randomized, triple-blind controlled clinical trial (n=28), Mouthwash containing 1.2% *P. atlantica* EO in a mixture of water and alcohol (80:20) in comparison with negative and positive control (CHX 0.2%), 10ml of mouthwash, for 30s, three times/ day, for 3 cycle of 4-day, treatment cycles separated by a 10-day wash-out. The day after mouthwash treatment, the patients' dental plaque bacteria were assessed.	- The mean count of aerobic plaque bacteria at baseline: 2.17×106, After 4 days: significant reduction in *P. atlantica* (7.25×104, p=0.006) and CHX (9.91×103, p=0.002) groups compared to placebo group (6.26×105). There was not significant difference in terms of anaerobic bacteria.	Arami et al., 2015
P. vera	EtOH extract of the hull	Rinsing mouth with 10 ml of extract (10%) or Placebo (PEG300: 20% v/v) for 1 min. Saliva sampling after 10 min, 1 and 3 hr post-rinsing for counting the colonies of *Mutans streptococci*.	Significant reduction at 10 min (75%), 1 hr (64%) and 3 hr (57%) compare to the vehicle.	Yari Kamrani et al., 2007

Table 3. Animal studies on the effect of *Pistacia* species on oral and dental disorders

***Pistacia* species**	**Plant part**	**Extract/ type of preparation/dosage**	**Study design**	**Outcome**	**Ref.**
P. atlantica	Gum	Gel prepared from Essential Oil	24 male Wistar rats with induced periodontitis, treated with *P. atlantica* gel (12.5 µl/ml) or CHX (0.2% gel) Inflammatory cells, osteoclast cells, and periodontal ligament (PDL) were histologically examined.	EO group: A significant reduction of inflammatory reaction and osteoclast numbers, improvement of PDL and low mean concentrations of NF-κB ligand and IL-1β	Azeez et al., 2020
	fruit hull	Essential oil	40 male hamsters with oral mucositis induced by 5-Fluorouracil received gels containing 5 and 10% oil.	Dose-dependent healing promotion in treated groups	Tanideh et al., 2017
P. vera	Nut	Hydroalcoholic extract	Rats with induced tongue wound (4 groups, n=12), were received the extract (50, 100, or 200 mg/kg, P.O.) or placebo (0.5 ml of 10% dimethyl sulfoxide) for 10 days. Number of arteries, the mean percentage of neutrophils, lymphocytes, and fibroblasts, was determined via histopathological examinations.	Dose of 50 mg/kg increased fibroblasts and decreased neutrophils significantly, No effect on the number of arteries.	Salari sedigh et al., 2022

Healing activity of the *P. atlantica* essential oil on oral mucositis (OM) in golden hamsters was evaluated. In this study, topical application of this oil led to increases in food consumption and weight gain and improved macroscopical (clinical) as well as microscopical (histopathological) OM scores. The blood samplings revealed roughly comparable pattern of pancytopenia which could be attributed to oil local effects (Tanideh et al., 2017).

Pistacia vera

In a study by Yari Kamrani et al, three young men were asked to rinse their mouths for 1 min with mouthrinse containing 10% ethanolic extract of *P. vera* hull in Polyethylene glycol (PEG) 300. Saliva samples were collected before and after 10 min, 1 and 3 hr post-rinsing, and *Mutans streptococci* colonies were counted. Mouthrinse significantly reduced salivary bacteria for three hours compared to PEG alone (Yari Kamrani et al., 2007).

In an animal study, rats with tongue ulcer were randomly received *P. vera* hydroalcoholic extract (PSE) or placebo. Eventually, the effect of PSE on oral wound healing was investigated by determining the mean percentage of neutrophils, lymphocytes, and fibroblasts, as well as the number of arteries. The histopathological examination demonstrated that administration of 50 mg/kg of PSE for 10 days significantly decreased and increased the number of neutrophils and fibroblasts respectively with no valuable effect on the number of arteries and lymphocytes (Salari Sedigh et al., 2022).

Discussion

Among *Pistacia* species, three species including *P. lentiscus, P. atlantica* and *P. vera* have been investigated for improvement of oral and dental disorders. Researchers have examined different parts of these plants, such as the leaves, fruits, and gum. However, the primary focus has been on the gum which has a long history of use in preventing and treating oral diseases.

Researches have primarily focused on the efficacy of *Pistacia* derivatives against a variety of oral health issues, including but not limited to dental caries, periodontal disease, halitosis, and *Candida* infections. There is an emphasis on studies that demonstrate the antimicrobial properties of these herbs against biofilm-associated diseases. These findings are critical in pointing towards the potential role of *Pistacia* species as a therapeutic alternative or adjuvants to conventional chemical agents for oral infections. Variety of oral diseases are directly related to the composition of the microbiota colonizing the oral cavity (Pytko-Polończyk et al., 2021). 29.4% of adults and 7.8% of children with deciduous teeth have untreated dental caries (Collaborators et al., 2020). Cariogenic pathogens like *S. mutans* and other *streptococci* species are highly resistant to common antimicrobial agents (Zhang et al., 2022).

Most of the included research has investigated the antimicrobial effects of *Pistacia* species against various microorganisms, including carious and periodontal pathogens. The oleoresin of *P. atlantica* and *P. lentiscus* contains a significant amount of essential oil. Monoterpenes are the major constituents of the essential oil obtained from different parts of *Pistacia* species, with α-pinene and myrcene, being the dominant monoterpenes (Memariani et al. 2017; Xanthis et al. 2021). According to phytochemical analysis, the amount of α-pinen in *P. atlantica* oleoresin is 70 % (Delazar et al., 2004). Some studies have reported the amount of α-pinen to be up to 90% (Memariani et al., 2017).

Different studies have found that α-pinene is effective against various types of bacteria. It has shown both bactericidal and bacteriostatic effects. α-pinene works by disrupting bacterial cell membranes integrity, interfering with their metabolism, and blocking their ability to efflux antibiotics (Figure 2) (Kovač et al., 2015). As bacteria become more resistant to traditional antibiotics, natural compounds like α-pinene are becoming increasingly important as additional treatments (Borgess et al., 2022). α-pinene possesses anti-inflammatory effect via the suppression of mitogen-activated protein kinases (MAPKs) and the nuclear factor-kappa B (NF-κB) pathway (Kim et al., 2015).

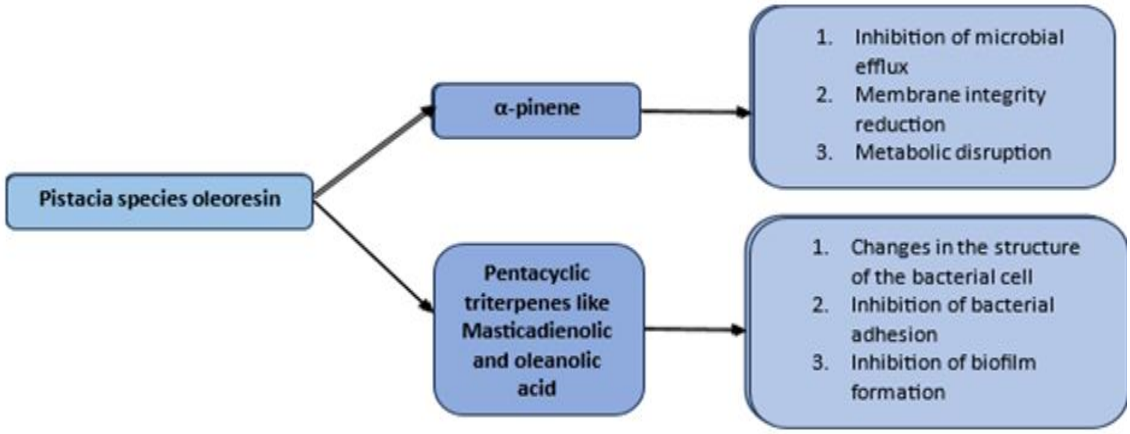

Figure 2. *Pistacia* species have considerable effect on periodontal pathogens: Main components and involved mechanisms

α-pinene was also investigated for its analgesic and anti-inflammatory effects on capsaicin-induced dental pulp pain in rats, exploring its interaction with GABAergic and opioid systems. Central administration of α-pinene significantly reduced capsaicin-induced nociception and decreased COX-2 expression in the subnucleolus caudalis, indicating anti-inflammatory properties (Rahbar et al., 2019).

Pistacia species gum also contains tetra- and pentacyclic triterpene compounds like masticadienolic acid, masticadienonic acid, oleanolic acid and ursonic acid (Bozorgi et al., 2013). These compounds exhibit a wide range of medicinal properties, including antioxidant, anti-inflammatory, and antibacterial activities. The antibacterial mechanism of pentacyclic triterpenes is primarily due to alterations in the structure and function of bacterial cells, as well as the inhibition of bacterial adhesion and biofilm formation (Sycz et al., 2022). Also, a study has shown anticancer effects of a pentacyclic triterpene compound via the mitochondrial pathway in bone-invasive oral squamous cell carcinoma (Adtani et al., 2021). More, another triterpene, oleanolic acid conjugated poly (D, l-lactide)-based micelles was effective in combination chemotherapy for oral cancer (Kumbham et al., 2020).

Phenolic compounds and flavonoids are also found in the leaves, fruits, and fruit skins of *Pistacia* species (Bozorgi et al., 2013). Research suggests that polyphenols may lower the risk of oral cancer by inhibiting microbial-related oral diseases (Esteban-Fernandez et al., 2017; Petty and Scully, 2009; Curutiu et al., 2020). These plants are rich in antioxidant compounds, which play a crucial role in preventing periodontitis and dental caries (Pytko-Polończyk et al., 2021). Additionally, *P. lentiscus* exhibited beneficial effect in oral carcinoma via apoptosis and caspase-3 activation (Li et al., 2011). α-pinene activates Natural killer (NK) cells and increases the release of perforins which induce cell apoptosis (Jo et al., 2021). Β-pinene has also been shown with anti-cancer activity against oral squamous cell carcinoma. It induced cell death in cancer cells through apoptosis (Machado et al., 2022).

In this study, eight clinical trials have been included, in which, chewing plant gum (*P. lentiscus* or *P. atlantica*) or using mouthwashes from gum essential oil has been evaluated. The clinical evaluation of the effects of the *Pistacia* genus herbs, particularly *P. lentiscus*, in the management of oral diseases appears to be a promising yet under-explored field. While there is evidence supporting the antimicrobial and anti-inflammatory properties of these herbs, clinical studies remain limited.

P. lentiscus has shown potential benefits in periodontal therapy, particularly in its ability to prevent gingival inflammation and possibly mitigate *Candida* infections in patients. The properties of these herbs not only provide an antimicrobial effect but also assist in reducing inflammation—a key factor in treating periodontal diseases.

Important limitations of these clinical trials are lack of positive control group, small sample sizes, lack of standardized formulations and absence of blinding in some trials. So, drawing conclusion about the clinical effect of these plants will be difficult due to methodological problems. Future research is necessary to establish clear protocols and efficacy data for the use of *Pistacia* species in oral health. This could encompass randomized controlled trials that assess the therapeutic effects and side effects of using *Pistacia* extracts in various oral diseases. Additionally, researchers should consider standardizing extraction processes and dosages to ensure consistent results across studies, providing a solid foundation for clinical application and acceptance.

Pistacia species contain phytochemicals such as monoterpenes, triterpenes, and phenolics. The compounds in *Pistacia* plants have antibacterial, anti-inflammatory, and antioxidant properties. Current literature indicates that although the *Pistacia* genus has a rich history in traditional medicine, the lack of extensive clinical trials specifically targeting oral diseases presents a significant gap in understanding its full potential. Previous studies primarily rely on *in-vitro* data and anecdotal evidence rather than robust clinical trials. There is a need for additional clinical and preclinical mechanistic studies to determine if these plants are safe and effective for oral conditions.

Conflicts of interest

There are no conflicts of interest.

Authors' Contributions

M.B. designed the research. M.Y. and Z.M. contributed to the data gathering and analysis the result. M.Y. wrote the manuscript with support from M.B. and Z.M. All authors discussed the results and contributed to the final manuscript.

Abbreviation

MBC: Minimum Bacterial Concentration. MIC: Minimum Inhibitory Concentration. EO: Essential Oil. COX-1/2 and: Cyclooxygenase (COX-1/2). LOX: lipoxygenase. MTT: Thiazolyl blue tetrazolium bromide. CHX: Chlorhexidine. GF: Gingival fibroblasts. CFU: colony-forming unit. PDLF: periodontal ligament fibroblasts. NF-κB: nuclear factor kappa-B. IL-1β: Interleukin-1β. GK: Gingival keratinocytes. DOK: Dysplastic oral keratinocytes. Essential oil: EO. Ethanolic: EtOH. IC50: Half-maximal inhibitory concentration. NR assay: Neutral Red Uptake assay. XTT assay: 2H-tetrazolium-5-carboxanilide assay. DMSO: Dimethyl sulfoxide

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