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Short Title: Plant-derived bioactive compounds of *Salvadora persica* and their role in regulating oral microbial communities: A review

REVIEW ARTICLE

Plant-derived bioactive compounds of *Salvadora persica* and their role in regulating oral microbial communities: A review

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Abstract

Background: Plant-derived natural products have gained increasing attention as sustainable sources of bioactive compounds with applications in human health. *Salvadora persica* L. (Meswak), a medicinal plant traditionally used for oral hygiene, contains a diverse range of phytochemicals including alkaloids, flavonoids, sulfur-containing compounds, essential oils, silica, and fluoride. These constituents exhibit antimicrobial, antifungal, antioxidant, and anti-inflammatory activities that may influence the composition and function of the oral microbiome. Understanding the biological properties of plant-derived compounds and their interactions with microbial communities is important for developing sustainable alternatives to synthetic antimicrobial agents.

Objective: This review evaluates the phytochemical composition and biological activities of *Salvadora persica* root, with particular emphasis on its effects against oral bacterial and fungal pathogens. The review also examines the role of plant-derived metabolites in modulating oral biofilms, microbial interactions, and oral health outcomes.

Main findings: Evidence indicates that phytochemicals present in Meswak root possess significant inhibitory activity against major oral pathogens, including *Streptococcus mutans*, *Porphyromonas gingivalis*, *Lactobacillus* spp., and *Candida albicans*. These bioactive compounds interfere with microbial adhesion, biofilm formation, and pathogen colonization while reducing inflammatory responses associated with periodontal diseases. Studies further suggest that Meswak-derived compounds contribute to plaque control, gingival health, and enamel protection. The antimicrobial efficacy of Meswak highlights the potential of medicinal plants as renewable sources of natural compounds for oral healthcare applications.

Conclusion: *Salvadora persica* represents a valuable plant resource with significant antimicrobial and antifungal properties that support oral health. Its phytochemical diversity and biological activities demonstrate the potential of plant-derived products as sustainable alternatives or adjuncts to conventional oral care strategies. Further investigations into the mechanisms of action, bioactive constituents, and plant–microbe interactions will enhance the development of phytotherapeutic approaches and contribute to broader applications of medicinal plants in health and biotechnology.

Keywords: Oral microbiome, Dental biofilms, Oral dysbiosis, Periodontal pathogens, *Candida albicans*, Oral microbiology

Introduction

Plants are a rich source of biologically active compounds that play important roles in human health, agriculture, and biotechnology. Medicinal plants, in particular, have attracted increasing scientific interest because they produce diverse secondary metabolites with antimicrobial, antioxidant, anti-inflammatory, and therapeutic properties. Understanding the biological activities of plant-derived compounds and their interactions with microbial communities is essential for developing sustainable and natural alternatives to synthetic chemicals used in healthcare. Among medicinal plants, *Salvadora persica* L., commonly known as Meswak or Miswak, has been extensively utilized in traditional oral hygiene practices across Asia, Africa, and the Middle East for centuries.

Salvadora persica belongs to the family Salvadoraceae and is a small evergreen tree or shrub adapted to arid and semi-arid environments. The plant is characterized by its extensive root system and remarkable tolerance to drought and saline conditions, making it an important species in sustainable ecosystems. The roots and stems of *S. persica* contain numerous bioactive phytochemicals, including alkaloids, flavonoids, tannins, saponins, sulfur-containing compounds, essential oils, silica, and fluoride. These compounds contribute to the plant's antimicrobial and anti-inflammatory activities and have been associated with its traditional use in maintaining oral health.

The oral cavity harbors a complex microbial ecosystem consisting of bacteria, fungi, viruses, and other microorganisms that interact dynamically with the host. Under healthy conditions, these microbial communities contribute to oral homeostasis; however, disturbances in microbial composition can lead to dysbiosis and the development of oral diseases. Biofilm formation by microorganisms is a major factor in oral disease progression because biofilms provide structural protection and enhanced resistance to environmental stresses. Among oral bacteria, *Streptococcus mutans* is recognized as a principal contributor to dental caries, whereas periodontal diseases are associated with pathogenic species such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*. Fungal species, particularly *Candida albicans*, also participate in oral biofilm formation and can contribute to opportunistic infections.

Recent studies have demonstrated that plant-derived metabolites from *S. persica* exhibit inhibitory effects against a wide range of oral microorganisms. Extracts from Meswak roots have been reported to suppress the growth of cariogenic and periodontopathogenic bacteria while reducing microbial adhesion and biofilm formation. Furthermore, antifungal activity against *Candida albicans* suggests that the plant may influence both bacterial and fungal components of the oral microbiome. These findings highlight the potential role of phytochemicals in regulating microbial communities and preventing pathogen colonization.

Advances in molecular biology, microbiome research, and phytochemical analysis have enhanced understanding of plant–microbe interactions and the mechanisms through which plant-derived compounds affect microbial physiology. Modern analytical techniques, including chromatography, metabolomics, genomic sequencing, and molecular profiling, have facilitated the identification of bioactive constituents responsible for the biological activities of medicinal plants. Such approaches provide opportunities to explore sustainable plant-based solutions for managing microbial-associated diseases while expanding knowledge of plant secondary metabolism and ecological interactions.

This review examines the phytochemical composition, biological activities, and antimicrobial potential of *Salvadora persica* root, with particular emphasis on its interactions with oral bacterial and fungal communities. By integrating current evidence on plant-derived bioactive compounds and microbial ecology, the review highlights the significance of *S. persica* as a medicinal plant and explores its potential applications in promoting oral health through natural and sustainable phytotherapeutic strategies.

Materials and Methods

Oral microbiome, plant-derived bioactive compounds, and oral homeostasis

One The oral cavity represents a complex microbial ecosystem inhabited by diverse bacterial, fungal, viral, and archaeal communities that colonize the teeth, tongue, gingival tissues, saliva, and mucosal surfaces. These microorganisms collectively constitute the oral microbiome and contribute to oral homeostasis through ecological balance, colonization resistance, and interactions with host immune mechanisms (Lamont, et al. 2018). The composition and activity of oral microbial communities are influenced by environmental factors, diet, salivary composition, oral hygiene practices, and exposure to natural or synthetic antimicrobial agents. Increasing attention has been directed toward medicinal plants as sustainable sources of bioactive compounds capable of modulating microbial communities and supporting oral health.

Among medicinal plants, *Salvadora persica* L. (Meswak) has been widely recognized for its traditional use in oral hygiene. This drought-tolerant species belonging to the family Salvadoraceae contains numerous phytochemicals, including alkaloids, flavonoids, tannins, saponins, sulfur-containing compounds, silica, fluoride, and essential oils. These secondary metabolites exhibit antimicrobial, antifungal, antioxidant, and anti-inflammatory activities that may influence the composition and function of oral microbial communities.

Under healthy conditions, oral microorganisms exist in a balanced ecological relationship with the host. Beneficial microbial populations contribute to oral health by limiting pathogen colonization, regulating local immune responses, and maintaining

biofilm stability (Marsh and Zaura, 2017). Saliva further supports this balance through buffering capacity, antimicrobial proteins, and mechanical cleansing. The fibrous structure of Meswak root enhances mechanical plaque removal and stimulates salivary flow, thereby contributing to oral hygiene maintenance.

Bacterial communities constitute the dominant component of the oral microbiome, with members of the phyla Firmicutes, Actinobacteria, Proteobacteria, Bacteroidetes, and Fusobacteria commonly detected (Human Microbiome Project Consortium, 2012). Commensal genera such as *Streptococcus*, *Actinomyces*, *Veillonella*, *Neisseria*, and *Haemophilus* are important contributors to microbial equilibrium. Disturbances in community structure can lead to dysbiosis and disease development. Experimental studies have demonstrated that extracts of *S. persica* inhibit the growth of pathogenic species including *Streptococcus mutans* and *Porphyromonas gingivalis*, suggesting a role for plant-derived metabolites in regulating oral microbial populations.

The oral mycobiome, consisting primarily of fungal species such as *Candida albicans*, also contributes to oral ecosystem dynamics. Although *Candida* species are commonly present as commensals, environmental disturbances may promote fungal overgrowth and biofilm-associated infections (Krüger, et al. 2019). Phytochemical analyses have shown that Meswak root contains compounds capable of suppressing fungal growth and biofilm development, indicating potential applications in controlling fungal colonization through natural plant-derived products.

Biofilms are highly organized microbial communities embedded within extracellular polymeric matrices that facilitate microbial communication, adhesion, and persistence (Koo, et al. 2017). Plant-derived secondary metabolites have been shown to interfere with microbial adhesion, quorum sensing, and extracellular matrix production. Extracts of *S. persica* have demonstrated anti-biofilm properties, reducing microbial attachment and limiting the establishment of pathogenic communities on oral surfaces.

Advances in molecular biology, metagenomics, and phytochemical profiling have improved understanding of the interactions between medicinal plants and microbial ecosystems. Modern analytical techniques have enabled the identification of specific metabolites responsible for antimicrobial activity and have provided insights into the mechanisms through which plant-derived compounds influence microbial community structure. These developments support the exploration of sustainable phytotherapeutic approaches based on medicinal plants and their bioactive constituents.

Overall, the oral microbiome functions as a dynamic ecological system whose stability depends on interactions among microorganisms, host tissues, and environmental factors. The bioactive compounds present in *Salvadora persica* demonstrate significant potential to influence microbial communities, inhibit pathogen colonization, and support ecological balance within the oral environment. Such findings highlight the importance of medicinal plants as renewable sources of natural compounds with applications in microbial management and oral healthcare.

Results and Discussion

Antimicrobial activity of *Salvadora persica* against oral bacterial pathogens

Medicinal plants produce diverse secondary metabolites that function in plant defense and exhibit biological activities against a broad range of microorganisms. Among these plants, *Salvadora persica* has received considerable attention because of its rich phytochemical composition and long-standing use in oral hygiene. The root tissues of *S. persica* contain alkaloids, tannins, flavonoids, sulfur-containing compounds, essential oils, silica, and fluoride, many of which possess antimicrobial properties that may contribute to microbial regulation within the oral ecosystem.

One of the most extensively studied oral bacterial pathogens is *Streptococcus mutans*, a microorganism associated with dental biofilm development and enamel demineralization. The ability of *S. mutans* to metabolize dietary carbohydrates and produce organic acids promotes localized acidification and ecological shifts within microbial communities (Bowen, et al. 2018). Several studies have demonstrated that extracts obtained from *S. persica* roots inhibit the growth and adhesion of *S. mutans*, suggesting that plant-derived metabolites interfere with bacterial colonization and biofilm establishment.

Biofilm formation depends on extracellular polysaccharide production and microbial adhesion to oral surfaces. Experimental evidence indicates that bioactive constituents present in Meswak extracts can reduce bacterial attachment and suppress extracellular matrix formation, thereby limiting biofilm development (Koo, et al. 2017). Such activities highlight the potential role of plant secondary metabolites in disrupting microbial community formation and reducing pathogen persistence.

In addition to *S. mutans*, other oral bacterial species including *Lactobacillus* spp., *Actinomyces* spp., and periodontal pathogens such as *Porphyromonas gingivalis* have been reported to be susceptible to Meswak-derived extracts. These observations suggest that *S. persica* exhibits broad-spectrum antimicrobial activity and may contribute to maintaining microbial balance within the oral cavity.

The antimicrobial effects of *S. persica* are attributed to the synergistic action of multiple phytochemicals rather than a single compound. Sulfur-containing constituents, tannins, alkaloids, and essential oils have all been implicated in inhibiting microbial growth, reducing adhesion, and altering biofilm architecture. Such multifunctional activities demonstrate how plant secondary

metabolites can influence microbial ecology and support the development of sustainable, plant-based antimicrobial strategies.

Collectively, current evidence indicates that *Salvadora persica* represents an important medicinal plant with significant antimicrobial potential against oral bacterial pathogens. Its phytochemical diversity and biological activities support further investigation into the mechanisms of plant–microbe interactions and the development of natural phytotherapeutic products for microbial management and oral health applications (Tab. 1 and Tab. 2).

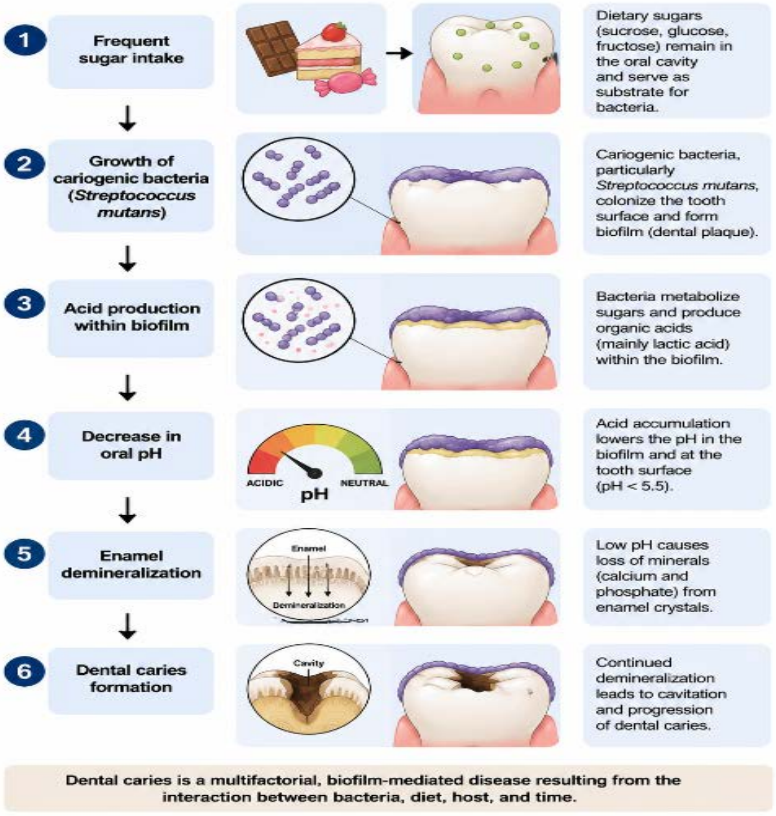

Figure 1. Mechanism of dental caries development.

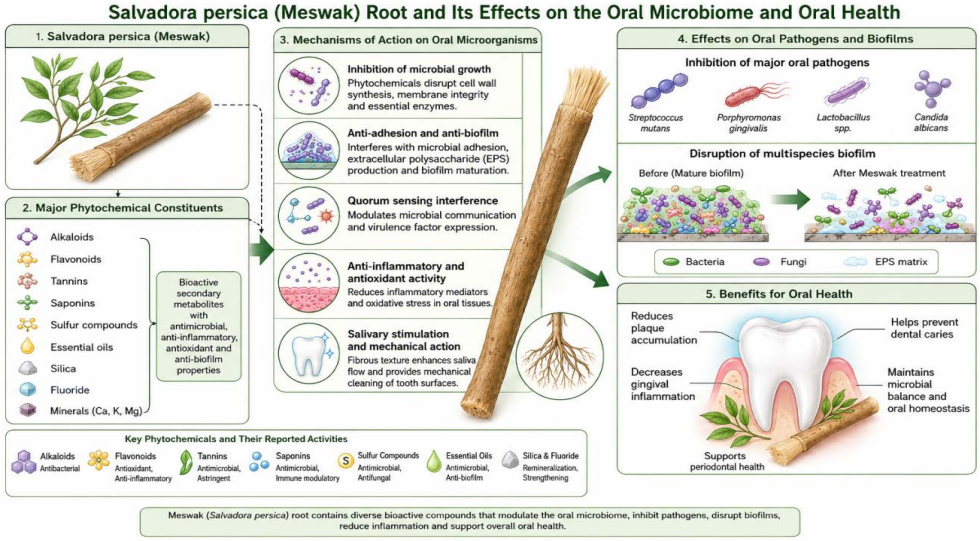

Figure 2. Antimicrobial and oral health-promoting effects of *Salvadora persica* (Meswak) root on the oral microbiome.

Antimicrobial activity of *Salvadora persica* against periodontal pathogens

Periodontal diseases are associated with complex microbial biofilms that develop on tooth and gingival surfaces and are characterized by persistent inflammatory responses within periodontal tissues. The composition and activity of these biofilms are influenced by interactions among microbial communities, host factors, and environmental conditions. Increasing interest has focused on medicinal plants as sources of bioactive compounds capable of modulating microbial populations and contributing to oral microbial homeostasis. Among these plants, *Salvadora persica L.* (Meswak) has received considerable attention because of its diverse phytochemical composition and traditional use in oral hygiene practices.

The roots of *S. persica* contain a wide range of secondary metabolites, including alkaloids, tannins, flavonoids, sulfur-containing compounds, saponins, essential oils, silica, and fluoride. These phytochemicals possess antimicrobial, antioxidant, anti-inflammatory, and anti-biofilm activities that may influence microbial colonization and community structure within the oral cavity. Studies have demonstrated that extracts of *S. persica* inhibit the growth of several microorganisms associated with periodontal biofilms, suggesting an important role for plant-derived metabolites in microbial regulation.

Among the microorganisms frequently associated with periodontal dysbiosis are *Porphyromonas gingivalis, Treponema denticola*, and *Tannerella forsythia*. These species possess virulence factors that facilitate biofilm persistence, tissue colonization, and microbial community disruption. Experimental investigations have reported that Meswak-derived extracts reduce the growth and adhesion of periodontal pathogens, thereby limiting biofilm establishment and microbial accumulation on oral surfaces.

The antimicrobial properties of *S. persica* are attributed to the synergistic effects of multiple phytochemicals. Sulfur-containing compounds and essential oils exhibit direct antimicrobial activity, while tannins contribute to microbial inhibition through protein precipitation and interference with microbial adhesion. Alkaloids and flavonoids may further enhance antimicrobial efficacy while providing antioxidant protection. These combined activities demonstrate the multifunctional role of plant secondary metabolites in influencing microbial ecology.

Recent studies have highlighted the importance of biofilm architecture and microbial interactions in determining oral microbial stability. Species such as *Fusobacterium nucleatum* function as bridging organisms that facilitate the integration of diverse microbial populations within biofilms. By interfering with microbial adhesion and extracellular matrix formation, Meswak-derived compounds may disrupt biofilm maturation and reduce the establishment of complex polymicrobial communities.

Additional oral microorganisms, including *Prevotella* species and *Veillonella* species, contribute to microbial diversity and participate in metabolic interactions within oral biofilms. The broad-spectrum antimicrobial activity of *S. persica* suggests that its bioactive compounds may influence multiple members of these microbial communities rather than targeting individual species alone. Such ecological effects may contribute to maintaining microbial balance and preventing the dominance of pathogenic organisms.

Advances in microbiome research, metabolomics, and phytochemical analysis have improved understanding of how medicinal plants interact with microbial ecosystems. These approaches have enabled the identification of specific metabolites responsible for antimicrobial and anti-biofilm activities and have provided insight into the mechanisms through which plant-derived compounds influence microbial community structure. Such findings support the development of sustainable phytotherapeutic strategies based on renewable plant resources.

Overall, *Salvadora persica* represents a valuable medicinal plant with significant antimicrobial potential against microorganisms associated with periodontal biofilms. Its diverse phytochemical composition and ability to modulate microbial communities highlight its importance as a natural source of bioactive compounds and underscore the broader significance of plant-derived products in microbial management and oral health applications (Tab. 1).

Table 1. Major oral bacterial species, their ecological roles, and potential targets of *Salvadora persica* phytochemicals.

Bacterial species	Ecological association	Major virulence/functional mechanisms	Potential effects of *Salvadora persica* phytochemicals
Streptococcus mutans	Cariogenic biofilms	Acid production, Extracellular Polysaccharide (EPS) synthesis, biofilm formation	Inhibition of bacterial growth, adhesion, and EPS production
Lactobacillus spp.	Caries progression	Acid tolerance and organic acid production	Suppression of microbial growth and acidogenic activity
Actinomyces spp.	Early plaque development, root caries	Initial colonization of tooth surfaces	Reduction of microbial adhesion and plaque establishment
Porphyromonas gingivalis	Periodontal biofilms	Gingipain production, immune modulation, tissue degradation	Antimicrobial activity and inhibition of biofilm formation
Treponema denticola	Periodontal dysbiosis	Motility, tissue penetration, protease production	Interference with microbial colonization and biofilm maturation

Tannerella forsythia	Periodontal biofilms	Induction of inflammatory responses and epithelial disruption	Suppression of bacterial growth and microbial persistence
Fusobacterim nucleatum	Biofilm maturation and microbial bridging	Coaggregation with diverse microbial species	Disruption of microbial interactions and biofilm architecture
Prevotella intermedia	Polymicrobial periodontal communities	Proteolytic activity and inflammatory stimulation	Reduction of microbial growth and community establishment

Improving dental prevention and treatment strategies requires an understanding of the pathogenic mechanisms of oral bacteria. Probiotics, biofilm disruption technologies, and precision antibacterial strategies—all of which aim to restore oral microbial equilibrium rather than eradicate microorganisms indiscriminately—are among the microbiome-targeted medicines that are increasingly the focus of modern research.

Fungal communities, oral ecology, and the antifungal potential of *Salvadora persica*

Fungi constitute an important component of the oral microbiome and contribute significantly to microbial diversity, ecological balance, and host–microbe interactions within the oral cavity. The oral fungal community, commonly referred to as the oral mycobiome, exists alongside bacterial populations in a dynamic ecosystem regulated by environmental conditions, microbial interactions, and host immune responses. Although fungi generally represent a smaller proportion of the oral microbiota than bacteria, they play critical roles in bioilm formation, nutrient cycling, and microbial community structure (Krüger, et al. 2019). Increasing scientific attention has focused on medicinal plants as sources of natural antifungal compounds capable of influencing fungal populations and maintaining microbial homeostasis.

Among medicinal plants, *Salvadora persica* L. (Meswak) has been widely recognized for its diverse phytochemical composition and long history of use in traditional oral hygiene practices. The roots of *S. persica* contain biologically active compounds, including alkaloids, flavonoids, tannins, sulfur-containing compounds, saponins, essential oils, silica, and various mineral constituents. These secondary metabolites exhibit antimicrobial, antifungal, antioxidant, and anti-inflammatory properties that may contribute to the regulation of fungal communities within the oral ecosystem.

Molecular studies have revealed that the oral mycobiome consists of a diverse assemblage of fungal genera, including *Candida, Cladosporium, Aspergillus, Saccharomyces, Fusarium,* and *Cryptococcus* (Ghannoum, et al. 2010). These fungi interact continuously with bacterial communities and host tissues, contributing to the overall structure and function of oral microbial ecosystems. Environmental factors such as diet, salivary composition, age, oral hygiene practices, and systemic health conditions influence fungal diversity and abundance. Under healthy conditions, fungal populations remain regulated through microbial competition, host immune surveillance, and ecological stability.

Recent evidence suggests that fungi are active participants in microbial communication networks rather than passive colonizers. Fungal species contribute to biofilm architecture, metabolic cooperation, nutrient acquisition, and signaling processes that influence the behavior of surrounding microorganisms. These ecological interactions affect microbial community composition and may determine the stability of oral microbial ecosystems. Plant-derived metabolites capable of disrupting fungal adhesion and biofilm formation therefore represent promising tools for microbial management.

Among oral fungi, *Candida albicans* is the most extensively studied species because of its prevalence and ability to adapt to changing environmental conditions. This dimorphic fungus can transition between yeast and filamentous forms, a characteristic associated with enhanced colonization, biofilm formation, and ecological competitiveness (Mayer, et al. 2013). Numerous studies have demonstrated that extracts derived from *S. persica* exhibit inhibitory effects against *C.* , reducing fungal growth, adhesion, and biofilm development. These antifungal activities are primarily attributed to the synergistic action of multiple phytochemicals present within the root tissues.

Tannins and flavonoids may interfere with fungal cell wall integrity and metabolic activity, while sulfur-containing compounds and essential oils exhibit direct antifungal effects against fungal cells. Alkaloids and other secondary metabolites may further contribute to growth inhibition and suppression of fungal colonization. The combined action of these phytochemicals highlights the importance of plant secondary metabolism in producing natural compounds capable of regulating fungal populations.

The antifungal properties of *S. persica* demonstrate the broader ecological significance of medicinal plants in influencing microbial communities. By reducing fungal growth, inhibiting adhesion, and disrupting biofilm formation, plant-derived compounds may contribute to maintaining microbial balance within complex oral ecosystems. These findings support the growing interest in renewable plant resources as sustainable alternatives to synthetic antimicrobial agents.

Advances in fungal ecology, metabolomics, and phytochemical analysis have improved understanding of the interactions between medicinal plants and microbial communities. Modern analytical approaches have facilitated the identification of bioactive metabolites responsible for antifungal activity and have provided valuable insights into the mechanisms through which plant-derived compounds influence fungal physiology and microbial ecology. Such knowledge contributes to the development of phytotherapeutic applications based on medicinal plants and their naturally occurring secondary metabolites.

Overall, *Salvadora persica* represents an important medicinal plant with significant antifungal potential against oral fungal communities. Its rich phytochemical profile and demonstrated biological activities highlight the role of plant-derived metabolites in microbial regulation and emphasize the importance of medicinal plants as sustainable sources of bioactive compounds for health-related applications.

Fungal pathogenicity, biofilm formation, and antifungal activities of *Salvadora persica*

Fungal species within the oral microbiome exist in a dynamic equilibrium with bacterial communities and host tissues. Under favorable ecological conditions, these microorganisms contribute to microbial diversity without causing disease. However, disturbances in microbial balance, environmental stressors, or alterations in host defense mechanisms can promote fungal proliferation, biofilm formation, and increased pathogenicity. Among oral fungi, *Candida* species are the most extensively studied due to their prevalence and ecological adaptability within the oral environment (Mayer, et al. 2013).

In addition to *Candida albicans*, several non-*albicans Candida* species, including *Candida glabrata*, *Candida tropicalis*, and *Candida krusei*, have been identified within oral microbial communities. These species exhibit distinct physiological characteristics and may demonstrate varying susceptibility to conventional antifungal agents. The increasing occurrence of diverse fungal species has stimulated interest in alternative antimicrobial strategies derived from natural plant resources.

The pathogenic potential of oral fungi is influenced by several biological mechanisms. Fungal adhesion to oral surfaces, epithelial tissues, and biomaterials represents a critical initial step in colonization. Adhesion is mediated by specialized surface proteins that facilitate attachment and promote subsequent biofilm development. Following attachment, fungal cells can proliferate and form highly organized biofilms embedded within extracellular polymeric matrices. These biofilms provide structural stability, facilitate microbial communication, and enhance resistance to environmental stresses.

A distinguishing characteristic of *Candida albicans* is its ability to undergo morphological transitions between yeast and filamentous forms. This developmental plasticity contributes to fungal persistence, ecological competitiveness, and biofilm maturation. The filamentous form enhances surface colonization and strengthens biofilm architecture, thereby increasing the resilience of fungal communities. Plant-derived compounds capable of inhibiting adhesion, morphological transition, and biofilm development are therefore of particular interest in microbial management.

Salvadora persica L. contains a diverse range of bioactive phytochemicals, including tannins, flavonoids, alkaloids, sulfur-containing compounds, saponins, and essential oils. Numerous studies have reported antifungal activity of Meswak extracts against *Candida* species, with inhibitory effects on fungal growth, adhesion, and biofilm formation. These activities are attributed to the synergistic action of multiple secondary metabolites that interfere with cellular integrity, metabolic processes, and microbial surface interactions.

Biofilm formation represents one of the most important ecological strategies employed by fungal microorganisms. Fungal biofilms are characterized by complex extracellular matrices that limit the penetration of antimicrobial compounds and protect resident cells from environmental challenges (Nobile and Johnson, 2015). Experimental evidence suggests that phytochemicals present in *S. persica* can disrupt biofilm development by reducing fungal attachment and interfering with extracellular matrix formation. Such anti-biofilm activities highlight the potential ecological role of plant metabolites in regulating microbial communities.

Fungal pathogenicity is further enhanced through the production of extracellular enzymes, including proteases, phospholipases, and lipases. These enzymes facilitate nutrient acquisition, surface colonization, and adaptation to changing environmental conditions. Antioxidant and anti-inflammatory constituents present in *S. persica* may contribute additional protective effects by reducing oxidative stress and supporting tissue integrity within microbial ecosystems.

Recent microbiome research has demonstrated that fungi rarely function in isolation. Instead, they participate in extensive cross-kingdom interactions with bacterial populations. Interactions between *Candida albicans* and bacterial species such as *Streptococcus mutans* have been shown to promote cooperative biofilm formation, enhance microbial persistence, and alter community structure (Koo, et al. 2018). These relationships illustrate the importance of understanding microbial ecology at the community level rather than focusing on individual species.

The ability of *Salvadora persica* phytochemicals to influence both bacterial and fungal populations suggests a broader role in the modulation of oral microbial ecosystems. By inhibiting microbial adhesion, suppressing biofilm development, and reducing the growth of diverse microorganisms, Meswak-derived compounds may contribute to maintaining microbial balance and ecological stability. Such findings emphasize the significance of medicinal plants as renewable sources of bioactive metabolites and support further investigation into plant–microbe interactions and phytotherapeutic applications (Tab. 2).

Table 2. Major oral fungal species, their ecological associations, and potential targets of *Salvadora persica* phytochemicals.

Fungal species	Ecological association	Major virulence/functional mechanisms	Potential effects of *Salvadora persica* phytochemicals
Candida albicans	Oral biofilms, oral candidiasis, denture-associated biofilms	Hyphal formation, biofilm production, adhesin-mediated attachment	Inhibition of fungal growth, adhesion, hyphal development, and biofilm formation
Candida glabrata	Opportunistic oral colonization	Stress tolerance and reduced susceptibility to antifungal agents	Suppression of fungal proliferation and biofilm establishment
Candida tropicalis	Oral fungal biofilms	Biofilm formation and persistence within microbial communities	Reduction of fungal adhesion and biofilm maturation
Candida krusei	Opportunistic fungal communities	Intrinsic resistance to several antifungal agents	Broad-spectrum antifungal activity and disruption of colonization
Aspergillus spp.	Environmental fungal colonizers occasionally detected in the oral cavity	Hyphal growth and tissue colonization capacity	Inhibition of fungal growth and colonization
Cryptococcus spp.	Opportunistic fungal populations	Capsule formation and protection from environmental stresses	Interference with fungal survival and community establishment

Fungal communities are increasingly recognized as major contributors to oral disease pathogenesis and biofilm complexity. Improved understanding of the oral mycobiome may support the development of microbiome-based diagnostics, targeted antifungal therapies, and personalized approaches in preventive and restorative dentistry..

Cross-kingdom interactions in oral biofilms and the role of *Salvadora persica* phytochemicals

Cross-kingdom interactions refer to ecological relationships among microorganisms belonging to different biological kingdoms, particularly bacteria and fungi. Within the oral cavity, these interactions play critical roles in microbial colonization, community organization, biofilm development, and ecosystem stability. Recent advances in microbiome research have demonstrated that oral microbial communities function as highly integrated ecological networks rather than collections of isolated species (Lamont, et al. 2018). Understanding these complex microbial relationships has become increasingly important for developing sustainable approaches to microbial management, including the use of bioactive compounds derived from medicinal plants.

Among medicinal plants, *Salvadora persica* L. (Meswak) has attracted considerable attention because of its rich phytochemical composition and broad-spectrum antimicrobial activities. The roots of *S. persica* contain diverse secondary metabolites, including flavonoids, tannins, alkaloids, sulfur-containing compounds, saponins, and essential oils. These compounds exhibit antimicrobial, antifungal, antioxidant, and anti-biofilm activities that may influence microbial interactions and contribute to the maintenance of oral microbial homeostasis.

Oral biofilms are highly structured microbial communities embedded within Extracellular Polymeric Substances (EPS) that facilitate microbial adhesion, communication, and persistence. The EPS matrix provides protection against environmental stresses and supports close physical associations among microorganisms. Within these biofilms, bacteria and fungi engage in cooperative interactions involving nutrient exchange, metabolic adaptation, and signaling processes that influence community structure and function (Koo, et al. 2018). Plant-derived metabolites capable of disrupting biofilm architecture therefore represent promising tools for microbial regulation.

One of the most extensively studied examples of cross-kingdom interaction involves the association between *Candida albicans* and *Streptococcus mutans*. These microorganisms exhibit synergistic relationships that promote biofilm formation and enhance microbial persistence. *S. mutans* produces extracellular glucans that facilitate fungal adhesion and contribute to the establishment of mixed-species biofilms (Falsetta, et al. 2014). In turn, *C.* provides structural support and increases the complexity of biofilm architecture. Studies have demonstrated that extracts of *S. persica* can inhibit both bacterial and fungal growth, suggesting that plant-derived compounds may interfere with the formation and stability of these mixed microbial communities.

Cross-kingdom biofilms exhibit greater structural complexity and metabolic activity than single-species biofilms. These polymicrobial communities benefit from cooperative interactions that enhance nutrient acquisition, environmental adaptation, and microbial survival. Such ecological cooperation contributes to biofilm resilience and long-term persistence. The anti-biofilm properties of Meswak-derived phytochemicals may reduce microbial aggregation, inhibit extracellular matrix formation, and limit the development of complex polymicrobial structures.

Microbial communication is another essential component of cross-kingdom interactions. Quorum sensing systems regulate gene expression, community behavior, and biofilm maturation through signaling molecules produced by both bacterial and fungal populations (Krüger, et al. 2019). Fungal signaling compounds such as farnesol influence morphological development and biofilm formation, while bacterial metabolites can modify fungal physiology and behavior. Emerging evidence suggests that plant secondary metabolites may interfere with these signaling pathways, thereby reducing microbial coordination and limiting biofilm development.

Metabolic cooperation further contributes to the stability of oral microbial communities. Bacteria and fungi frequently exchange nutrients and metabolic byproducts, creating mutually beneficial relationships that support survival under fluctuating environmental conditions. Such interactions enhance community resilience and facilitate long-term colonization. The broad-spectrum antimicrobial activity of *S. persica* phytochemicals may disrupt these cooperative metabolic networks and reduce the persistence of pathogenic microorganisms within biofilms.

Physical interactions between microorganisms also contribute significantly to biofilm organization. Fungal hyphae can serve as scaffolding structures that facilitate bacterial attachment and spatial organization within the biofilm matrix (Jenkinson and Lamont, 2005). By reducing microbial adhesion and interfering with biofilm establishment, bioactive compounds from *S. persica* may influence these structural interactions and alter microbial community architecture.

Recent advances in metagenomics, transcriptomics, and metabolomics have greatly improved understanding of cross-kingdom microbial ecology. These technologies have revealed the extensive communication networks and cooperative interactions that govern microbial community behavior. Simultaneously, phytochemical investigations have identified numerous plant-derived metabolites capable of modulating microbial growth, signaling pathways, and biofilm development. Such discoveries highlight the importance of medicinal plants as sources of natural compounds for microbiome-targeted applications.

Overall, cross-kingdom interactions between bacteria and fungi are fundamental determinants of oral microbial ecology and biofilm stability. The diverse phytochemicals present in *Salvadora persica* demonstrate significant potential to influence microbial communication, adhesion, biofilm formation, and community composition. These findings underscore the ecological importance of plant-derived secondary metabolites and support further exploration of medicinal plants as sustainable resources for microbial management and phytotherapeutic development (Tab.3).

Table 3. Major cross-kingdom interactions in oral microbial communities and potential modulation by *Salvadora persica* phytochemicals.

Microorganisms involved	Type of interaction	Ecological consequences	Potential effects of *Salvadora persica* phytochemicals
Streptococcus mutans + *Candida albicans*	Synergistic biofilm formation through extracellular polysaccharide production and fungal adhesion	Enhanced biofilm biomass, increased acid production, and microbial persistence	Inhibition of microbial adhesion, suppression of biofilm development, and disruption of mixed-species interactions
Candida albicans + *Porphyromonas gingivalis*	Cooperative interaction promoting inflammatory and pathogenic responses	Increased microbial virulence and biofilm complexity	Antimicrobial and anti-inflammatory activities that may reduce microbial growth and community stability
Fusobacterium nucleatum + *Candida* spp.	Structural cooperation and biofilm stabilization	Enhanced microbial coaggregation and persistence within polymicrobial communities	Interference with microbial adhesion and disruption of biofilm architecture
Oral bacterial communities + fungal biofilms	Cross-kingdom communication, metabolic cooperation, and stress-response enhancement	Increased resilience, ecological stability, and resistance to environmental challenges	Broad-spectrum antimicrobial and anti-biofilm effects that may alter microbial community dynamics and reduce biofilm formation

Phytochemical modulation of oral microbial communities: Future perspectives for *Salvadora persica*

Recent advances in microbial ecology, metabolomics, and phytochemical research have highlighted the potential of medicinal plants as sustainable sources of bioactive compounds capable of influencing complex microbial ecosystems. Rather than indiscriminately eliminating microorganisms, contemporary approaches increasingly focus on maintaining microbial homeostasis and regulating microbial interactions through naturally derived compounds. This strategy is particularly relevant in oral microbial ecosystems, where ecological balance is essential for long-term health and microbial stability.

Salvadora persica L. (Meswak) represents an important medicinal plant with a rich diversity of secondary metabolites that contribute to its biological activities. Phytochemical investigations have identified alkaloids, flavonoids, tannins, sulfur-containing compounds, saponins, terpenoids, essential oils, and mineral constituents within root tissues. These metabolites exhibit antimicrobial, antifungal, antioxidant, anti-inflammatory, and anti-biofilm activities that may influence both bacterial and fungal populations within oral microbial communities.

The antimicrobial properties of *S. persica* are attributed to multiple complementary mechanisms. Plant-derived metabolites may interfere with microbial adhesion, inhibit Extracellular Polymeric Substance (EPS) production, disrupt biofilm architecture, and alter microbial signaling pathways. Such activities reduce the ability of microorganisms to establish stable polymicrobial communities while promoting a more balanced microbial ecosystem. Unlike many synthetic antimicrobial agents that target specific cellular processes, phytochemicals often act through multiple pathways simultaneously, potentially reducing the likelihood of microbial adaptation.

Recent studies suggest that plant secondary metabolites may also influence quorum sensing, a communication system that regulates microbial cooperation and biofilm development. By interfering with signaling molecules involved in bacterial and fungal

communication, phytochemicals from *S. persica* may suppress coordinated microbial behaviors associated with biofilm maturation and community persistence. These findings emphasize the ecological significance of plant metabolites in shaping microbial interactions.

The growing application of metabolomics and advanced analytical techniques has enabled the identification of specific compounds responsible for the biological activities of medicinal plants. High-Performance Liquid Chromatography (HPLC), Gas Chromatography–Mass Spectrometry (GC–MS), Liquid Chromatography–Mass Spectrometry (LC–MS), and Nuclear Magnetic Resonance (NMR) spectroscopy have facilitated the characterization of bioactive metabolites in *S. persica*. Such approaches provide valuable insights into the relationship between phytochemical composition and biological function.

Emerging technologies may further expand the applications of *S. persica*-derived compounds. Incorporation of plant metabolites into biomaterials, nanostructured delivery systems, and bioactive coatings could enhance their stability and antimicrobial efficacy. The integration of phytochemicals with modern biotechnology offers opportunities for the development of sustainable plant-based products designed to regulate microbial communities and inhibit biofilm formation.

Advances in microbiome science have also shifted attention toward ecological approaches that support beneficial microbial populations while limiting opportunistic microorganisms. Plant-derived compounds may contribute to this objective by selectively influencing microbial interactions and promoting community stability. Such microbiome-oriented strategies align with broader efforts to develop environmentally sustainable alternatives to synthetic antimicrobial agents.

Future research should focus on elucidating the molecular mechanisms underlying the interactions between *S. persica* metabolites and microbial communities. Investigations combining phytochemistry, genomics, transcriptomics, metabolomics, and microbial ecology will improve understanding of how plant-derived compounds influence microbial behavior, biofilm architecture, and community dynamics. These multidisciplinary approaches may facilitate the development of innovative phytotherapeutic applications and contribute to the sustainable utilization of medicinal plants.

Overall, *Salvadora persica* serves as a valuable model for exploring plant–microbe interactions and the ecological functions of plant secondary metabolites. Its diverse phytochemical profile and demonstrated biological activities highlight the potential of medicinal plants as renewable sources of bioactive compounds for regulating microbial ecosystems and supporting health-related applications (Tab. 4).

Table 4. Strategies for modulating oral microbial communities and their ecological significance.

Strategy	Primary target	Purpose in microbial ecosystem management
Antibiotics	Periodontal and pathogenic bacteria	Reduction of pathogenic bacterial populations and control of microbial overgrowth
Antifungal agents	*Candida* spp. and other fungal populations	Suppression of fungal proliferation and biofilm development
Chlorhexidine mouthwash	Oral biofilms	Inhibition of microbial adhesion and reduction of biofilm accumulation
Photodynamic therapy	Bacterial and fungal communities	Disruption of established polymicrobial biofilms through oxidative damage
Nanotechnology-based antimicrobials	Resistant microbial biofilms	Enhanced delivery of antimicrobial agents and improved biofilm penetration
Probiotics	Oral microbial dysbiosis	Promotion of beneficial microorganisms and restoration of microbial balance
Fluoride-based approaches	Tooth-associated biofilms and enamel surfaces	Support of enamel stability and reduction of cariogenic microbial activity
Oral hygiene practices	Dental plaque and microbial deposits	Prevention of excessive biofilm accumulation and maintenance of microbial homeostasis
Salvadora persica (Meswak) phytochemicals	Bacterial and fungal communities, biofilms, and microbial interactions	Inhibition of microbial growth, disruption of biofilm formation, modulation of microbial communication, and maintenance of ecological balance

Contemporary oral healthcare increasingly emphasizes preventive and microbiome-based approaches for managing oral diseases. Integrating antimicrobial therapies with biofilm disruption technologies, probiotics, and preventive clinical practices may improve long-term treatment outcomes and support the development of personalized dentistry strategies.

Conclusion

The oral microbiome represents a complex ecological system in which bacterial and fungal communities interact continuously to maintain microbial balance and ecosystem stability. The structure and function of these microbial communities are strongly influenced by interspecies and cross-kingdom interactions, biofilm formation, environmental conditions, and host-associated factors. Disruptions in these ecological relationships can alter microbial community composition and promote the establishment of pathogenic

microorganisms. Consequently, understanding the mechanisms that regulate microbial homeostasis has become an important area of research in microbial ecology and health sciences.

Among medicinal plants, *Salvadora persic*a L. (Meswak) has emerged as a valuable natural source of bioactive compounds with significant antimicrobial, antifungal, antioxidant, anti-inflammatory, and anti-biofilm properties. The roots of *S. persica* contain a diverse range of secondary metabolites, including alkaloids, flavonoids, tannins, sulfur-containing compounds, saponins, essential oils, silica, and mineral constituents. These phytochemicals have demonstrated the ability to inhibit microbial growth, reduce microbial adhesion, interfere with biofilm formation, and modulate microbial community interactions. Such activities highlight the ecological importance of plant-derived metabolites in regulating complex microbial ecosystems.

Current evidence indicates that *S. persica* phytochemicals influence both bacterial and fungal populations, including key oral microorganisms such as *Streptococcus mutans*, *Porphyromonas gingivalis*, and *Candida albicans*. Furthermore, the ability of these compounds to affect microbial communication pathways, biofilm architecture, and cross-kingdom interactions suggests a broader role in maintaining microbial equilibrium. These findings emphasize the significance of plant secondary metabolites as natural regulators of microbial community structure and function.

Advances in molecular microbiology, metabolomics, phytochemical profiling, and microbiome research have substantially improved understanding of plant–microbe interactions and the mechanisms through which medicinal plants influence microbial ecology. Integrating these multidisciplinary approaches will facilitate the identification of novel bioactive compounds and support the development of sustainable plant-based applications for microbial management.

Future research should focus on the molecular characterization of *S. persica* metabolites, elucidation of their mechanisms of action, and investigation of their effects on microbial communities using genomics, transcriptomics, proteomics, and metabolomics approaches. Such studies will provide valuable insights into the ecological functions of plant secondary metabolites and their potential applications in biotechnology, microbial regulation, and phytotherapeutic development.

Overall, *Salvadora persica* represents an important medicinal plant with considerable potential as a renewable source of bioactive compounds. Its rich phytochemical diversity and demonstrated biological activities underscore the broader significance of medicinal plants in microbial ecology and highlight their potential contribution to the development of sustainable, plant-based strategies for managing complex microbial communities.

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