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REVIEW

PROTECTIVE EFFECTS OF *ARTEMISIA* SPP. EXTRACTS AGAINST ORAL DISEASES: A REVIEW

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Abstract. Plant extracts represent valuable resources of bioactive phytoconstituents with potent antimicrobial, antioxidant, and antitumoral properties, making them suitable alternatives to conventional oral health treatments. This review examines the stomatological applications of the genus Artemisia, focusing on its efficacy in managing dental caries, periodontal disease, endodontic infections, and oral malignancies. Key species like A. princeps, A. herba-alba, and A. annua demonstrate targeted abilities to inhibit primary pathogens such as Streptococcus mutans and Porphyromonas gingivalis. Furthermore, compounds like eupatilin and artesunate offer therapeutic benefits ranging from selective cytotoxicity against oral carcinoma cells to the alleviation of diabetic xerostomia. By integrating high biocompatibility with potent bioactivity, Artemisia species emerge as promising candidates for natural, pharmaceutical-grade oral hygiene and therapeutic formulations.

Keywords: Artemisia species, stomatology, phytotherapy

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1. Introduction

The genus *Artemisia*, in the *Asteraceae* family, comprises over 500 species mainly adapted to temperate regions across Europe, East Asia, North America, North Africa, and Australia, with highest diversity in Asia (~150 species in China) and ~57 in Europe [1,2]. *Artemisia* species are renowned for their abundance of bioactive compounds, which underpin their extensive medicinal properties and wide-ranging biological effects. More than 260 species have been analyzed to date for essential oil content and secondary metabolite profiles. Key compound classes include terpenoids, flavonoids, coumarins, phenolic acids, alkaloids, essential oils, and sterols, supporting their medicinal value [3]. In the field of stomatology, these extracts address critical oral health problems where conventional treatments often face challenges such as bacterial resistance and side effects from synthetic drugs [4]. *Artemisia* species offer multifaceted solutions by targeting the primary initiators of dental caries, such as *Streptococcus mutans*, to prevent biofilm synthesis and enamel demineralization [5,6]. Beyond surface-level decay, these compounds manage the inflammatory complexities of periodontal disease by reducing

alveolar bone loss and suppressing pro-inflammatory cytokines induced by pathogens like *Porphyromonas gingivalis* [7–9]. Furthermore, they provide targeted disinfection for resilient endodontic and fungal pathogens like *Enterococcus faecalis* and *Candida albicans*, while exhibiting selective cytotoxicity against oral squamous cell carcinoma cells without harming healthy tissue [10,11]. By integrating antimicrobial, antioxidant, and antitumoral properties, the genus *Artemisia* provides a potent and biocompatible framework for modern oral care (Fig. 1).

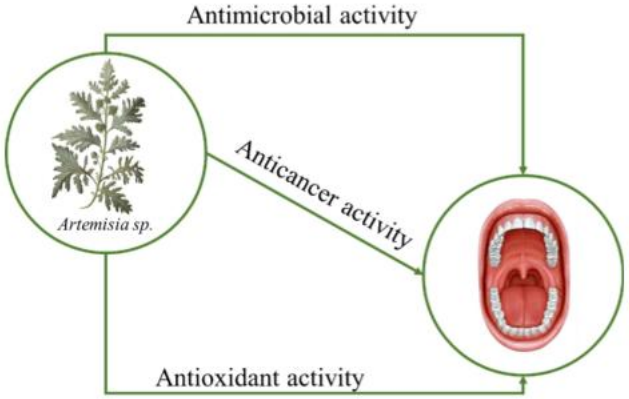

Fig. 1. Schematic illustration of Artemisia species activities applied in oral health.

2. Applicability in oral health

2.1. Dental caries and biofilm management

Artemisia species offer a multifaceted approach to preventing dental decay by targeting *Streptococcus mutans*, the primary initiator of dental caries. The ethanol extract of *Artemisia princeps* demonstrates potent anticariogenic properties by inhibiting growth and acid production. Rich in organic acids and glycosides, it exerts a concentration-dependent bactericidal effect (peaking at 0.4 mg/mL) and downregulates essential virulence genes, such as *gtfB*, *gtfC*, and *gbpB*, effectively preventing the pH drop that leads to enamel demineralization [5]. Similarly, its methanol extract establishes a minimum bactericidal concentration (MBC) of 1,250 ppm and inhibits biofilm formation by 70%, outperforming the standard antiseptic chlorhexidine [12]. Further expanding this antimicrobial repertoire, the essential oil of *Artemisia vulgaris* utilizes hydrophobic components like α-pinene and camphor to disrupt bacterial cell walls, resulting in a direct bactericidal effect rather than mere suppression [13]. For broad-spectrum applications, various extraction methods have shown efficacy against bacteria sampled directly from human tooth decay and *S. pyogenes* [14]. Additionally, *A. dracunculus*, rich in estragole, provides direct bactericidal effects against *S. mutans* and *S. salivarius* at low concentrations [4] and *A. herba-alba* stands out by inhibiting water-insoluble glucan synthesis by 46%, preventing *S. mutans* adhesion to enamel and halting the glucose utilization required for acid production [6].

2.2. Periodontal disease

Beyond surface-level decay, *Artemisia* compounds address the inflammatory complexities of gum disease. Bioconverted milk formulated with *A. herba-alba* and the probiotic *Lactiplantibacillus plantarum* (BM3) has shown a targeted ability to inhibit *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* [8]. This formulation effectively heals local periodontitis by reducing alveolar bone loss and shifting the microbiome toward beneficial *Actinobacteria*. Beyond the oral cavity, it reverses systemic side effects by lowering blood glucose and liver enzymes, driven by high concentrations of bioavailable flavonoids and phenolics [7]. Extracts of *Artemisia annua* L. demonstrate significant antimicrobial activity against major periodontopathic bacteria, with the methanol extract achieving the lowest minimum inhibitory concentration (MIC) of 7 mg/ml against *Prevotella intermedia*. Additionally, these extracts exhibit powerful antioxidant properties, achieving up to a 91% DPPH free radical scavenging rate that is comparable to the antioxidant α-tocopherol. The combined antioxidant and antimicrobial efficacy of *A. annua* makes it a highly promising natural candidate for pharmaceutical treatments targeting dental and periodontal diseases [15]. Furthermore, phytoconstituents like apigenin and quercetin effectively reduce the secretion of IL-6 and IL-15 in human gingival fibroblasts. By inhibiting this local response, these compounds may prevent systemic inflammatory cascades linked to neurodegenerative conditions like Alzheimer's disease [16]. For aggressive cases, the aqueous extract of *A. herba-alba* rivals synthetic antibiotics, producing massive inhibition zones against anaerobic pathogens with a remarkably low MIC of 0.058 mg/mL [9]. Artesunate (ART), a therapeutic derivative of *Artemisia annua*, offers relief for diabetic xerostomia (dry mouth) by restoring microbial balance and suppressing oxidative tissue damage via the NF-κB/NLRP3 pathway [17].

2.3. Oral cancer and cytotoxicity

The most advanced application of *Artemisia* lies in its selective cytotoxicity against oral malignancies. *Artemisia absinthium* extract can reduce human tongue squamous carcinoma (HSC-3) cell viability by 99% by triggering Caspase 3 and 9 apoptotic markers. Remarkably, the extract remains highly biocompatible with healthy periodontal stem cells (hPDLSCs), even stimulating their proliferation at high concentrations [18]. Supporting this anticancer profile, Eupatilin, a flavonoid found in various *Artemisia* species, induces G0/G1 cell cycle arrest in oral squamous cell carcinoma (OSCC). It further triggers mitochondrial-mediated apoptosis by increasing the Bax/Bcl-2 ratio and blocks the invasive capabilities of cancer cells by suppressing matrix metalloproteinases MMP-2 and MMP-9, highlighting its promise as a multifaceted therapeutic agent for oral cancer [19].

2.4. Endodontic infections and fungal pathogens

For persistent infections within the root canal system, *Artemisia* provides targeted disinfection. While *A. absinthium* shows high efficacy against *Actinomyces odontolyticus*, it remains less effective against resistant cariogenic strains like *S. mutans* [20]. However, the ethanol extract of *Artemisia afra* demonstrates broad-spectrum activity against Gram-

positive and Gram-negative bacteria, alongside the fungus *Candida albicans* [10]. Finally, Artemisinin (from *A. annua*) effectively suppresses *Enterococcus faecalis* and *C. albicans*, two pathogens frequently responsible for treatment failures. By neutralizing free radicals and reducing periapical inflammation, it serves as a promising, biocompatible alternative to conventional, potentially cytotoxic endodontic irrigants [11].

Table 1. Antimicrobial effects of *Artemisia* species extract on oral health pathogens

Artemisia Species	Extract Type	Primary Activity	Recorded Results	Ref.
A. princeps	Ethanol	Anticariogenic	Bactericidal at 0.4 mg/mL; downregulates *gtfB/C* genes.	[5]
	Methanol	Antibiofilm	MBC: 1,250 ppm; 70% biofilm inhibition at 1,000 ppm.	[12]
A. vulgaris	Essential Oil	Bactericidal	14.5 mm inhibition zone; disrupts plasma membrane.	[13]
Artemisia spp.	Methanolic	Antibacterial	15 mm inhibition zone against tooth decay bacteria.	[14]
A. dracunculus	Essential Oil	Antimicrobial	MIC: 1.8 mg/mL (*S. mutans/salivarius*); 7–30 mm inhibition zones.	[4]
A. herba-alba	Dioxane	Anticariogenic	MIC: 2.5 mg/mL; 46% inhibition of glucan synthesis.	[6]
	Bioconverted (BM3)	Periodontal	3.6 mm zone (*A. actinomycetemcomitans*); reduced bone loss.	[8]
	Aqueous	Periodontal	MIC: 0.058 mg/mL (*P. gingivalis*); 49 mm inhibition zone.	[9]
A. annua L.	Methanol	Anti-inflammatory	MIC: 7 mg/mL (*P. intermedia*); 91% DPPH scavenging.	[15]
A. spp. (apigenin and quercetin)	-	Immunomodulatory	Significant decrease in IL-6 and IL-15 secretion.	[16]
A. annua (artesunate)	-	Microbiota Balance	Normalizes salivary gland metabolism; inhibits NF-κB/NLRP3.	[17]

A. absinthium	Ethanol: Water 1:1	Anticancer	99% HSC-3 cell death; 150% growth of healthy stem cells.	[18]
	Ethanol	Antibacterial	MIC: 37.5 µg/mL (*A. odontolyticus*); 300 µg/mL (*S. mutans*).	[20]
A. spp. (Eupatilin)	-	Anticancer	Induces G0/G1 arrest; suppresses MMP-2/MMP-9.	[19]
A. afra	Ethanol	Antimicrobial	MIC: 0.25 mg/mL (*Actinomyces*); 6.3 mg/mL (*C. albicans*).	[10]
A. annua (Artemisinin)	Methanol, Ethanol, and Acetone	Endodontic	Maximum antioxidant efficacy at 10 mg/mL.	[11]

Conclusions

Given the escalating global challenge of antibiotic resistance and the adverse side effects associated with synthetic medications, plant-based therapies are emerging as crucial alternatives for the prevention and treatment of oral cavity disorders. This review highlights the diverse bioactive phytoconstituents, including terpenoids, flavonoids, and essential oils, found within the *Artemisia* genus, detailing their targeted mechanisms against dental caries, periodontitis, root canal infections, and oral malignancies.

Consequently, *Artemisia* extracts warrant comprehensive in vitro and in vivo exploration to fully understand their pharmacological scope. They exhibit notable capabilities, serving as biocompatible alternatives that can effectively mitigate alveolar bone loss, suppress pro-inflammatory cytokines, and destroy resilient pathogens like Streptococcus mutans and Porphyromonas gingivalis. Furthermore, their ability to act as selective antitumoral agents and natural endodontic disinfectants positions them as highly versatile tools in stomatology.

To fully harness these botanical assets, future research must adopt a highly interdisciplinary strategy. Bridging the fields of dentistry, oncology, and phytotherapy will be essential to accurately define clinical protocols, standardize administration methods, and determine optimal therapeutic dosages for these pharmaceutical-grade formulations. We conclude by emphasizing the exceptional, multifaceted potential of *Artemisia* species in modern oral care. Further clinical investigations remain imperative to successfully translate these potent pharmacological benefits into everyday dental practice.

Abbreviations

ART: Artesunate;

BM3: Bioconverted milk (formulated with *A. herba-alba* and the probiotic *Lactiplantibacillus plantarum*);

DPPH: 2,2-diphenyl-1-picrylhydrazyl (used to measure free radical scavenging/antioxidant activity);
hPDLSCs: Healthy periodontal stem cells;
HSC-3: Human tongue squamous carcinoma;
IL-6 / IL-15: Interleukin-6 / Interleukin-15 (pro-inflammatory cytokines);
MBC: Minimum bactericidal concentration;
MIC: Minimum inhibitory concentration;
MMP-2 / MMP-9: Matrix metalloproteinases;
NF-κB/NLRP3: Nuclear factor kappa B / NLR family pyrin domain containing 3 (cellular signaling pathway);
OSCC: Oral squamous cell carcinoma.

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