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Research Progress on the Mechanism of Action of Traditional Chinese Medicine Extracts in the Prevention and Treatment of Periodontitis

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Abstract: Periodontitis is an inflammatory infectious disease affecting the periodontal supporting tissues and is the primary cause of tooth loosening and tooth loss in adults. Clinically, supragingival scaling, subgingival scaling, root planing, and other basic periodontal treatments, often combined with antibiotic therapy, are commonly employed with moderate efficacy. However, the increasing prevalence of antibiotic resistance and associated adverse reactions has become a growing concern. Recent studies have demonstrated the significant impact of traditional Chinese medicine (TCM) extracts in both the prevention and treatment of periodontitis, exhibiting remarkable effectiveness. This review explores the role and mechanisms of TCM extracts in the prevention and treatment of periodontitis, providing a reference for further elucidation of their mechanisms and a theoretical basis for the development of Chinese herbal medicine-based care products.

Keywords: Traditional Chinese medicine extracts; Prevention and treatment of periodontitis; Mechanism of action

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1. Introduction

Periodontitis is a multifactorial and complex disease resulting from an imbalance between pathogenic microorganisms in dental plaque and the host immune system [1]. The primary clinical manifestations of periodontitis include gingival redness, swelling, bleeding, formation of periodontal pockets, alveolar bone resorption, and tooth mobility. In severe cases, these symptoms can lead to tooth loss, making periodontitis a leading cause of impaired chewing function in adults [2].

Standard treatment for periodontitis typically involves a combination of basic periodontal therapies and drug interventions. However, as a chronic inflammatory condition, prolonged use of pharmacological treatments can result in adverse effects such as bacterial resistance, gastrointestinal discomfort, allergic reactions, and potential

damage to liver and kidney functions [3].

In recent years, traditional Chinese medicine (TCM) has gained considerable attention for its role in the prevention and treatment of periodontitis. Compared to antibiotics, TCM offers antibacterial, anti-inflammatory, and immune-regulatory properties, which can help reduce the recurrence and complications associated with periodontal diseases [4]. Advances in the isolation, purification, and analysis of active components in TCM have enabled the identification and pharmacological evaluation of these components. Numerous studies have confirmed the significant efficacy of various TCM extracts in the prevention and treatment of periodontitis [5].

This review summarizes the effects and mechanisms of TCM extracts in the prevention and treatment of periodontitis, providing a foundation for further research into the mechanisms of TCM in managing periodontitis and a theoretical basis for the development of herbal-based care products.

2. Research on the effects and mechanisms of traditional Chinese medicine extracts in the prevention and treatment of periodontitis

2.1. Flavonoids

2.1.1. Rhodiola rosea flavonoids

Rhodiola rosea flavonoids have been shown to reduce the gingival index (GI) and sulcus bleeding index (SBI), downregulate the expression levels of interleukin-6 (IL-6), interleukin-18 (IL-18), matrix metalloproteinase-2 (MMP-2), and matrix metalloproteinase-9 (MMP-9) in the serum of rats with periodontitis, thereby alleviating periodontal inflammation [6,7].

2.1.2. Naringin

Naringin inhibits autophagy in mouse embryonic osteoblast precursor cells (MC3T3-E1) mediated by the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, promotes osteogenic differentiation and mineralization, and alleviates periodontitis [8]. Additionally, naringin upregulates the expression of lncRNA MEG3 in periodontitis-derived periodontal ligament stem cells (PDLSCs), inhibits the Wnt/β-catenin pathway, and promotes osteogenic differentiation [9].

2.1.3. Icariin (ICA)

ICA activates the EphB4-EphrinB2 signaling pathway, promoting the osteogenic differentiation of MC3T3-E1 cells [10].

2.1.4. Isoliquiritigenin (ISL)

ISL inhibits the nuclear factor-κB (NF-κB)/NLR family pyrin domain containing 3 (NLRP3)/gasdermin D (GSDMD) pathway, reduces Pg-LPS/ATP-induced pyroptosis in human gingival fibroblasts (hGFs), and alleviates periodontitis [11].

2.1.5. Puerarin

Puerarin exhibits anti-periodontitis effects by reducing alveolar bone resorption and inhibiting the differentiation of mouse monocyte macrophage leukemia cells (RAW264.7) into osteoclasts. It suppresses p38 MAPK phosphorylation and alleviates periodontal inflammation [12]. Furthermore, puerarin inhibits the interleukin-23/

helper T cell 17 (Th17) inflammatory axis and upregulates osteoprotegerin (OPG) expression, reducing alveolar bone resorption [13]. It also promotes the proliferation of new osteoblasts, mitigates periodontal inflammation in rats with periodontitis, and inhibits alveolar bone resorption [14]. Additionally, puerarin downregulates the Notch signaling pathway, preventing the differentiation of RAW264.7 cells into osteoclasts [15].

2.1.6. Eriodictyol

Eriodictyol reduces inflammation in rats with periodontitis and promotes the osteogenic differentiation of human periodontal ligament stem cells (hPDLSCs) by activating the Yes-associated protein (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ) signaling pathway [16].

2.1.7. Soy isoflavones (SIF)

Soy isoflavones alleviate periodontal inflammation and inhibit alveolar bone resorption. They suppress the Slit homolog 2 (Slit2)/ p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway, thereby reducing alveolar bone resorption and periodontal inflammation in rats with periodontitis [17]. Genistein (GEN), a major subclass of soy isoflavones, also inhibits alveolar bone resorption and alleviates periodontal inflammation [18,19].

2.1.8. Hyperoside (Hyp)

Hyperoside inhibits the Toll-like receptor 4 (TLR4)/myeloid differentiation factor 88 (MyD88)/NF-κB pathway, reduces the number of osteoclasts in periodontal tissues, and suppresses the periodontitis response in rats [20].

2.1.9. Baicalin

Baicalin possesses antibacterial properties, promotes immunity, alleviates alveolar bone resorption, and inhibits periodontitis. Gong *et al.* [21] found that baicalin inhibits *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans*. It reduces the number of osteoclasts in periodontal tissues, prevents alveolar bone resorption, and counters systemic inflammatory responses. Further research indicates that baicalin downregulates the mTOR signaling pathway, inhibits macrophage polarization to M1, and promotes immune responses, thereby mitigating periodontitis in mice [22]. In periodontal ligament cells (PDLCs) induced by interleukin-1β (IL-1β), human oral keratinocytes (HOKs), and hPDLSCs, baicalin suppresses matrix metalloproteinase-1 (MMP-1)/tissue inhibitor of metalloproteinase 1 (TIMP-1), negatively regulates TLR signaling, inhibits the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway, promotes cell proliferation and migration, reduces apoptosis, and alleviates periodontal inflammation [23]. Clinically, baicalin combined with metronidazole is effective in treating periodontitis of the stomach-fire and kidney-deficiency type, reducing oxidative stress and improving periodontal conditions [24].

2.1.11. Luteolin

Luteolin blocks the NF-κB and NLRP3/IL-1β signaling pathways in gingival tissues of rats with periodontitis, thereby preventing periodontal tissue destruction and promoting alveolar bone remodeling [25].

2.1.12. Astragalus extract

Astragalus extract contains total flavonoids from astragalus (TFA) and astragaloside IV (AS-IV). The combination of TFA and gingival mesenchymal stem cells (GMSCs) effectively treats periodontal inflammation [26]. AS-IV

inhibits the TLR4/MyD88/NF-κB pathway and promotes periodontal tissue remodeling in rats with periodontitis [27].

2.1.13. Quercetin (Quer)

Quercetin promotes osteogenesis, inhibits alveolar bone resorption, and reduces periodontal inflammation. In a cigarette smoke-related periodontitis (CSRP) model of human periodontal ligament cells (hPDLCs) induced by cigarette smoke extract (CSE) and lipopolysaccharide (LPS), quercetin enhances the expression of alkaline phosphatase (ALP), runt-related transcription factor 2 (RUNX2), and collagen type I (COL1), promoting osteogenesis [28]. Additionally, quercetin inhibits the JAK/STAT pathway, promotes hPDLF migration, and alleviates smoking-related periodontal lesions [29]. It further alleviates alveolar bone resorption and reduces periodontal inflammation through the Nrf2, NF-κB/NLRP3, and microRNA-21a-5p/PDCD4/NF-κB pathways [30]. In rats with diabetic periodontitis, quercetin liposomes lower blood glucose levels, reduce advanced glycation end products (AGEs), and alleviate periodontal inflammation and alveolar bone resorption [31].

2.1.14. Kaempferol

Kaempferol reduces the levels of phosphorylated extracellular signal-regulated kinase (p-ERK), phosphorylated p38 MAPK (p-p38), and phosphorylated c-Jun N-terminal kinase (p-JNK) in the MAPK signaling pathway, thus inhibiting periodontitis and osteoclast formation, differentiation, and proliferation [32].

2.1.15. Nobiletin

Nobiletin significantly inhibits periodontal inflammation by blocking the chemokine CCL2/CCR2 signaling axis, reducing inflammatory damage in rats with periodontitis [33,34].

2.2. Polyphenols

2.2.1. Proanthocyanidins (PA)

Proanthocyanidins (PA) are natural pigments widely present in plants, with the highest concentration found in grape seeds [35]. Grape seed proanthocyanidin extract (GSPE) inhibits the TLR4/NF-κB signaling pathway, thereby alleviating periodontal inflammation in rats with diabetic periodontitis [36]. Additionally, PA restores lysine lactylation in periodontal ligament stem cells (PDLSCs) under inflammatory conditions and promotes their osteogenesis through the Wnt/β-catenin pathway [37].

2.2.2. Protocatechuic acid

Protocatechuic acid, the primary metabolite of anthocyanins, upregulates silent information regulator 1 (SIRT1), inhibits the thioredoxin-interacting protein (TXNIP)-NLRP3 axis, and alleviates inflammatory damage in human periodontal ligament fibroblasts (hPDLFs) induced by LPS [38].

2.2.3. Ellagic acid

Ellagic acid reduces the adhesion ability of *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, thereby exhibiting antibacterial effects [39]. Moreover, ellagic acid downregulates the expression of IL-6, C-reactive protein (CRP), and vascular endothelial growth factor-A (VEGF-A), while upregulating interleukin-10 (IL-10), thus inhibiting periodontal inflammation and reducing alveolar bone resorption [40].

2.2.4. Curcumin (Cur)

Curcumin (Cur) induces the expression of early growth response factor 1 (EGR1), activates the Wnt/β-catenin signaling pathway, and promotes osteogenic differentiation in hPDLSCs, as well as the proliferation and osteogenesis of PDLSC-extracellular vesicles (EVs) [41]. In rats with periodontitis, Cur regulates the solute carrier family 7 member 11 (SLC7A11)/glutathione peroxidase 4 (GPX4) axis, increases antioxidant glutathione (GSH) levels, inhibits ferroptosis, and mitigates periodontal inflammation [42]. Furthermore, in hGFs and hPDLSCs induced by LPS, Cur inhibits the NF-κB pathway, suppresses cyclooxygenase-2 (COX-2) expression, and alleviates periodontal inflammation [43].

2.2.5. Farrerol

Farrerol suppresses the mTOR/STAT3 signaling pathway, reduces the distance between the cementoenamel junction (CEJ) and alveolar bone crest (ABC), decreases levels of IL-1β, IL-6, and tumor necrosis factor-α (TNF-α), and alleviates periodontal inflammation and alveolar bone resorption in rats with periodontitis [44].

2.2.6. Resveratrol (RSV)

Resveratrol (RSV) exhibits anti-inflammatory properties, promotes osteogenesis, and suppresses alveolar bone resorption. Pterostilbene (4'-MR), a derivative of RSV, inhibits the NF-κB pathway, reduces inflammation in hGFs induced by LPS under high-glucose culture conditions, and alleviates periodontal inflammation in rats with diabetic periodontitis [45]. RSV also activates the SLC7A11/GPX4 pathway, downregulates the NF-κB pathway, inhibits ferroptosis in osteocytes, and mitigates diabetic periodontitis [46]. In hGFs induced by LPS, RSV inhibits the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway and alleviates the periodontal inflammatory response [47]. Additionally, RSV activates the extracellular signal-regulated kinase (ERK)/Wnt/β-catenin signaling pathway, induces apoptosis of activated T cells, modulates immune responses, and alleviates periodontal inflammation [48]. Both *in vivo* and *in vitro* studies have demonstrated that RSV activates the nuclear factor-E2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway, inhibits the NF-κB pathway, reduces inflammation in hPDLSCs induced by LPS, promotes osteogenesis, and mitigates alveolar bone resorption in rats with periodontitis [49]. Moreover, RSV suppresses the osteoprotegerin (OPG)/receptor activator of nuclear factor-κB ligand (RANKL)/receptor activator of nuclear factor-κB (RANK) signaling pathway in periodontal tissues, reducing alveolar bone resorption [50].

2.2.7. Pomegranate peel polyphenols

Pomegranate peel polyphenols reduce gingival bleeding and the risk of periodontal disease progression [51]. Punicalagin, a bioactive compound found in pomegranate peel polyphenols, inhibits the growth and adhesion of *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, thereby alleviating periodontal inflammation [52].

2.3. Polysaccharides

2.3.1. Lycium barbarum glycopeptide

Lycium barbarum glycopeptide enhances the phosphorylation of ERK, thereby promoting osteogenic repair and regeneration in rats with periodontitis [53].

2.3.2. Morinda officinalis polysaccharide

Morinda officinalis polysaccharide upregulates SIRT1, reduces the expression and acetylation of NLRP3,

and inhibits periodontal inflammation in hPDLFs stimulated by LPS [54]. Furthermore, *Morinda officinalis* polysaccharide suppresses the expression of fibronectin (FN) and fibronectin-containing extra domain A (FN-EDA) in hPDLFs, thereby alleviating periodontal inflammation [55].

2.4. Glycosides

2.4.1. Ginsenosides

Ginsenosides exhibit antibacterial effects, inhibit biofilm formation, suppress periodontal inflammation and alveolar bone resorption, promote osteogenesis, and reduce osteoclast formation. Ginsenoside Rd (GSRd) inhibits the growth, virulence, and biofilm formation of *Porphyromonas gingivalis*, reduces osteoclast formation, and thereby mitigates the pathogenicity of periodontal bacteria, periodontal inflammation, and bone resorption [56]. Ginsenosides (Re, Ra8, and Rf) bind to the epidermal growth factor receptor (EGFR), enhance the expression of HO-1, promote the osteogenic differentiation of periodontal ligament cells (PDLCs), and inhibit alveolar bone resorption and periodontal inflammation [57]. Furthermore, ginsenoside Rg1 promotes the phosphorylation of AMP-activated protein kinase (AMPK), inhibits the dynamin-related protein 1 (Drp1)/NLRP3 signaling pathway, downregulates the expression of Caspase-1 and gasdermin D N-terminal fragment (GSDMD-NT), and alleviates pyroptosis and inflammatory injury [58]. Ginsenoside Rb3 suppresses the ERK/NF-κB, mitogen-activated protein kinase (MAPK)/AKT/NF-κB, and STAT3 signaling pathways, reduces osteoclast formation, alleviates gingivitis and alveolar bone resorption, and inhibits periodontal inflammation [59]. Additionally, ginsenoside Rg6 exhibits antibacterial activity against *Porphyromonas gingivalis*. Rg6 also reduces the expression of IL-6, TNF-α, IL-1β, and monocyte chemoattractant protein-1 (MCP-1) in hPDLCs induced by Pg-LPS. Simultaneously, it increases the expression of catalase (CAT), superoxide dismutase (SOD), alkaline phosphatase (ALP), and osteocalcin (OCN), thereby exhibiting anti-periodontitis, antioxidative, and osteogenic effects [60].

2.4.2. Salidroside

Salidroside and *Scrophularia ningpoensis* exhibit significant inhibitory effects on the biofilm formation of *Porphyromonas gingivalis* and *Fusobacterium nucleatum* and demonstrate bactericidal activity [61].

2.5. Terpenoids

2.5.1. Ursolic acid

Ursolic acid activates the AMPK/SIRT1 signaling pathway, reduces alveolar bone resorption, and promotes the repair and reconstruction of alveolar bone [62].

2.5.2. Carvacrol

Carvacrol hydrogel significantly reduces alveolar bone resorption and improves periodontal inflammation [63].

2.5.3. Isodon excisa

A decoction of *Isodon excisa* inhibits the release of IL-1β, IL-6, and TNF-α in the gingival tissues and serum of rats with periodontitis, alleviating periodontal inflammation and tissue destruction [64].

2.5.4. Genipin

Genipin increases the expression of Nrf2 and HO-1 in hPDLCs, alleviates oxidative stress, and reduces damage to

periodontal tissues in rats with periodontitis [65].

2.5.5. Glycyrrhizin

Glycyrrhizin mitigates periodontal inflammation by activating liver X receptor alpha (LXRα) and inhibiting the COX-2/NF-κB pathway [66].

2.6. Alkaloids

2.6.1. Berberine (BBR)

Berberine hydrochloride exhibits antibacterial activity, inhibits periodontal inflammation, promotes osteogenesis, and alleviates alveolar bone resorption. BBR significantly suppresses the occurrence and development of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and periodontitis [67]. In rats with periodontitis associated with type 2 diabetes mellitus (T2DM), BBR demonstrates therapeutic effects by blocking the NF-κB pathway and inhibiting M1 polarization of macrophages [68]. Additionally, BBR binds to the EGFR on the cell membranes of hPDLSCs, mediating and activating the extracellular signal-regulated kinase (ERK)-FOS pathway, thereby promoting osteogenesis [5]. BBR-loaded hydrogel facilitates the phosphorylation of PI3K/AKT, contributing to anti-periodontal inflammation and osteogenesis [69]. Furthermore, BBR enhances the expression of G protein-coupled receptor 30 (GPR30) and blocks the p38 MAPK/NF-κB signaling pathway, thereby inhibiting alveolar bone resorption and periodontal inflammation, ultimately contributing to the treatment of periodontitis in rats [70].

2.6.2. Emodin

Emodin inhibits the NLRP3 inflammasome and upregulates microRNA-218 expression, thus suppressing periodontal inflammation and bone resorption in rats [71]. In clinical applications, emodin effectively treats moderate to severe chronic periodontitis by downregulating NF-κB and suppressing the expression of IL-1β, IL-4, and IL-6 [72].

2.7. Other compounds

2.7.1. Forsythin

Forsythin inhibits the phosphorylation of p38 MAPK, alleviating periodontal inflammation and osteoclast activation, and improving periodontitis symptoms [73].

2.7.2. Moringa oleifera leaf extract

Moringa oleifera leaf extract suppresses periodontal inflammation and alveolar bone resorption. It inhibits the phosphorylation of p38α/mitogen-activated protein kinase 14 (MAPK14) and enhances the expression of osteoprotegerin (OPG)/receptor activator of nuclear factor-κB ligand (RANKL), interleukin-1 receptor antagonist (IL-1Ra), and IL-10, thereby inhibiting periodontitis [74]. Cryptochlorogenic acid and orientin, constituents of *Moringa oleifera* leaf extract, exhibit specific effects. Cryptochlorogenic acid inhibits the p38 MAPK signaling pathway, resulting in anti-inflammatory and anti-bone-resorption effects [75]. Furthermore, it blocks the NF-κB/Jumonji domain-containing protein 3 (JMJD3) signaling axis, inhibits M1 polarization of macrophages, promotes cell survival, and suppresses periodontal inflammation [76]. Orientin reduces the expression of autophagy protein LC3-II, thereby inhibiting periodontal inflammation and alveolar bone resorption through autophagy modulation [77].

2.7.3. Tripterygium wilfordii polyglycoside

Tripterygium wilfordii polyglycoside decreases the sulcus bleeding index (SBI), periodontal probing depth (PD), and clinical attachment loss (CAL) while alleviating periodontal inflammation and alveolar bone resorption [78].

2.7.4. Eupatol

Eupatol inhibits the growth of *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, blocks activation of the NF-κB signaling pathway, and suppresses the secretion of TNF-α, IL-1β, and prostaglandin E2 (PGE2) in hGFs induced by LPS, thereby reducing periodontal inflammation [79].

2.7.5. Allicin

Allicin inhibits the TLR4/MyD88 signaling pathway and reduces the levels of fasting plasma glucose (FPG), IL-6, and TNF-α, thereby mitigating periodontal inflammation in obese rats with periodontitis [80].

2.7.6. Cannabidiol (CBD)

CBD inhibits the TLR4/NF-κB pathway, thereby alleviating periodontal inflammation in rats and hPDLCs induced by LPS [81]. CBD also reduces CAL, lowers tissue inflammation, inhibits the growth of *Porphyromonas gingivalis*, and demonstrates significant therapeutic effects on experimental periodontitis in mice. Moreover, CBD promotes the proliferation and migration of hGFs under inflammatory conditions and suppresses periodontal inflammation [82].

3. Conclusion

Periodontitis is a chronic, progressive disease resulting from an imbalance in oral microecology. Its pathogenesis centers on the interaction between periodontal pathogenic bacteria and the host immune system, leading to the destruction of periodontal supporting tissues and, in severe cases, tooth loosening and loss [1,2]. Clinically, basic periodontal treatment is commonly employed, often combined with antibiotics to significantly alleviate the symptoms of periodontitis [4].

In recent years, the understanding of TCM has advanced significantly, with numerous studies demonstrating its unique advantages in the prevention and treatment of periodontitis. This review highlights that TCM extracts, including flavonoids, polyphenols, polysaccharides, glycosides, naphthoquinones, terpenes, alkaloids, and other compounds, exert therapeutic effects through pathways such as MAPK (ERK, ERK1/2, p38, JNK), mTOR, Wnt/β-catenin, SLC7A11/GPX4, NF-κB, EphB4-EphrinB2, YAP/TAZ, Slit2/p38MAPK, JAK2/STAT3, CCL2/CCR2, SIRT1/TXNIP/NLRP3, AMPK/Drp1/NLRP3, and Nrf2/HO-1. These compounds inhibit autophagy and ferroptosis, promote cell proliferation, and reduce oxidative stress. As a result, they suppress the growth of periodontal pathogenic bacteria, mitigate periodontal inflammation and alveolar bone resorption, promote the repair and reconstruction of alveolar bone, enhance periodontal tissue regeneration, and modulate the host immune response.

Nevertheless, the clinical application of TCM extracts warrants further research and validation. With the growing understanding of the molecular mechanisms underlying the effects of TCM in the prevention and treatment of periodontitis, the influence of TCM active ingredients on specific targets and intracellular effector factors will provide a solid theoretical foundation for their broader application in managing periodontitis.

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Disclosure statement

The authors declare no conflict of interest.

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