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New advances in natural medicine assisted treatment of periodontal disease

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Abstract: *Chronic periodontitis is a chronic infectious disease that causes the loss of teeth in adults in China. Treatment for it mainly includes periodontal scaling, scraping, periodontal surgery, and local or systemic antibiotics. This article therefore reviews the different natural remedies used in the treatment of periodontitis, which has antibacterial, antiviral and immunomodulatory effects. This article therefore reviews the different natural remedies used in the treatment of periodontitis.*

Keywords: *chronic periodontitis, natural medicine, antibacterial*

1. Introduction

Chronic Periodontitis (CP) is a chronic infectious disease and the leading cause of tooth loss in our adult population, CP affects 10-15% of the world's population and is caused by bacterial inflammation in the gum pockets that can destroy the tissues around the teeth[1]. Treatment therefore aims to prevent further progression of the disease, with the aim of reducing the risk of tooth loss, minimizing the symptoms and sensation of the disease and possibly restoring lost periodontal tissue[2]. The current clinical treatment of periodontal disease consists of basic treatment, supplemented by local treatment with drugs and post-treatment prevention and treatment. In the adjunctive treatment of periodontitis, chlorhexidine and antibiotics can control plaque and gingivitis, but it can imbalance the oral flora. The development of multidrug-resistant pathogens and the need for economical, safe and effective products has led to the development of plant-derived alternative oral care products. Natural medicines have recently attracted increasing interest. There is a growing public interest in natural or herbal health care products, especially for patients with chronic diseases[3]. Natural products including Acacia arabica, aloe vera, neem, turmeric, lemongrass, camellia and comfrey have antibacterial, anti-inflammatory, antiseptic and antifungal properties and may promote wound healing[4]. Therefore, this paper provides a review of topical therapeutic agents for periodontitis.

2. Chronic periodontitis pathogenic factors

Periodontal disease is a chronic inflammatory disease in which plaque biofilm is the initiating factor. As the disease progresses, periodontal tissues are gradually destroyed, resorption of alveolar bone occurs, and clinical symptoms such as bleeding and recession of the gums, loosening and even loss of teeth occur. It is due to the exposure of the host periodontal tissue to a microbiota that adheres to the teeth in the form of biofilm-long known as plaque. The bacteria (and possibly other microorganisms such as viruses, fungi and parasites) interact with each other and with the host. The development of periodontitis is accompanied by a dramatic change in the composition of the subgingival flora, and in most cases a different gram-negative flora emerges than the one enriched during gingivitis. Among the enriched flora are the classically described red complexes, including Fosetanella (formerly known as Fosetylomycetes), Porphyromonas gingivalis, and the dense spirochete of dental tartar[5]. Over time, the resulting dysregulated microbiota, combined with dysregulated host inflammation, promotes the growth of specific microorganisms within the biofilm, producing substances that exacerbate inflammation and, in some patients, lead to tissue destruction and tooth loss.

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3. Antibiotic drugs to assist in the treatment of periodontitis

In severe chronic periodontitis, recent randomized clinical trials[6,7] and a systematic review and Meta-analysis[8,9] reported significant improvements in scaling and root planing outcomes when antibiotics were administered systemically or topically as an adjunctive therapy. In a recent systematic evaluation of a total of 28 double-blind randomized controlled trials investigating the benefit of systemic antibiotics as an adjunctive therapy to scaling and root planing in the treatment of moderate to severe periodontitis, this Meta-analysis reported a statistically significant reduction in mean full-mouth probing depth of 0.448 mm and a statistically significant increase in attachment level of 0.389 mm in the antibiotic control group at 6-month follow-up. This improvement appeared to persist at the 12-month follow-up (i.e., a 0.485-mm decrease in probing depth and a 0.285-mm increase in attachment level). These improvements were further supported by a reduction in probing bleeding and a reduction in periodontal pocket depth. Amoxicillin and metronidazole had the most dramatic improvements[10]. For localized sites with deep periodontal pockets, administration of topically delivered antibiotics (i.e., minocycline microspheres[11,12]) or antimicrobial medications (i.e., chlorhexidine chips[13,14]) may be considered. However, they also have adverse effects such as staining of the teeth or mucosa, cytotoxicity, and can imbalance the normal oral flora with long-term use, so they should not be used for long periods of time either.

4. Probiotics and vaccines to assist in the treatment of periodontitis

Probiotics have recently received a lot of attention as a potential method of preventing periodontitis. Probiotics are defined by the Food and Agriculture Organization/World Health Organization as "living microorganisms" that confer health benefits to their hosts. Many mechanisms have been proposed to explain the benefits of probiotics. Probiotics can reverse inflammation-induced epithelial damage by stimulating the upregulation of structural proteins. These probiotics may also colonize and proliferate to deprive pathogenic bacteria of nutrients and thus inhibit their growth. Probiotics may also produce antimicrobial products that inhibit Gram-negative bacteria, such as acetic acid and lactic acid. In addition, probiotics may influence the host to downregulate pathways that may damage host tissues while upregulating other pathways that inhibit the growth or virulence of pathogens[15-17] . Another type of periodontitis that is thought to be preventable is the development of vaccines. Vaccines have long been used in medicine as an effective public health intervention to prevent disease. Periodontal vaccines are a topic of research from the 1970s and are a proposed method of preventing periodontitis based on its multiple microbial etiology. Several research groups have reported a periodontal vaccine under development that targets antigens of specific oral gram-negative anaerobic pathogens[15] .

5. Natural medicine to assist in the treatment of periodontitis

The relationship between herbal medicine and oral microecology has become a hot research topic in recent years, where herbal medicine, as a natural agent with low side effects and wide sources, has shown good efficacy in the management of oral diseases such as caries, periodontal disease, oral mucosal disease and even oral tumors [18]. A systematic evaluation assessed the effectiveness of herbal oral care products in reducing plaque and gingivitis, and the use of adjunctive plant-derived active ingredients in the management of patients with periodontitis can be an alternative to chemicals because of their significant benefits in clinical outcomes and lack of associated side effects, and can be recommended as an alternative[19]. The main natural drugs that are currently used in periodontal disease treatment studies are comfrey, honeysuckle, pentaphyllum, propolis, bitter ginseng, and red peony.

5.1 Lithospermum

The Xinjiang native herb soft comfrey, the best quality among comfrey, contains the fat-soluble naphthoquinone component comfreyin and its derivatives as its main active ingredients to exert anti-inflammatory effects[20]. As a traditional Chinese herb, comfrey has anti-inflammatory activity and its main constituent comfreyin inhibits the expression of pro-inflammatory mediators in the ischemic cortex, comfreyin inhibits IL-6β- or TNF-α-stimulated production of IL-8, IL-20 and CCL1 in HPDLC [21]. Meanwhile, comfrey has antibacterial, antiviral and immunomodulatory effects[22], comfreyin can down-regulate the expression level of Toll-like receptor 4 stimulated by lipopolysaccharide, inhibit the secretion of IL-1β, IL-6 and TNF-α, and promote the secretion of IL-10. Treatment with comfrey polysaccharide inhibited the expression of TNF-α, IL-18 and other related inflammatory factors expressed by LPS-activated PBMC, possibly by suppressing the MAPK signaling pathway of PBMC

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and thus the high expression of LPS-induced inflammatory factors such as TNF-α[23]. Huang et al. reported that comfreyin treatment inhibited ERK phosphorylation while activating p38 in human lens epithelial cells MAPK and JNK phosphorylation in human lens epithelial cells [24] and in addition, Chen et al. found that Shikonin activated the p145 MAPK, ERK and JNK pathways in prostate cancer cells (PC-38 and DU3 cells)[25]. Wang Li et al. found that shikonin can promote osteoblast expression of OPG through the OPG/RANKL signaling axis, directly promoting osteoblast osteogenic differentiation and indirectly inhibiting osteoclast differentiation to inhibit bone resorption and promote bone formation[26].

5.2 Honeysuckle

Honeysuckle is sweet in taste and cold in nature, and chlorogenic and isochlorogenic acids are its important antibacterial components. Honeysuckle has the effect of clearing heat and detoxifying, cooling wind and heat, and has a long-term inhibitory effect on many bacteria such as Gram-positive bacteria, Gram-negative bacteria and spirochetes, which can directly destroy toxins in the body. In an animal study, for the treatment of periodontitis, mechanical plaque control is still the preferred option, and the use of compound honeysuckle herbal mouthwash can achieve better results. The compound honeysuckle herbal mouthwash had no acute toxic effects on rats in the short term and had a significant reduction in inflammation in experimental periodontitis in rats[27].

5.3 Pentaphyllum

It is bitter, sour, flat and non-toxic. Pharmacological research shows that the main component in rhubarb is rhubarb anthraquinone derivative, which has antibacterial, anti-swelling and analgesic effects[28], and its antibacterial effect is achieved through the inhibition of bacterial nucleic acid respiratory process and biosynthesis. Pentaphyllum is known to be antibacterial, detoxifying, astringent, precipitates coagulated proteins, and inhibits bacterial biofilm formation[29]. To date, several studies have demonstrated the clinical effects of AE on periodontitis. In an animal study, YANG et al. found that Porphyromonas gingivalis induced periodontitis in rats with significantly lower alveolar bone resorption levels and periodontal pocket depth after periodontitis. amCase protein expression was significantly higher in the disease group than in healthy controls. However, rhodopsin inhibited periodontal inflammation by down-regulating AMCase expression in saliva and periodontal pocket tissue. Rhodopsin significantly reduced RANKL-stimulated osteoclast formation by regulating AMCase [30-31].

5.4 Propolis

Propolis, also known as propolis, is a dark, dense and viscous combination of resins and waxes composed of active natural ingredients such as volatile oils, plant balsam, phenolic acids, flavonoids, aromatic alcohols, fatty acids, mineral salts and vitamins. It is collected by bees from trees, buds, flowers and other plant products. Propolis has been shown to have antibacterial, anti-inflammatory, antioxidant, antiviral, antifungal, antitumor and hepatoprotective properties [32]. A study by Bhat et al. showed the role of propolis in reducing dental biofilm accumulation. Among 30 healthy students divided into 3 groups, the Forever Bright (propolis-containing) dental gel group had the lowest mean modified gingival marginal plaque index (MGMPI) score, which was significantly different from the other 2 groups. This double-blind randomized study showed that propolis-containing tooth gel or toothpaste was able to reduce the rate of biofilm accumulation.

5.5 Bitter ginseng

The active ingredients of bitter ginseng, bittersweetine and oxymatrine, were approved for hepatoprotective and immunomodulatory use in China more than 30 years ago. Numerous studies have found that bitter ginseng bases and oxymatrine have a wide range of biological activities[33-34], such as antibacterial, antiviral, antioxidant, anti-inflammatory, antitumor, and cardioprotective, hepatic, pulmonary, and vascular effects. Among them, studies on antitumor, antibacterial, antiviral, immunomodulatory, cytoprotective and antifibrotic effects have also been extended to the treatment of dentistry patients. According to Chen Ling et al.[35], rats were pre-divided into blank group, control group, and experimental group and intervened with oxymatrine, and then executed after 6 weeks to examine the alveolar bone loss, and the results showed that the alveolar bone resorption of rats after oxymatrine intervention was less than that of the control group.

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5.6 Red peony

Red peony has the effect of clearing heat and cooling blood, dispersing blood stasis and relieving pain, and its extract has good antibacterial and anti-inflammatory effects[36]. Radix Paeoniae contains paeonol, which inhibits RANKL-induced activation of ERK, p38 and NF-κB in macrophages to inhibit osteoclastogenesis and ovariectomy-induced osteoporosis. In addition, Gong Yi et al. preliminarily described that the main components, targets of action and related pathways of Paeonia lactiflora have important research value in the prevention and treatment of CP[37].

6. Conclusions

Periodontal disease is defined as a multifactorial inflammatory disease characterized by destruction of the supporting tissues around the teeth (including periodontal ligaments, gums, and alveolar bone) and is a major cause of tooth loss if left untreated. Mechanical plaque removal has been shown to be ineffective in adult patients, and further measures are needed to establish good oral hygiene. In the general population, maintaining good plaque control with conventional products is difficult. Therefore, it is important to use adjunctive antiseptics to improve oral hygiene and further improve periodontal treatment response. The use of antiseptics is essential to assist periodontal treatment, especially when non-surgical periodontal treatment is inadequate. Chlorhexidine is considered the gold standard for periodontal antiseptic treatment and is widely used as an adjunctive antimicrobial agent for root surface leveling[38]. However, patient compliance is not ideal due to its disgusting taste and the staining it causes in teeth. Natural pharmaceutical products including mouthwashes, dental cleaners and gels have made advances in the past few years. The active ingredients in natural pharmaceutical oral products penetrate biofilms and prevent plaque buildup, thereby minimizing bacterial colonization of tooth surfaces. In addition, they have antimicrobial efficacy against caries and periodontal pathogens, while reducing the development of drug resistance due to their synergistic combination. Natural drug extracts also inhibit osteoclast differentiation as well as the expression of pro-inflammatory cytokines, thus inhibiting bone resorption in periodontitis. However, herbal medicines also have many drawbacks such as slow and short duration of action, long treatment period, and poorly defined therapeutic mechanisms.

There are fewer studies on the mechanisms by which herbal medicines regulate oral microorganisms and thus influence disease progression and treatment from a macroscopic perspective, and in-depth investigations of the downstream genes and products that influence them are still lacking. In addition, there are some microbial-related diseases in the oral cavity, such as oral cancer, oral mucosal disease, peri-implantitis, etc., but few studies have been conducted to correlate herbal medicine with these diseases by regulating oral microecological balance. Therefore, future directions can focus on herbal medicine to assist periodontitis prevention and treatment.

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