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Protective role of flavonoid baicalin from *Scutellaria baicalensis* in periodontal disease pathogenesis: A literature review

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ABSTRACT

Introduction: Periodontal disease is characterized by a chronic infection, leading to the irreversible destruction of tissues supporting the teeth. Bacteria, pro-inflammatory mediators and host immune response play important role in the progress of periodontal disease. Baicalin is a bioactive flavone extracted from the dry raw root of *Scutellaria baicalensis*, with pharmaceutical actions of anti-inflammation, anti-oxidants, anti-tumor, antivirus, and so on. The present review summarizes the efficacy of baicalin in periodontal treatment.

Methods: A computer-based literature search was carried out using Pubmed, Scopus and Web of Science to identify papers published until 2017. Keywords used in the search were “baicalin”/“baicalein” and various words related to periodontal disease (periodontal, periodontitis, periodontal tissue, gingival, gingivitis, gingival tissue, periodontal disease, gingival disease, gingiva, periodontium).

Results: A total of 28 original studies were found, including 3 bacteriological studies, 7 zoological studies and 18 cytological studies. 15 of them were published in English and 13 of them were published in Chinese. Results from these 28 studies could not be pooled to conduct meta-analysis due to the heterogeneity. The pharmacological properties and mechanisms of baicalin for treating periodontal disease is mainly focused on five aspects: antibacterial effect on putative periodontopathic bacteria, protective effect on periodontal tissues, regulatory effect on pro-inflammatory mediators and matrix metalloproteinases, and regulatory effect on innate immune response.

Conclusions: Baicalin have been shown to possess multiple pharmacological activities in periodontal tissues. However, the underlying mechanisms have not been fully defined. Further researches are needed to provide more scientific evidence for the clinical periodontal treatment.

1. Introduction

Periodontal disease is characterized by a chronic infection associated with bacteria in the dental biofilm. It causes the irreversible destruction of tissues supporting the teeth, with the clinical signs of alveolar bone loss and deepening periodontal pocket, progressively leading to loosening of teeth and ultimately to teeth loss [1]. Gingivitis and periodontitis are the two main clinical manifestations of periodontal disease. Gingivitis refers to the inflammation of gingiva caused by bacteria and periodontitis is a more advanced inflammation of periodontal disease, with the breakdown of periodontal tissues. Periodontal destruction may be caused by local factors directly, such as periodontopathic bacteria, or it may reveal an inadequate host immune response [2]. Dysregulation of innate immunity plays a key role in the progress of periodontal disease [3]. The host immune response could be suppressed upon the low-level stimulation of critical pattern recognition receptors (PRRs), leading to a local immune response, thus enabling periodontopathic bacteria to evade the host immune system [4,5]. Furthermore, host immunological cells activated by bacteria produce various pro-inflammatory mediators, eventually leading to tissues breakdown.

The classical and radical treatment for periodontal disease is removing the dental plaque and calculus from the teeth by mechanical debridement. However, the bacteria on tooth surface cannot be removed thoroughly by mechanical procedures due to the presence of the clinical inaccessible regions [6]. Therefore, antibiotics are prescribed as an adjunct to the mechanical debridement, in a way of local and/or systemic administration(s). Tetracycline, metronidazole, doxycycline, amoxicillin, azithromycin, clindamycin, chlorhexidine, spiramycin and certain combinations have been extensively investigated for use in

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periodontal therapy [7,8]. However, long-term administration of antibiotics carries the risk of promoting the development of bacterial antibiotic resistance. Other potential side effects of antibiotics, such as nausea, headache, diarrhea and so on, are annoying as well [9]. As an alternative medical therapy, medicinal herbs have drawn more and more attention in recent years due to its pharmacological activities in periodontal treatment with less side effects [10,11].

Scutellaria baicalensis (*S. baicalensis*), also named Huang-chin in Chinese, is a traditional Chinese herb officially used for purging fire, cleaning away heat, moistening aridity, detoxifying toxicosis, stoppage of bleeding and preventing miscarriage [12]. Six flavones are proven to be the major bioactive flavones in the dry raw root of *S. baicalensis*, existing in the forms of aglycones (baicalein, wogonin, oroxylin A) and glycosides (baicalin, wogonoside, oroxylin A-7-glucuronide) [13]. Among them, baicalin ($C_{21}H_{18}O_{11}$, 7-glucuronic acid, 5,6-dihydroxy flavone) is identified as the marker compound for quality control of the dry raw root of *S. baicalensis* [12]. Baicalein, the aglycone and metabolite of baicalin, is hydrolyzed from baicalin by intestinal microflora [14]. As a couple of active compounds, their pharmacological effects are always discussed together. Both baicalin and baicalein have been found to exhibit several pharmaceutical actions, such as anti-inflammation, antioxidants, anti-tumor, eye protection and antivirus [15–19]. These biological activities are mainly related to their antioxidant properties and their ability to inhibit enzymes and regulate the immune response and certain pro-inflammatory mediators.

The present review summarizes the efficacy of baicalin in periodontal treatment. A computer-based literature search was carried out using Pubmed, Scopus and Web of Science to identify papers published until 2017. Keywords used in the search were “baicalin”/“baicalein” and various words related to periodontal disease (periodontal, periodontitis, periodontal tissue, gingival, gingivitis, gingival tissue, periodontal disease, gingival disease, gingiva, periodontium). A total of 28 original studies (15 in English and 13 in Chinese) were found, including 3 bacteriological studies (Table 1), 7 zoological studies (Table 2) and 18 cytological studies (Table 3). The pharmacological properties and mechanisms of baicalin for treating periodontal disease is mainly focused on five aspects: antibacterial effect on putative periodontopathic bacteria, protective effect on periodontal tissues, regulatory effect on pro-inflammatory mediators and matrix metalloproteinases (MMPs), and regulatory effect on innate immune response.

2. Antibacterial effect of *S. baicalensis* solution

It is well-known that periodontal disease is a chronic infective disease of the periodontium which results from aberrant and exaggerated immune-inflammatory response to pathogenic plaque biofilms. Oral bacteria present in dental plaque play a pivotal role in initiation and progress of periodontal disease. Pathogenic bacteria activate host immunological cells, which produce various mediators and effectors of tissues breakdown. Therefore, anti-biofilm and anti-bacteria therapy is a keystone in periodontal disease control and treatment. Recent studies indicated that *S. baicalensis* has potent antibacterial effect on oral pathogens. Tsao et al. reported that decoction of Huang-chin had both bacteriostatic and bactericidal effect on selected oral bacteria, including *Streptococcus salivarius (S. salivarius)*, *Streptococcus sanguis (S. sanguis)*, *Bacteroides gingivalis (B. gingivalis)*, *Bacteroides melaninogenicus ss intermedius (B. mel. ss intermedius)*, *Capnocytophaga* OM 0502, *Capnocytophaga* 155, *Fusobacterium nucleatum (F. nucleatum)*, *Actinomyces naeslundii (A. naeslundii)*, *Actinomyces odontolyticus (A. odontolyticus)*, *Actinomyces viscosus (A. viscosus)* and *Actinobacillus actinomycetemcomitans (A. actinomycetemcomitans)*, with the minimum inhibitory concentration (MIC) being 2% and minimum bactericidal concentration (MBC) being 3.13%. Among these bacteria, *B. mel. ss intermedius* was the most sensitive and *A. viscosus* was the least sensitive to Huang-chin decoction. Meanwhile, the authors also found that, at higher concentration, Huang-chin was more effective against gram-negative than against gram-positive bacteria [20]. The result from another recent study indicated that combined use of nanoparticles encapsulated *S. baicalensis* and chlorhexidine at 9:1 (w/w) ration, which enable the containment and release of baicalin, had synergistic effect against mixed oral bacterial biofilms, such as *Streptococcus mutans (S. mutans)*, *F. nucleatum*, *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans)*, and *Porphyromonas gingivalis (P. gingivalis)*, with the MIC of 12.5 μg/ml [21]. Single component baicalin also showed a moderate bacteriostatic effect on *Prevotella nigrescens (P. nigrescens)* and *A. viscosus*, with the MIC being 0.313 mg/ml [22].

3. Protective effect of baicalin on periodontal tissues

Periodontal disease is characterized by periodontal degradation, such as the destruction of supporting connective tissue and bone loss. Results from animal studies demonstrate the protective effect of baicalin on periodontal tissue in periodontitis. Cai et al. found that baicalin could significantly reduce the amelocemental junction to alveolar crest height distance, and meanwhile, increase the area fraction of collagen fibers with a dosage of 200 mg/kg/day, in ligature-induced periodontitis in rats [23,24]. In another animal study, researchers found that treatment with 100 or 200 mg/kg/day baicalin mitigated the ligature

Table 1
Bacteriological studies on the effect of baicalin in periodontal disease pathogenesis.

Type of bacteria	Intervention	Results	Reference
S. sanguis, S. salivarius, A. viscosus, A. naeslundii, A. odontolyticus, Capnocytophaga, B. mel. ss intermedius, B. gingivalis, F. nucleatum, A. actinomycetemcomitans	Bacterial species were separately cultured and treated by Huang-chin decoction for 48 h.	1. Decoction of Huang-chin had both bacteriostatic and bactericidal effect on *S. salivarius, S. sanguis, B. gingivalls, B. mel. ss intermedius, Capnocytophga OM 0502, Capnocytophaga 155, F. nucleatum, A. naeslundii, A. odontolyticus, A. viscosus* and *A. actinomycetemcomitans* (MIC 2%, MBC 3.13%). 2. *B. mel. ss intermedius* was the most sensitive and *A. viscosus* was the least sensitive to Huang-chin decoction. 3. At higher concentration, Huang-chin was more effective against gram-negative than against gram-positive bacteria.	20
S. mutans, S. sobrinus, F. nucleatum, A. actinomycetemcomitans, E. faecalis, P. gingivalis	Mono/multi-species biofilms were treated by the mixed nanoparticles of *S. baicalensis* and chlorhexidine for 24 h and 48 h.	1. Mono-species biofilms of *S. mutans, S. sobrinus, F. nucleatum, A. actinomycetemcomitans* were inhibited at 24 h. (MIC 50 μg/ml) 2. Multi-species biofilms (*S. mutans, F. nucleatum, A. actinomycetemcomitans* and *P. gingivalis*) were inhibited at 24 h. (MIC 12.5 μg/ml)	21
A. actinomycete mitans, A. viscosus, P. gingivalis, F. necrophorum, A. naeslundii, P. nigrescens	Bacterial species were separately treated and cultured by baicalin for 96 h.	Bacteriostatic effect on *P. nigrescens* and *A. viscosus*. (MIC 0.313 mg/ml)	22