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Herbs as an antioxidant arsenal for periodontal diseases

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ABSTRACT

Herbal medicines have long been used as a traditional mode of therapy for various ailments in India. They are being used increasingly as dietary supplements to ward off common diseases. Periodontal diseases are highly prevalent and can affect up to 90% of the world population. Gingivitis is the mild form whereas periodontitis results in an irreversible loss of supporting structures of the teeth. Even though periodontal pathogens form a crucial component in the etiopathogenesis of periodontitis, there is a growing body of evidence suggesting oxidative stress playing a pivotal role in the disease initiation and progression. Studies have shown a direct correlation between increased levels of biomarkers for tissue damage induced by reactive oxygen species (ROS) to the severity of periodontal disease. Thus, the focus of attention has revolved back to herbal medicines due to their wide spectrum of biological and medicinal activities, lower costs, and higher safety margin. Internet databases Pubmed and Google Scholar were searched, and the most relevant articles were considered for review. This review briefly describes the various herbs with antioxidant capacity and their potency in the treating periodontal disease.

KEY WORDS: Antioxidant capacity, herbal medicine, periodontitis

INTRODUCTION

Herbal medicines, including herbs, herbal preparations and finished herbal products, contain as active ingredients parts of plants or other plant materials perceived to have therapeutic benefits [1]. About 80% of the worldwide population use herbal products for their basic health care (primary care) such as extracts, teas and other active principles, a market estimated at US$ 50 billion per year [2]. Herbal products are preferred over conventional drugs due to wide biological activity, higher safety margin, and lower costs. Furthermore, the conventional drugs are known to cause various side effects, and continuous intake has resulted in antibiotic resistance. Thus, herbal medicines are being used increasingly as dietary supplements to fight or prevent common diseases [3].

Periodontitis is a chronic inflammatory disease which results in the destruction of supporting structures of the teeth. The etiology is multifactorial with periodontopathogens forming a major crux in the initiation and progression of the disease. Plaque build-up allows the growth of anaerobic bacteria [4], which eventually leads to the recruitment and activation of neutrophils. This further results in the upregulation of pro-inflammatory cytokines and also leads to the release of neutrophilic enzymes and ROS. Prolonged exposure of the connective tissue to these insults results in the degradation and subsequent loss of ligamentous support and alveolar bone, eventually leading to tooth loss [5].

Periodontal therapy includes both surgical and nonsurgical management of the disease process. Various antimicrobials and chemotherapeutic agents, such as chlorhexidine, triclosan, cetylpyridinium chloride, have been tried and tested in the management of periodontal diseases. Due to its multifactorial etiology and complex disease process, the treatment of periodontitis is still a formidable task to dentists. Therefore, herbal remedies have been sought to achieve antimicrobial, antioxidant, antiseptic, anti-inflammatory, and anti-collagenase effects. The following review briefly describes the role of oxidative stress in periodontitis and the various herbs with antioxidant potential used in its management.

OXIDATIVE STRESS IN PERIODONTITIS

It is well-established that oxidative stress is an important cause of cell damage associated with the initiation and progression of many chronic diseases [6-8]. A recent review by Bullon describes the mounting evidence that the basis for the interrelationships between chronic periodontitis and atheromatous disease and diabetes lies at the fundamental intracellular level, namely oxidative stress and mitochondrial dysfunction [9]. Oxidative stress is the disturbance in the pro-oxidant and antioxidant balance, in favor of the former, resulting in potential tissue damage. Consecutive oxidation-reduction reactions of molecular oxygen by various enzymes results in the production of molecules such as superoxide anion, hydrogen peroxide, hydroxyl radical, singlet oxygen,

nitric oxide, hypochlorous acid which together constitute the term "ROS" [10]. All the cells in the body are capable of generating ROS, of which polymorphonuclear neutrophils are of prime importance with respect to periodontitis. Neutrophils are a part of innate immunity which comprise the first line of host defense and are located at sites of microbial invasion. They are activated by inflammatory mediators and can generate increased levels of ROS, which not only attack the periodontopathogens but also the surrounding tissues [11]. The ROS is generated by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox) system present in the neutrophils and it catalyzes the reduction of molecular oxygen to superoxide anion. Subsequent reductions result in the production of hydrogen peroxide and hydroxyl radical. Similarly, superoxide dismutase enzyme present in all the cells catalyzes the dismutation of superoxide radical to hydrogen peroxide. Many studies have shown that ROS regulate the formation and function of osteoclasts, i.e., the activation and bone resorption ability [12-14]. Bone resorption which results in alveolar bone loss and ultimately tooth loss is the hallmark feature of the periodontal disease. NADPH oxidase system plays a role in periodontal pathologies and its involvement is the strongest in aggressive periodontitis [15].

To combat the oxidative stress, all the cells in the body are equipped with an intrinsic store of molecules known as "antioxidants." Antioxidants may be regarded as "those substances which when present at low concentrations, compared to those of an oxidizable substrate, will significantly delay, or inhibit oxidation of that substrate" [16]. They function by scavenging free radicals as and when they form and thereby preventing oxidative stress. They can also sequester transition metal ions and prevent Fenton's reaction or catalyze the oxidation of other molecules. Various antioxidant molecules include vitamins C, E, coenzyme Q, carotenoids, enzymes such as glutathione reductase, glutathione transferase, superoxide dismutase, and peroxiredoxin.

Numerous studies have shown that the total antioxidant capacity in periodontitis patients is significantly lower when compared to healthy controls [17-19] or in subjects who have received periodontal therapy [20]. These findings have triggered the use of exogenous supplements for the treatment of periodontal disease. Herbal antioxidant remedies have been the focus of research in recent times. A literature search was performed using keywords such as "plant extracts," "herbs," "herbal medicine," "antioxidants," "oxidative stress" "periodontal disease" in PubMed, and Google Scholar. The most relevant articles were included in this review and it gives an overview about the potential of herbal medicine in the management of periodontitis.

GREEN TEA

Components

Green tea is made from the leaves of *Camellia sinensis* that have undergone minimal oxidation during processing. It contains the highest concentrations of antioxidants called polyphenols [21]. Polyphenols contained in teas are classified as catechins. There are six primary catechin compounds in green tea: Catechin, gallocatechin, epicatechin, epigallocatechin, epicatechin gallate (ECg), and epigallocatechin gallate (EGCg). EGCg has been the focus of extensive research among all the other compounds and it is a very potent antioxidant. Green tea also contains carotenoids, tocopherols, ascorbic acid, minerals such as zinc, selenium, chromium, and certain phytochemical compounds.

Role in Periodontitis

Green tea catechins have been observed to have profound effects on periodontal pathogens. Anaerobic bacteria like *Porphyromonas gingivalis* and *Prevotella* spp. are the main etiological agents in periodontitis. *In vitro* studies have shown that these compounds inhibit the growth of *P. gingivalis*, *Prevotella intermedia* and *Prevotella nigrescens* [22-24]. It also prevents the adherence of *P. gingivalis* onto human buccal epithelial cells [25]. A study also showed that both ECg and EGCg inhibited *P. gingivalis* derived collagenase activity [26].

Bone resorption which occurs in periodontitis is due to the interplay between osteoblasts and osteoclasts. In an animal study, it was shown that EGCg reduced lipopolysaccharide-mediated bone resorption in both *in-vivo* and *in-vitro* conditions. It also showed that EGCg suppressed LPS mediated gene expression such as RANKL, cyclooxygenase-1 and the cytokine PGE2 in mouse osteoblasts. This clearly suggests that the catechin present in green tea is highly potent in suppressing the bone resorption mediated by an inflammatory response as seen in periodontal disease [27].

There are various reports about the use of green tea in various forms in the management of periodontitis. Pilot studies on the usage of green tea as a dentifrice and a local drug delivery system have observed an improvement in the periodontal status of the patients suffering from chronic periodontitis [28,29]. A clinical trial indicated that green tea mouthwash had a comparable antiplaque efficacy to chlorhexidine gluconate (gold standard) when used for a period of 1 week [30]. These preliminary results show that further research is needed to explore and tap the benefits of green tea, and utilize it in the management of periodontal diseases.

TRIPHALA

Components

Triphala is a well-known powdered preparation in ayurvedic medicine used since ancient time. It consists of equal parts of Amalaki (*Emblica officinalis*), Haritaki (*Terminalia chebula*) and Bahera (*Terminalia belerica*). Amalaki is an excellent source of vitamin C and also contains carotene, nicotinic acid, D-glucose, D-fructose, riboflavin, empicol, and mucic and phyllemblic acids. Haritaki contains anthraquinone glycoside, chebulinic acid, tannic acid, terchebin, vitamin C, and arachidonic, linoleic, oleic, palmitic, and stearic acids. Bahera contains chebulagic acid, ellagic acid and its ethyl ester, gallic

acid, fructose, galactose, glucose, mannitol, and rhamnose. All the three components present in triphala have a wide range of pharmacological activity and are potent antioxidants.

Role in Periodontitis

Triphala has a strong antimicrobial, antioxidant and anti-collagenase properties. The antioxidants present in Triphala reduce the oxidative burden and protect cells from the damage caused by free radicals [31,32]. Bahera is the most active antioxidant followed by Amalaki and Haritaki. A clinical trial has shown that Triphala mouthwash is as efficacious as 0.2% chlorhexidine in antiplaque and anti-inflammatory activities [33].

The antibacterial effect has been assessed in an *in-vitro* study where Triphala concentrations of 50 μg/ml inhibited *Streptococcus mutans* species. This antiplaque effect may be attributable to tannic acid present in Triphala, which is well adsorbed on the surface of bacterial cells resulting in protein denaturation and ultimately to bacterial cell death [34].

Triphala has also been known to inhibit the collagenases derived from polymorphonuclear leukocytes which are responsible for connective tissue destruction in periodontal disease. This has been corroborated by an *ex-vivo* study where tissue samples were treated with triphala, kamillosan extracts, and doxycycline, and gelatin zymography was done. Triphala showed 76.6% reduction of matrix metalloproteinase-9 (MMP-9) activity, whereas kamillosan and doxycycline showed 46.36% and 58.7%, respectively, at concentrations of 1500 μg/ml [35].

RUBIA CORDIFOLIA

The roots of this plant have been used in ayurvedic medicine. It also contains an organic compound known as Alizarin, which gives the red color to textile dyes. Mollugin, a major component of *R. cordifolia* has been shown to possess anti-inflammatory property [36]. A recent study showed that mollugin inhibited RANKL-induced osteoclast differentiation and bone resorbing activity of mature osteoclasts. Mollugin reduced the phosphorylation of signaling pathways activated in the early stages of osteoclast differentiation, including the MAPK, Apt, and GSK3β and inhibited the different genes associated with osteoclastogenesis such as *Osteoclast-associated* receptor, tartrate resistant acid phosphatase, ICAM-1, cathepsin K, DC-STAMP and OC-STAMP. Furthermore mice treated with mollugin showed significant restoration of lipopolysaccharide-induced bone loss as indicated by micro-computed tomography and histological analysis of femurs [37]. However, further studies are required to use this herbal product as a novel therapeutic approach to treat bone degenerative disorders such as periodontitis, rheumatoid arthritis, and osteoporosis.

PIPERINE

It is an alkaloid which is present in plants such as *Piper nigrum* and *Piper longum*. It is shown to have antioxidant and anti-inflammatory properties. In an animal model, LPS stimulated mice when treated with piperine showed reductions in the nitrite level and lowered the TNF-α level. This study corroborates the free radical scavenging activity of piperine [38]. Another study on rat periodontitis model revealed that piperine significantly down-regulated the production of interleukin-1β, MMP-8, and MMP-13. Piperine clearly inhibited alveolar bone loss and reformed trabecular microstructures in a dose-dependent manner. Histological staining showed that piperine significantly reduced the infiltration of inflammation in soft tissues [39].

SUMAC

Sumac (*Rhus coriaria*) is a well-known spice used widely as an herbal medicine for its anti-inflammatory, antimicrobial, and antioxidant properties [40]. The existing literature on sumac fruit extracts show that they has marked antioxidant activity against lipid peroxidation and free radicals *in vitro* [41,42]. In an experimental animal study, Wistar rats with ligature-induced periodontitis were administered with sumac extracts orogastrically at a dosage of 20 mg/kg/day. Serum total oxidant status (TOS) and oxidative stress index (OSI) were significantly reduced in the sumac extract treated rats. Furthermore, the serum total antioxidant status was similar to the non-ligated rats. Sumac extracts have the potential to reduce alveolar bone loss by affecting TOS and OSI levels in periodontal disease in rats [43].

GINKBO BILOBA

G. biloba (EGb) leaf extract is among the widely used herbal dietary supplement in the US [44]. It is composed of ginkgo flavone glycosides (24%), terpenoids (6%) and less than 5ppm of ginkgolic acid. Its purported biological effects include: Scavenging free radicals [45], lowering oxidative stress [46], and anti-inflammation [47]. In ligature-induced periodontitis rat model, systemic administration of EGb (28-56 mg/kg/day) resulted in reduced osteoclastic counts, decreased inflammation and induced osteoblastic activity [48].

PSIDIUM GUAJAVA

Guava has an excellent antioxidant property because it is primarily rich in Vitamin C (Ascorbic acid). It also has quercetin, carotenoids, and polyphenols which augment its antioxidant action [49,50]. Guava leaf extracts and essential oil from the stem have the ability to scavenge hydrogen peroxide, superoxide anion and inhibit the formation of hydroxyl radical [51,52]. The decoction of the root bark is recommended as a mouthwash and decoction of leaves as an effective gargle for bleeding gums [53].

CURRENT DEVELOPMENTS

Recent *in vitro* studies have shown that herbs such as *Lythrum salicaria* and *Ascophyllum nodosum* have shown to possess potent antioxidant properties. *L. salicaria* aqueous extracts inhibited ROS production from stimulated neutrophils which were isolated and cultured from humans [54]. A polyphenol rich

extract from *A. nodosum* demonstrated significant anti-lipid peroxidation activity and antioxidant activity by scavenging superoxide anion, hydroxyl, and peroxyl radicals [55]. Preliminary studies on a mouthwash containing microencapsulated natural extracts such as avocado oil, manuka oil, propolis oil, grapeseed extract, *Aloe vera*, green tea, coenzyme Q10 (6% GingiNat) have shown significant efficiency on plaque, gingivitis and halitosis due to its antioxidant and immunoregulatory properties [56,57]. Pradeep *et al*. showed that a gel and powder formulation derived from *Acacia arabica* demonstrated a significant improvement in plaque and gingival scores when compared to 1% chlorhexidine in gingivitis patients [58].

CONCLUSION

The herbal medicines have shown to possess a wide array of biological properties such as antimicrobial, antioxidant, and anti-inflammatory effects. The natural phytochemicals present in these herbs aid in suppressing the alveolar bone loss, which is the striking feature in periodontitis. Furthermore, the oxidative burden established due to the chronicity of the disease can be alleviated with the antioxidant property of these herbs. Although many studies, have shown the potency of herbal medicines as an alternative to conventional therapy, there still lies a void in research with respect to the clinical application of these agents in periodontics. Future targeted trials in learning the mechanism of action of these herbal remedies are warranted.

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