Abstract. Since ancient times, pharmacologically active ingredients derived from natural sources, including plants and microbials have been used in the treatment of a wide array of diseases, such as atherosclerosis, diabetes mellitus and cancers. Herbal extracts and polyphenols are produced from herbs that contain a variety of ingredients, most of which exhibit anti-inflammatory, anti-oxidative and anti-microbial actions. Gingivitis is triggered by the infection of the periodontal tissues with periodontal disease-causing pathogens present in the dental biofilm. This is accompanied by weak inflammatory immune reactions in the gingiva. In periodontitis, prolonged and excessive inflammation results in the destruction of gingival connective tissue and in the resorption of alveolar bone, leading to tooth loss. There are a number of clinical reports showing the effectiveness of both herbal extracts and polyphenols on periodontal diseases when applied as a mouthwash or dentifrice into the oral cavity. However, to date, at least to the best of our knowledge, there is no clinical report available on the therapeutic effects of garlic or its extract on periodontal diseases, apart from a recent study, which reported that the intake of aged garlic extract (AGE) containing various pharmacologically active sulfur compounds, alleviated the symptoms of gingivitis clinically. The finding suggests that AGE may be a promising candidate for use in the treatment of periodontal diseases, although additional clinical trials are warranted to confirm this. In addition, further studies are required for the clarification of the basic molecular mechanisms through which AGE attenuates gingivitis. In this review, we summarize the beneficial effects of several natural compounds on periodontal disease and describe the possible applications of garlic ingredients in detail.

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1. Periodontal disease

Approximately 80% of adults worldwide suffer from gingivitis, which is the mild form of periodontal diseases (1). Gingivitis is initiated by infections caused by periodontal anaerobic pathogens, such as Porphyromonas gingivalis (P. gingivalis), which are present in the oral biofilms, leading to prolonged inflammatory reactions in the gingival tissue (2). Without the mechanical removal of biofilm and/or supplemental treatment with antibiotics, the retraction of the gingiva occurs, followed by the resorption of the alveolar bone, and tooth loss (periodontitis) due to the chronic inflammation induced by inflammatory mediators, such as prostaglandin E2 (PGE2) (3,4). Furthermore, the accumulation of reactive oxygen species (ROS) produced by immune cells is the cause for the aggravation of gingival tissue injury (5).

Since ancient times, various natural products derived from plants have been utilized in the treatment of various disease symptoms (6). These products contain herbal extracts, polyphenols, garlic and etc. For the clinical treatment of periodontal disease, antimicrobials, such as chlorhexidine (CHX) have long been used (7). However, infections by bacteria resistant to antibiotics often become a severe clinical concern (5). Therefore, it is desirable to develop therapeutic substances for the treatment of periodontal diseases other than antibiotics. Promising candidates having no antibiotic resistance and few side-effects are naturally occurring products, such as polyphenols and garlic, which exert anti-inflammatory and antioxidant effects (2-4,7). In this review, we summarize several natural products which have been shown to alleviate...
periodontal diseases mainly in clinical trials and in vivo experiments (Tables I and II). Furthermore, we introduce the anti-gingivitis effect of aged garlic extract (AGE) containing a variety of sulfur amino acids having the anti-inflammatory and antioxidant effects (2), and discuss the possibility for its application to treat periodontal diseases.

2. Evidence of the inhibitory effect of various naturally occurring products on gingivitis and periodontitis

**Herbal extract.** A number of herbal extracts consisting of plant-derived herbs have been used in the treatment of inflammatory diseases, such as stomatitis due to their wide range of biological activities, including anti-inflammatory effects, few side-effects and low costs (3-5). For the clinical treatment of periodontitis, non-steroidal anti-inflammatory drugs (NSAIDs) are systemically administered for the treatment of gingival inflammations (4,8). However, NSAIDs often elicit side-effects, such as gastrointestinal dysfunction and bronchoconstriction (4). In human gingival cells, herbal extracts, such as kakkonto, shosaikoto and hangeshashinto have been shown to reduce the production of PGE2, which plays an important role in the progression of the gingival tissue degradation and alveolar bone loss, through the suppression of arachidonic cascade, similar to NSAIDs (4). Sumac (*Rhus coriaria*) is a spice widely used as an herbal medicine (5) and its extract has been shown to inhibit alveolar bone loss via its antioxidant properties in rats with periodontitis (9). Thus, herbal extracts may be possible candidates which can be used, in place of NSAIDs, to attenuate and prevent periodontal diseases.

**Catechin.** Green tea is known to contain 6 primary antioxidants, namely catechin, gallicatechin, epiccatechin, epigallocatechin, epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) (5). EGCG is a major polyphenol extracted from the leaves of *Camellia sinensis* (5) and is known to possess antioxidant and anti-bacterial activities (10). The O-methylated form of synthetic EGCG also exerts beneficial effects, such as the suppression of allergies (10). It has also been shown that ECG inhibits the biofilm formation of periodontal pathogens, such as *P. gingivalis* and *Prevotella intermedia* (11). It has been demonstrated that EGCG inhibits the resorption of alveolar bone induced by lipopolysaccharide (LPS) in mice suffering from periodontitis (12). In a preliminary clinical trial, the local application of green tea in the form of mouthwash or dentifrice was shown to produce an improved effect comparable to that of CHX on chronic periodontitis (13,14).

**Theaflavin.** Theaflavin is a main polyphenol found in black tea made from the leaves of *Camellia sinensis*, and exerts anti-oxidant, anti-inflammatory and anti-tumor effects (15). In human gingival cells, theaflavin has been shown to decrease the secretion of interleukin (IL)-6 and IL-8 induced by LPS or tumor necrosis factor-α (TNF-α) (16,17). Recently, it was shown that theaflavin inhibited alveolar bone resorption in ligature-induced periodontitis rats, along with the reduction of immune cell infiltration and osteoclast formation in gingival tissues (15).

**Curcumin.** Turmeric is a yellow-orange spice derived from a rhizome of the plant *Curcuma longa*, and one of the main components in turmeric is curcumin (diferuloyl methane) (18). Clinical studies have demonstrated that curcumin exhibits a variety of therapeutic actions, such as anti-cancer, anti-platelet aggregation and vascular protective effects through its

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**Table I. Effect of naturally occurring compounds in animal models of periodontitis and gingival cells.**

| Compounds                        | Pharmacological actions                                                                 | (Refs.) |
|----------------------------------|-----------------------------------------------------------------------------------------|---------|
| Herbal extracts (Kakkonto etc.)  | Inhibition of PGE2 production in human gingival cells                                    | (4)     |
| Sumac extract                    | Inhibition of alveolar bone resorption in rats                                           | (9)     |
| Epicatechin gallate (ECG)        | Inhibition of biofilm formation by *P. gingivalis*                                       | (11)    |
| Epigallocatechin gallate (EGCG)  | Inhibition of alveolar bone resorption in mice                                           | (12)    |
| Theaflavin                       | Inhibition of alveolar bone resorption in rats                                           | (15)    |
| Curcumin                         | Reduction of TNF-α, IL-6, PGE2 levels in gingiva of rats                                  | (19,20) |
| Curcumin derivative (CMC 2.24)   | Inhibition of alveolar bone resorption in rats                                           | (7)     |

**Table II. Effect of garlic in gingival cells and gingivitis patients.**

| Compounds                       | Pharmacological actions                                                                 | (Refs.) |
|---------------------------------|-----------------------------------------------------------------------------------------|---------|
| Ethanol and aqueous garlic extract | Inhibition of growth of *P. gingivalis* and *A. actinomycetemcomitans*                     | (21)    |
| Garlic extract                  | Inhibition of growth of *P. gingivalis*                                                   | (25)    |
| Allicin                          | Inhibition of growth of *A. actinomycetemcomitans* and *F. nucleatum*                       | (26)    |
| Diallyl sulfide                 | Inhibition of growth of *A. actinomycetemcomitans*                                        | (27)    |
| Aged garlic extract             | Alleviation of gingivitis in patients suffering from gingivitis                           | (3)     |
anti-inflammatory and anti-oxidant actions (18). Furthermore, curcumin has been shown to decrease blood cholesterol and triglyceride levels, despite its low bioavailability (18). In periodontitis, the oral administration of curcumin has been shown to reduce the levels of the inflammatory mediators, IL-6, TNF-α and PGE2 in the gingival tissues of rats with both ligature- or LPS-induced periodontitis, whereas it was not shown to affect the resorption of alveolar bone (19,20).

On the other hand, chemically modified curcumin, but not curcumin per se, has been shown to inhibit bone loss in rats with LPS-induced periodontitis (7). In addition, gel and mouthwash containing the extract of Curcuma longa or curcumin have been found to decrease the several indices of gingivitis and the number of periodontal pathogens in clinical trials, along with or without the mechanical treatments, such as scaling and root planing (3).

Garlic components. Garlic has been used since ancient times to suppress the growth of bacteria, fungi and viruses (21). It has been demonstrated that garlic extract and its components attenuate atherosclerosis (22) and hypertension (23), and exert immunomodulatory and anti-tumor effects (24). It has also been found that the aqueous extract of garlic (21,25) and its components, allicin (26) and diallyl sulfide (27), inhibit the growth of the periodontal pathogens, P. gingivalis, Aggregatibacter actinomycetemcomitans and Fusobacterium nucleatum in vitro. However, to date, at least to the best of our knowledge, no clinical study or in vivo experiment has been performed to determine whether garlic, the extracts of garlic and these garlic-derived substances can affect gingivitis or periodontitis. AGE, which is made by extracting and aging in water/ethanol solution for >10 months, contains a variety of pharmacologically active sulfur amino acids, such as S-allylcysteine (SAC), S-1-propenylcysteine (S1PC) and S-allylmercaptocysteine (SAMC) (28). AGE has been shown to attenuate atherosclerosis (29,30) and lower hypertension (31), possibly due to the anti-inflammatory (28,32) and antioxidant effects (33,34) of the sulfur compounds. Recently, the oral administration of AGE was shown to alleviate both the gingival index (GI) and gingival bleeding index (GBI) in a clinical trial (2), suggesting a promising application of AGE to relieve periodontal diseases. However, the mechanisms through which AGE attenuates gingivitis remain to be elucidated.

3. Conclusions and future perspectives

As described above, a variety of naturally occurring products, such as herbal extracts and polyphenols have been used in the treatment of periodontal diseases. A number of compounds are clinically applied directly into the oral cavity in the form of mouthwash or dentifrice. On the other hand, at least to the best of our knowledge, no clinical study or in vivo experiment has been performed to describe the therapeutic efficacy of garlic or its extract, either clinically or in vivo, until a recent clinical trial, in which the intake of AGE was shown to significantly alleviate gingivitis (2). Thus, AGE may be a promising candidate for use in the treatment of periodontal disease. However, additional clinical trials are warranted to confirm this. Furthermore, further studies are required for the clarification of the basic molecular mechanisms through which AGE exerts its anti-gingivitis effects.

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Competing interests

The authors declare that they have no competing interests.

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