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Japanese Apricot (*Ume*): A Novel Therapeutic Approach for the Treatment of Periodontitis

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1. Introduction

A lot of fruits contain nutrient substances that can prevent, cure or suppress various diseases. They are nature's true medicines, and diets rich in fruits are consistently associated with a decreased risk of cancer and other chronic diseases. Apricot "*Prunus armeniaca*" is the fruit of a rosaceous tree (*rosaceae*), which is produced in most parts of the world (Gur, 1985). The name *Prunus armeniaca* is thought to be a misnomer based upon the long-held view that apricots initially originated in Armenia. It is known that apricots originated in the Far East, most likely in the Himalayas, the Northern and Western regions of China from where they spread to Armenia and Russia (Gu, 1979; Gulcan, 1988). Apricot is found semi-wild and wild in the northern hills of China and in a broad belt across the hills, mountains, and plateaus of Central Asia as far as the Caucasus Mountains. The first record of the domestication of apricots is an account of their cultivation in China, about 4000 years ago. It is likely that tribe people of Central Asia established traditional rights to harvest their parts of the apricot forests for millennia before this time.

The apricot variety found in Japan is "*Prunus mume Sieb. et Zucc*'' widely known as *Ume* (Figure 1). The Japanese people started to grow *Ume* trees more than 2000 years ago, most likely imported from China. Soon they discovered the health enhancing effects of apricot fruits, and over many centuries, through cultivation, they have improved their apricot tree variety to produce healthier fruits. Accordingly, there is a long-standing view that the Japanese apricot juice can suppress cancer in tumour bearing hosts and inhibit the growth of bacteria.

This article reviews the current knowledge on *Ume*, including its correlation with some diseases and periodontitis.

Japanese apricot fruits

MK615

Fig. 1. MK615 is made from Japanese apricot (*Ume*).

2. Anti-cancer effects of an extract from *Ume*

MK615 is an extract mixture containing hydrophobic substances from *Ume* (AdaBio, Gunma, Japan) (Figure 1). It contains several triterpenoids and has been shown to exert an anti-neoplastic effect against human cancers, such as breast cancer, stomach cancer, hepatocellular carcinoma, colon cancer and malignant melanoma. The mechanisms responsible for the anti-neoplastic effects of MK615 include induction of apoptosis and autophagy, and suppression of Aurora A kinase in cancer cells (Nakagawa et al., 2007; Adachi et al., 2007; Okada et al., 2007; Mori et al., 2007; Matsushita et al., 2010).

3. Inhibitory effects of an extract from *Ume* on *Helicobacter pylori*

Helicobacter pylori infection is an important factor in human gastric disorders, including chronic active gastritis, peptic ulcers, intestinal metaplasia and cancer.

In the *in vitro* study, *Ume* extract had an immediate bactericidal effects on *H. pylori* (Miyazawa et al., 2006; Enomoto et al., 2010). In the *in vivo* study, *Ume* extract suppress chronic active gastritis in the glandular stomachs of *H. pylori*-infected Mongolian gerbils (Otsuka et al., 2005). *H. pylori*-inoculated gerbils were given *Ume* extract in their drinking water for 10 weeks. The microscopic scores for gastritis and mucosal hyperplasia in the *Ume* extract groups were significantly lower than in the *H. pylori*-inoculated control group, with dose-dependence. Additionally, it was reported that *Ume* extract showed the antibacterial effect on *H. pylori* in the human stomach in vivo pilot study (Nakajima et al., 2006). Therefore, *Ume* extract may have potential as a safe and inexpensive agent to control *H. pylori*-associated gastric disorders, including gastric neoplasia.

4. Anti-inflammatory effects of an extract from *Ume*

The high mobility group box 1 protein (HMGB1), a nuclear protein, has two distinct functions in cellular systems. In the nucleus, HMGB1 acts as an intracellular regulator of the transcription process with a crucial role in the maintenance of DNA functions (Lu et al., 1996). In the extracellular space, HMGB1 is released by all eukaryotic cells upon necrosis or by various cells in response to inflammatory stimuli such as endotoxins, tumor necrosis

factor (TNF)- α, and C-reactive protein (Wang et al., 1999; Taniguchi et al., 2003; Kawahara et al., 2008). Extracellular HMGB1 can act as a potent inducer of proinflammatory cytokines including TNF- α, interleukin (IL)-6, and IL-1s from a wide variety of cells, thus playing a major role in various inflammatory diseases such as sepsis, rheumatoid arthritis, disseminated intravascular coagulation, periodontitis, xenotransplantation and atherosclerosis (Wang et al., 1999; Taniguchi et al., 2003; Kawahara et al., 2008; Ito et al., 2007; Morimoto et al., 2008; Kawahara et al., 2007; Porto et al., 2006). Therefore, agents capable of inhibiting HMGB1 can be considered to possess therapeutic potential.

It was reported that an extract of *Ume*, an abundant source of triterpenoids, strongly inhibited HMGB1 release from lipopolysaccharide (LPS)-stimulated macrophage-like RAW264.7 cells (Kawahara et al., 2009). The inhibitory effect on HMGB1 release was enhanced by authentic oleanolic acid (OA), a naturally occurring triterpenoid. Similarly, the HMGB1 release inhibitor in *Ume* extract was found to be OA. Regarding the mechanisms of the inhibition of HMGB1 release, the OA or *Ume* extract was found to activate the transcription factor Nrf2, which binds to the antioxidative responsive element, and subsequently the heme oxygenase (HO)-1 protein was induced, indicating that the inhibition of HMGB1 release from LPS-stimulated RAW264.7 cells was mediated via the Nrf2/HO-1 system; an essentially antioxidant effect. These results suggested that natural sources of triterpenoids warrant further evaluation as 'rescue' therapeutics for sepsis and other potentially fatal systemic inflammatory disorders.

5. Periodontal disease

5.1 Symptoms

Periodontal disease, which includes gingivitis and periodontitis, is the most common chronic disorder of infectious origin known in humans, with a prevalence of 10–60% in adults depending on the diagnostic criteria used (Papapanou, 1996). Periodontitis is a chronic inflammatory disease of which the primary etiological factor is microbial dental plaque which causes an inflammatory response (Loe et al., 1965). Periodontitis destroys the periodontal tissue and eventually causes loss of teeth . Chronic and progressive bacterial infection leads to gingival connective tissue destruction and irreversible alveolar bone resorption (Ranny, 1993). Periodontal disease has various states and stages, ranging from easily treatable gingivitis to irreversible severe periodontitis and is increased by several risk factors such as systemic disease, medications (hypotensors, anti-epilepsy drugs and anti-cancer drugs), cigarette smoking, ill-fitting bridges, and trauma caused by occlusion (Papapanou, 1996; Slavin & Taylor, 1987; Grossi et al., 1997; Bjorn et al., 1969; Glickman, 1965). In addition to these variables, medical conditions that trigger host antibacterial defense mechanisms, such as neutrophil disorders and human immunodeficiency virus (HIV) infection, are likely to promote periodontal disease (Clark et al., 1977; Mealey, 1996).

The most prevalent form of periodontal disease is a mild form called gingivitis. Gingivitis is characterized by inflammation of the gums, redness, swelling, and frequent bleeding on probing (Greenstein, 1984). More advanced forms of periodontitis are also prevalent. The symptoms are similar to those of gingivitis, but are more severe due to the stronger inflammatory responses. Periodontitis is characterized by loss of gingival connective tissue attachments and alveolar bone resorption.

For diagnosing the extent of periodontal disease, probing depth is a good indicator of how far the disease has advanced (Greenstein, 1997). In clinically healthy periodontium, there is no apical migration of epithelial attachment or pocket formation and the probing depth is 1-3 mm . Patients with probing depths of 4 mm or more are diagnosed with periodontitis. Patients with probing depths of 6 mm or more are diagnosed with advanced, or severe periodontitis. Due to mild nature of symptoms, such as gingival bleeding and attachment loss many individuals neglect to treat their disease which, if left untreated, may progress to irreversible periodontitis and eventually tooth loss.

5.2 Pathogenesis of periodontal disease

The presence of large numbers of oral bacteria can induce tissue destruction indirectly by activating host defense cells, which in turn, release mediators that stimulate the effectors of connective tissue destruction. The components of microbial plaques have the capacity to induce an initial infiltrate of inflammatory cells that includes lymphocytes, macrophages, and polymorphonuclear leukocytes (PMNs) (Kowashi et al., 1980; Zappa et al., 1991). Microbial components, especially LPS, activate macrophages, which synthesize and secrete a variety of proinflammatory mediators including IL-1, IL-6, IL-8, TNF-α, prostaglandin E_2 (PGE_2) and hydrolytic enzymes (Birkedal-Hansen, 1993). Similarly, bacterial substances induce T lymphocytes to produce IL-1 and lymphotoxin (LT), a molecule with similar properties to TNF-α. These cytokines play a key role in periodontal tissue destruction through the induction of collagenolytic enzymes such as matrix metalloproteinases (MMPs) (Sorsa et al., 1992). These latent collagenolytic enzymes are activated by reactive oxygen species in the inflammatory environment, leading to elevated levels of interstitial collagenase in inflamed gingival tissue.

5.3 Periodontal disease and systemic disease

In the last decade, many studies have been published indicating a positive relationship between periodontal disease and various systemic diseases. Significant associations between periodontal disease and cardiovascular disease, diabetes mellitus, preterm low birth weight and osteoporosis have been reported (Jemin, & Salomon, 2006), bridging the once wide gap between medicine and dentistry. Researchers have hypothesized the etiologic role of periodontitis in the pathogenesis of these systemic diseases. Therefore, patients diagnosed with periodontal disease may be at a higher risk due to a compromised immune system as infectious and opportunistic microbes responsible for periodontal infection may prove a burden to the rest of the body. Furthermore, these microbes can release products that elicit an inflammatory response. Periodontal lesions are recognized as continually renewing reservoirs for the systemic spread of bacterial antigens, Gram-negative bacteria, cytokines and other proinflammatory mediators. Therefore, development of new treatment modalities for periodontitis may contribute to the effective inhibition of systemic inflammatory diseases.

5.4 Treatment of periodontal disease

Once diagnosed, most periodontal diseases can be treated successfully. Therapeutic goals are to eliminate bacteria and other contributing risk factors, thereby preventing progression of the disease and maintaining healthy state of periodontal tissues. The recurrence of periodontitis must also be prevented. In severe cases, regeneration of the periodontal

attachment must be attempted. The nonsurgical step involves a special cleaning technique called scaling and root planing. Supplemental treatment tools may include an antiseptic mouth rinse and other medications, either to aid the healing process, to suppress inflammation, or to further control the bacterial infection. Often, antibiotics are administered. Tetracyclines, or a combination of amoxicillin and metronidazole, may be used to kill a broad range of bacteria in microbial dental plaque(Hayes et al., 1992; Van Winkelhoff et al., 1992). However, if overused, these agents may become uneffective. Another drawback to antibiotic therapy lies in the difficulty of identifying and targeting a specific pathogen due to the numerous species residing in the plaque.

6. Possible new treatments for periodontitis

6.1 Anti-inflammatory effects of an extract from *Ume*

Natural compounds such as catechins in green tea, naringenin, a major flavanone, in grapefruits, and polyphenols in cranberries may be useful for the prevention and treatment of inflammatory periodontal diseases (Makimura et al., 1993; Bodet et al., 2008; Bodet et al., 2008). Consequently, natural compounds with the capacity to modulate host inflammatory responses have received considerable attention, with the suggestion that they may be potential new therapeutic agents for the treatment of periodontal disease (Paquette & Williams, 2000). Some studies indicate that MK615 extracted from *Ume* may have not only anti-cancer effects, but also strong anti-inflammatory effects. MK615 contains several triterpenoids, including oleanolic acid and ursolic acid, and may have anti-inflammatory effects. Recent studies have suggested that triterpenoids have both anti-tumor and anti-inflammatory effects (Nakagawa et al., 2007; Adachi et al., 2007; Okada et al., 2007; Okada et al., 2008; Kawahara et al., 2009). MK615 inhibits the release of HMGB1, a novel inflammatory mediator, by LPS-stimulated RAW264.7 cells (Kawahara et al., 2009). The inhibitory mechanism is mediated via the antioxidant compounds heme oxygenase-1, NQO-1 and glutathione-s transferase, which are induced by oleanolic acid. This strongly suggests that MK615 may suppress inflammation.

In the periodontal field, MK615 inhibits cytokine release, including that of TNF-α and IL-6, by *P. gingivalis* LPS-stimulated cells in dose-dependent manners (Morimoto et al., 2009). It is clearly indicating that MK615 contains an inhibitor of cytokine release. The continuous high secretion of various cytokines including TNF-α and IL-6 by host cells following stimulation with periodontal pathogens and their products is a critical determinant of periodontal tissue destruction. Therefore, blockade of TNF-α and IL-6 secreted by periodontal pathogens or other cytokines may suppress pro-inflammatory responses, and inhibit the development and progression of periodontal disease. It has been reported that LPS possibly induces TNF-α and IL-6 expressions through transient phosphorylation of ERK1/2, JNK, and p38MAPK (Matsuzaki et al., 2004; Kim et al., 2007; Son et al., 2008; Neuder et al., 2009; Xiao et al., 2007). Additionally, it has been also reported that the production of inflammatory cytokines requires nuclear factor kappaB (NF-κB) activation (D'Acquisto et al., 1997). The inhibitory mechanism of MK615 is mediated by the attenuation of MAPK phosphorylation (Figure 2) and subsequent inactivation of NF-κB to suppress LPS-induced translocation and phosphorylation of the p65 subunit (Figure 3 &4). These results support the notion that MK615 has anti-inflammatory effects, and MK615 may represent a key molecule with therapeutic potential for periodontitis. Therapeutic approaches that inhibit cytokine production are receiving increasing attention as options for managing chronic periodontitis.

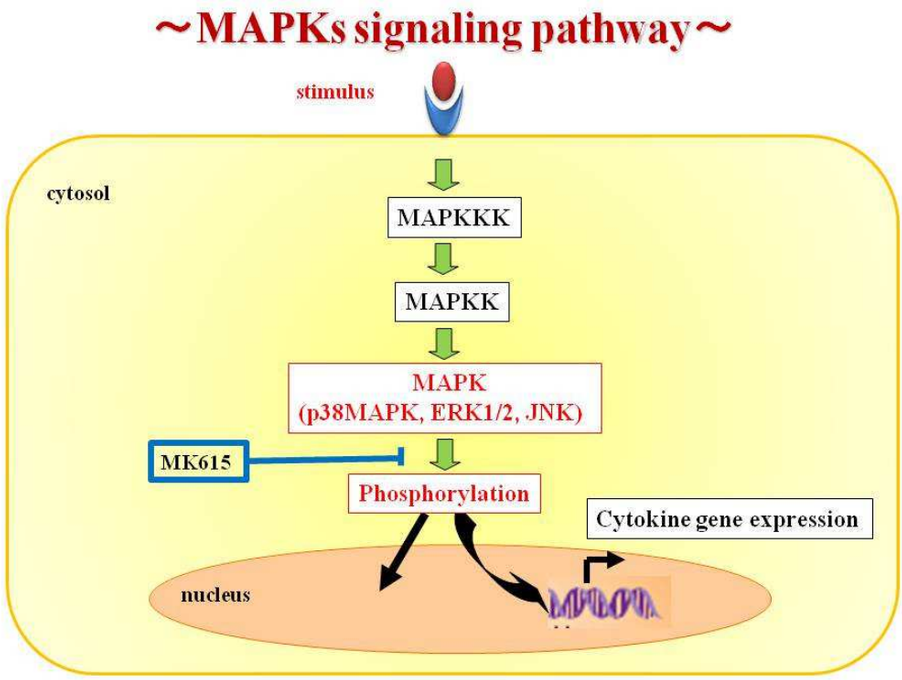

Fig. 2. MK615 inhibits phosphorylation of MAPKs.

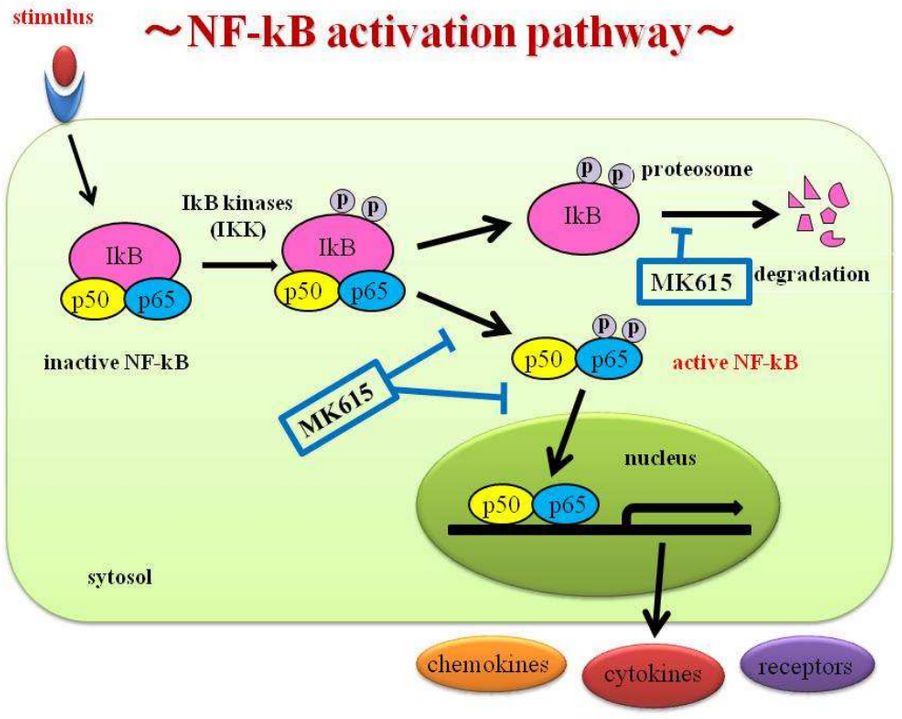

Fig. 3. MK615 suppresses NF-κB activation but not degradation of IκB.

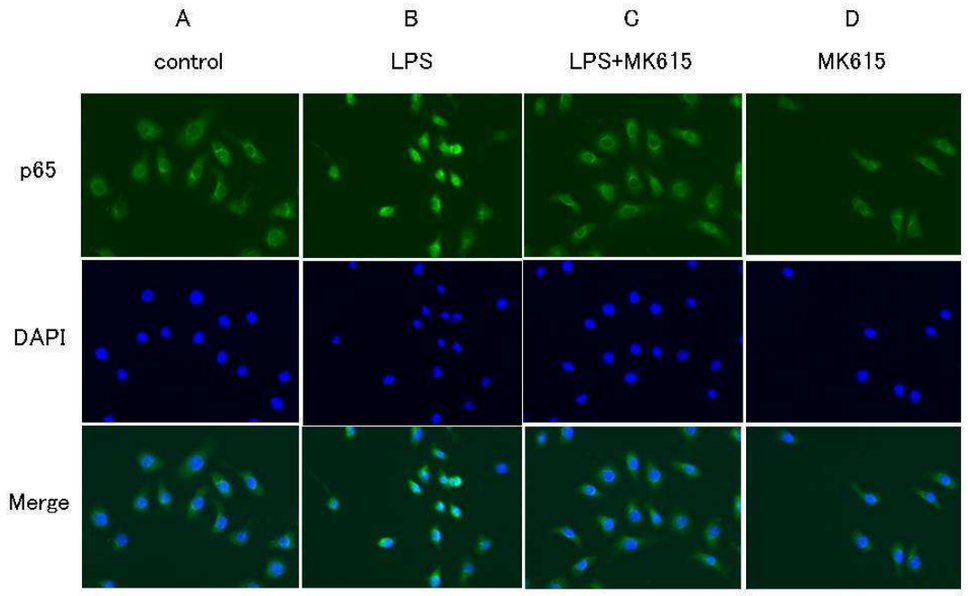

Figure 4 Morimoto et.al

Fig. 4. MK615 suppresses *P. gingivalis* LPS-induced nuclear translocation of NF-κB p65 in RAW264.7 cells. Cells were left untreated or pretreated with MK615 and stimulated with LPS. (A) In untreated cells, NF-κB p65 is limited to the cytoplasm. (B) LPS-stimulated cells show NF-κB p65 (green) translocation into the nucleus. (C) LPS-stimulated cells pretreated with MK615 show a significant reduction in p65 nuclear translocation. (D) Cells treated with MK615 alone show no effect. Cells stained with DAPI were used to verify the nuclear localization (blue). Original magnification: ×400.

6.2 Anti-microbial effects of an extract from *Ume*

Periodontitis and dental caries are major oral diseases. The formation of dental plaque, which plays an important role in the development of periodontal disease and caries in humans, can be initiated by several strains of oral streptococci (Freedman & Tanzer, 1974; Tanzer et al., 1974). *Streptococcus mutans* is the main pathogen for dental caries, although other acidogenic microorganisms can also be involved (Murata, 2008). *S. mutans* produces three types of glucosyltransferase (GTFB, GTFC and GTFD), and synthesizes an adherent and water-insoluble glucan from sucrose that allows adherence of *S. mutans* to the tooth surface and dental plaque formation (Edwardsson, 1968; Hamilton-Miller, 2001).

There is great interest in the use of antimicrobial agents for the prevention and treatment of periodontitis and caries. The prevention of periodontal disease and dental caries requires control of the pathogens that exist in the oral dental plaque biofilm. Chlorhexidine is a potent antiplaque chemical agent. However, it has some side effects, such as altered taste sensation, desquamation and soreness of the oral mucosa (Makimura et al., 1993). Thus, it is important to develop alternative antiplaque agents from natural sources that have no side effects.

It is reported that MK615 has not only anti-inflammatory effects for periodontal tissues but also antimicrobial activity against periodontal bacteria, such as *A. actinomycetemcomitans* and *P. gingivalis* (Table 1). In addition, MK615 exerted antibacterial activity against cariogenic bacteria, such as *S. mutans*, *S. gordonii* and *S. sanguinis*, with an expected anti-caries effect (Table 1). Moreover, it was found that MK615 exhibited an inhibitory effect on *S. mutans* biofilm formation. The most effective treatment against dental caries and periodontitis would be one that prevents early biofilm formation (Wei et al., 2006). MK615 is known to contain active components with anti-inflammatory and anti-oxidative properties, such as oleanolic acid (Kawahara et al., 2009). A previous study suggested that oleanolic acid has antimicrobial actions against *S. mutans* (Kozai et al., 1999), while another study showed that oleanolic acid markedly inhibits water-insoluble glucan synthesis from sucrose by the crude glucosyltransferase of *S. mutans* (Kozai et al., 1987). Therefore, MK615 has potential as a therapeutic agent for treating and preventing oral diseases such as periodontitis and dental caries. Further studies will focus on the active antimicrobial components in MK615, which should be identified and investigated for their mechanisms of action. Additionally, further studies are required to investigate the effects of local application of MK615 as an adjunctive treatment to conventional therapy for patients with periodontitis. Such studies may lead to the development of novel periodontal therapies and improved strategies for public oral health.

MICs of MK615 against oral microorganisms.

Species	**(mg/ml)**
A. actinomycetemcomitans 57	6.5
A. actinomycetemcomitans IDH	6.5
P. gingivalis	1.6
S. mutans UA159	13
S. mutans MT403R	13
S. mutans RIMD	13
S. gordonii	13
S. salivarius	(-)
S. sanguinis	13

Table 1.

7. Conclusion

With the growing recognition of their benefits for public health in recent years, natural foods are now being highlighted with special reference to their effects on human health in addition to their pharmacological actions. Japanese *Ume* has been used as a herbal medicine with several biological activities, including anticancer, antioxidant and anti-inflammation effects (Nakagawa et al., 2007; Adachi et al., 2007; Okada et al., 2007; Mori et al.,2007; Kawahara et al., 2009).

MK615, an extract of compounds from Japanese *Ume*, has not only anti-inflammatory effects for periodontal tissues but also antimicrobial activity against periodontal bacteria, such as *A. actinomycetemcomitans* and *P. gingivalis*. In addition, MK615 exerted antibacterial activity against cariogenic bacteria, such as *S. mutans*, *S. gordonii* and *S. sanguinis*, with an expected anti-caries effect. Moreover, it was found that MK615 exhibited an inhibitory effect on *S. mutans* biofilm formation. MK615 has potential as a therapeutic agent for treating and preventing oral diseases such as periodontitis and dental caries. Further studies will focus on the active anti-inflammatory and antimicrobial components in MK615, which should be identified and investigated for their mechanisms.

MK615 is safe in food for providing health benefits, and this remains unquestioned even when it is prescribed for oral therapy. Moreover, it is also used as a treatment for patients with liver cancer. In the future, it may be added to toothpastes, mouth rinses and other oral products that can be used easily by the majority of the populationranging from youngsters to the elderly. In addition, MK615 may be applicable to the total body through examining its possible effects on not only oral bacteria but also *Staphylococcus aureus* and *Candida albicans*.

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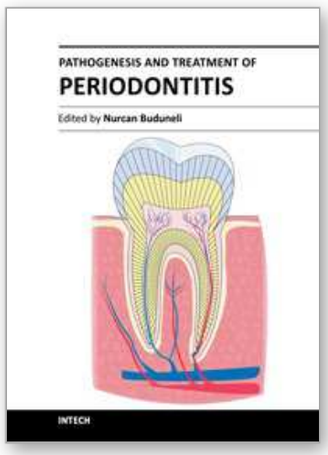

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Pathogenesis and Treatment of Periodontitis includes comprehensive reviews on etiopathogenic factors of periodontal tissue destruction related to microbial dental plaque and also host response components. Adjunctive treatment modalities are also addressed in the book. Topics covered range from microbial pathogenic factors of P. gingivalis to the relationship between metabolic syndrome and periodontal disease, and from management of open gingival embrasures to laser application in periodontal treatment.

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