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THE HEALTH BENEFITS OF POMEGRANATE IN PERIODONTAL DISEASES

PERİODONTAL HASTALIKLARDA NAR'IN SAĞLIK FAYDALARI

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Abstract

Pomegranate (Punica granatum) is known for its antimicrobial, anti-inflammatory and antioxidant capability. Since ancient times, its consumption has been thought to be beneficial for health. Periodontal disease is a common contributor to adult tooth loss. Previous studies have shown that inflammation is crucial in the pathogenesis and perpetuation of periodontal disease. Multiple herbal remedies have gained popularity recently for the treatment of periodontal disease for the overall safety and effectiveness. Multiple reports have evaluated the effectiveness of pomegranate to combat periodontal disease. Today, the food industry has turned to obtain antioxidants and antimicrobials from natural sources. Pomegranate and its extracts are used in different food products and satisfactory results have been obtained. The purpose of this review was to investigate the benefits of pomegranate for periodontal disease and to create a resource for alternative mouthwash production in the future.

Keywords: *Antioxidants; Dentistry; Food; Herbal Medicine; Mouthwashes; Periodontitis, Pomegranate.*

Özet

Nar (Punica granatum) antimikrobiyal, anti-inflamatuar ve antioksidan özelliğiyle bilinir. Antik çağlardan beri tüketiminin sağlık açısından faydalı olduğu düşünülmüştür. Periodontal hastalık yetişkinlerde diş kaybına neden olan yaygın bir etkendir. Önceki çalışmalar, iltihabın periodontal hastalığın patogenezinde ve devam etmesinde önemli olduğunu göstermiştir. Son zamanlarda periodontal hastalığın tedavisinde genel güvenlik ve etkinlik açısından çok sayıda bitkisel ilaç popülerlik kazanmıştır. Çok sayıda rapor, narın periodontal hastalıkla mücadeledeki etkinliğini değerlendirmiştir. Günümüzde gıda endüstrisi antioksidanları ve antimikrobiyalleri doğal kaynaklardan elde etmeye yönelmiştir. Nar ve özleri farklı gıda ürünlerinde kullanılmakta ve tatmin edici sonuçlar elde edilmektedir. Bu incelemenin amacı, narın periodontal hastalık için faydalarını araştırmak ve gelecekte alternatif gargara üretimi için bir kaynak oluşturmaktır.

Anahtar Kelimeler: *Antioksidanlar; Diş Hekimliği; Gıda; Bitkisel İlaç; Ağız Gargaraları; Periodontitis, Nar.*

OVERVIEW / GENEL BAKIŞ

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Punica granatum, or pomegranate, means apple *("Pomum")* and seed *("granatus")* (1). Pomegranates are known to be grown in Southern China, India and Southeast Asia and are used for consumption, traditional medicine and decoration (2). Pomegranates contains beneficial compounds including ellagitannins, flavonoids, punicic acid, anthocyanins, anthocyanidins and estrogenic flavones (3). The peel of the pomegranate has anti-inflammatory, anti-mutagenic, and anti-fungal activities and is full of beneficial compounds. Tannins found in pomegranates are antioxidant, antihypertensive, antiatherosclerotic and anti-aging (4,5). Pomegranate fruit extract has two major types of polyphenolic compounds: anthocyanins and tannins. Anthocyanins contribute to the rich red color and tannins have many beneficial abilities (6).

Periodontal disease is an inflammatory complication affecting the gingiva and the periodontium (7). Periodontitis is a chronic, infectious disease caused by bacteria and their products in dental plaque, characterized by inflammatory destruction of the tooth-supporting periodontal ligament, alveolar bone and soft tissues (8). Gingival inflammation onset starts with bacterial biofilm formation. Dysbiotic ecological changes and inflammation begin in the microbiome in response to nutrients from gingival inflammatory and tissue breakdown products that enrich some species. Periodontitis then begins and progresses depending on the anti-bacterial mechanisms that try to keep the microbial challenge in the gingival sulcus area (9). That is, although periodontitis is a disease that develops in response to bacteria and their products, the course of the disease is regulated by the host tissue response. Genetic, acquired, and environmental factors may increase the susceptibility to periodontitis by affecting the tissue response to the pathogens (8).

Microbial dental plaque is considered the main etiological agent in the onset and progression of periodontal disease (10). The first thing to do in order to prevent inflammation is mechanical removal of plaque (11). Aiming to control inflammatory processes and improve clinical parameters, periodontal therapy has been used mainly to alter the periodontal environment by reducing or eliminating periodontopathogens in dental plaque (12). For this purpose, many researchers recommend the use of mouthwashes together with mechanical therapy (11,13). Arora et al. reported in their study involving 45 dental students that using chlorhexidine mouthwash in addition to tooth brushing was more effective in reducing plaque and gingival scores than using a toothbrush alone or with dental floss. Mechanical plaque control methods have the potential to maintain adequate levels of oral hygiene among individuals. However, clinical experience and population-based studies have shown that these methods are not used as correctly as they should by a large number of people. Therefore, various antiplaque agents, such as triclosan, essential oils and chlorhexidine, have been developed to increase the effectiveness of daily hygiene control measures and to control bacterial plaque (1).

Chlorhexidine is the gold standard to reduce plaque build up. It works through broad-spectrum antimicrobial activity (14). There was no difference in plaque inhibiting action of 0.1%, 0.12% and 0.2% of chlorhexidine rinses. However, long-term use may cause staining of the teeth, unpleasant taste, and mucosal erosion (15). In addition, pharmacological agents (antiseptics, nonsteroidal anti-

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inflammatory drugs and antibiotics) are used as adjunctive therapy to prevent microorganisms' destruction (16). When these drugs are used, they may cause complications such as systemic antibiotic resistance and other side effects at high doses (17). Alternatively, plant products or phytopharmaceuticals have been used to control microbial infection with success (3). They have fewer side effects and are cost effective. The natural products can be useful and beneficial in the prevention and treatment of periodontal disease (18).

Numerous studies have been conducted on the potential health benefits of pomegranate and its components in addition to their nutritional value. The findings have increased the interest shown in this fruit over the past few years. In vitro and in vivo studies have shown that pomegranate, rich in polyphenols, has many health-related properties, such as antioxidant, anti-inflammatory and antihypertensive (19). This review was prepared with a comprehensive literature review on the benefits of pomegranate for periodontal disease.

Literature Search

In this review, database including Google Scholar and PubMed were searched from 1984- 2024 for terms including antioxidant capacity, anti-inflammatory, gingivitis, herbal medicine, pomegranate, periodontitis, herbal mouthwash, pomegranate mouthwash, experimental periodontitis.

Antiplaque Effects of Pomegranate

Accumulation of dental biofilm (microbial dental plaque) brings about changes in bacterial composition (20). A biofilm is defined as a cluster of microorganisms attached to each other or to a surface and coated with a self-generated extracellular polymeric substance. Bacterial colonization starts from the bottom layer of the dental biofilm. Early colonizers attach to the teeth by attachment to the dental pellicles, while later colonists attach to previous colonies (21).

Over seven hundred microbes have been identified in the oral cavity (22). Among these species, *F. nucleatum* (Fn), *P. gingivalis* (Pg), *P. intermedia* (Pi), *A. actinomycetemcomitans* (Aa) and *oral spirochetes*, especially *Treponema denticola*, are closely related to periodontal disease (23, 24). *S. Sanguinis* also contributes to the bacterial colonization process (25). Bacteria can trigger the host response by penetrating the periodontium. Over time, the initial response to protect the surrounding tissue from bacterial invasion results in periodontal destruction. The consequence results in tooth loss if not properly treated (26).

There are many reports investigating the antibacterial effect of pomegranate (27-29). Pomegranate has natural protective components that disrupt the bacterial cell wall, inhibit bacterial enzymes and interaction with proteins, and interfere with coagulation processes (3). Hydrolyzed tannins and polyphenols, particularly punikalagin and gallagic acid, may also play a role in the antibacterial properties of pomegranate juice. Bacteriostatic and bactericidal effects are achieved by tannins' ability to chelate metal ions essential for the production of nucleic acids, which are found in both hydrolyzable and condensed forms. Additionally, punicalagin (an essential pomegranate

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compound) has been revealed to have a bactericidal action. This compound is a derivative of tannins (300). Ellagic acids break down bacterial membranes, potentially leading to bacterial cell lysis. Therefore, ellagic acids are considered toxic to bacteria (31). However, the antibacterial compounds of pomegranate depend on the amount and concentration of the juice (32). The pomegranate juice concentration to block bacterial growth is dependent on the extraction method, solvent types, and the type of bacteria targeted (33). Pomegranate juice is composed of approximately 85.4 percent water and 15.6 percent dry compounds. If the juice is extracted from the whole fruit, then the extracts are also from the skin and seeds of the fruit, including punicalagins which may contain significant amounts of derived polyphenols. Yet, the level of compounds obtained may vary depending on the type of fruit, storage method and length, and level of maturity (34).

Vasconcelos and colleagues investigated the antimicrobial effects of a pomegranate gel against *S. mutans*, *S. mitis* and *C. Albicans*. They reported an effective inhibition of microbial adhesion. This report suggested that phytotherapeutics can be beneficial in the control of microorganisms adhesion (29). Pomegranate was shown to also have antibacterial activity against *Aa*, *Pg*, and *Pi* (35). In another study, the juice of the pomegranate was shown to inhibit biofilm formation from multiple bacterial strains including *Pg, Aa,* and *Td*. In this study, pomegranate juice was diluted at 12.5%, 25%, 50%, 100% concentrations and incubated for 1, 6 and 24 hours followed by optical density measurement of biofilm mass. The biofilm mass was shown to be significantly reduced in comparison to controls for all dilutions and incubation times. Pg at 100% pomegranate juice had a biofilm optical density of 0.34 ± 0.03, Td at 25% pomegranate juice had an optical density of 0.87 ± 0.08, while 50% had an optical density 0.22. ± 0.01. Also, pomegranate juice at a 50% concentration showed optical density at 0.09 ± 0.02 and in multi-type biofilms for all bacteria. Based on these results, the authors suggested that pomegranate juice has strong anti-biofilm activity and can be used in the treatment of periodontal disease (27). In another report, a juicer was used to obtain pomegranate juice and it was diluted to five different concentrations using brain-heart infusion (BHI) broth: 100%, 50%, 25%, 12.5%, and 6.25%. For biofilm analysis, F. nucleatum and S. sanguinis were cultured at 37° C for 48 hours in BHI broth. It has been shown to prevent biofilm formation (28). The antimicrobial efficacy of chlorhexidine and pomegranate juice mouthwash was compared in vitro. The study concluded that both types of mouthwash exhibited antimicrobial activity against several bacteria that form biofilms (36).

Previous research has suggested that the anti-inflammatory properties of pomegranate, when used as an adjunct to mechanical debridement, may be effective in the treatment of periodontal disease (37). In addition, pomegranate juice was found to reduce plaque formation and periodontal pocket depth over a three-month period (38).

Experimental Model Studies of Pomegranate and Its Relationship with Periodontitis

Punicic acid, the major compound in pomegranate, is also anti-inflammatory. It suppresses *Punica granatum* production (39). It has been found to block nuclear factor kappa B ligand (RANKL) activity, and prevents bone resorption, and may be beneficial in the treatment of periodontal disease

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(40). Pomegranate has also been shown for its role in wound healing. It has been shown to induce collagen formation and angiogenesis, as well as fibroblast proliferation and migration (41).

Ellagic acid (EA), found in pomegranate, has been reported to exhibit multiple beneficial effects including those related to oxidative stress (42). Ogawa and colleagues demonstrated that EA was more effective than α-tocopherol and had superoxide dismutase activity. They suggested that EA suppressed cytokine levels includinig IL-1β, IL-8 and TNF-α (43). Furthermore, Promsong and colleagues demonstrated EA is protective against IL-2 and IL-8 in gingival epithelial cells, which suppressed defense factors hBD2 and secretory leukocyte protease inhibitor (44).

ROS (reactive oxygen species) and inflammatory cytokines play a role in the pathogenesis of periodontitis (45). Host cells produce myeloperoxidase, 8-hydroxydeoxyguanosine, and inflammatory cytokines such as TNF-α and interleukin IL-6 in response to bacterial infiltration. These markers leads to the destruction of periodontal tissues (17). In a study investigating the effect of EA on periodontitis, the therapeutic effects of orally administered EA on gingival and alveolar bone loss during the repair process associated with experimental periodontitis in rats, measuring gingival and serum myeloperoxidase, 8-hydroxydeoxyguanosine and glutathione levels, IL-6 aimed to evaluate the expression of IL-10 and TNF-α. The findings showed that EA provided significant improvements in alveolar bone resorption during the repair process a-ssociated with gingival oxidative stress and inflammatory markers and experimental periodontitis. Therefore, EA may have a therapeutic potential on periodontitis (46).

RANKL and osteoprotegerin (OPG) receptors are important in the regulation of bone remodelling, and treatment of periodontal disease (47). Osteoblasts as well as many other cells types express RANKL (48). Pomegranate extract has been shown to regulate RANKL expression in osteosarcoma cells (49). Pomegranate extract (22 μg) was used for 3 weeks in an experimental periodontitis study. The study showed that the extract resulted in decreased COX-1 and COX-2 expression levels, which led to blocking the bone loss caused by periodontal inflammation (50). Four different concentrations of pomegranate extract, 12.5, 6.25, 3.1, and 2.5 mg/mL, have been proven to have antimicrobial effects against P. gingivalis using an in vivo model (29). All these studies are promising because of the structure of periodontal tissues and the mechanisms of progression of their diseases.

Effects of Pomegranate on Periodontal Diseases in Clinical Studies

Pomegranate can improve oral health and reduce the the risk of gingivitis. A 2009 report involving adults investigated pomegranate extract as a mouthwash (3 times a day for a month). The study showed that pomegranate mouthwash reduced gingivitis and led to many salivary changes. These changes were: reduced total protein; lowered aspartate aminotransferase activity; reduced alpha-glucosidase activity; increased ceruloplasmin acitivity; and increased radical scavenging capacity. These data suggest that pomegranate extract in mouthwash may have oral health benefits (51). In a study in which pomegranate gel was used for 7 days in patients with chronic gingivitis, the

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group using pomegranate gel and mechanical disturbance demonstrated improved clinical outcomes (37). A clinical study was conducted on healthy volunteers to investigate the effect of pomegranate juice on dental plaque microorganisms. Dental plaque was collected from each subject before and after gargling with 30 ml of unsweetened pomegranate juice. Samples were grown on plates. There was a 23% decrease in *streptococci* and *lactobacilli* colony forming units (46%) (52). Comparing the antiplaque efficacy of pomegranate mouthwash against chlorhexidine was also noted by Smruti et al. This study also suggested that gargling with pomegranate could be investigated as a long-term antiplaque gargle with prophylactic benefits (35). Furthermore, data from a study investigating the effect of Punica granatum on S. mutans showed that gargling with pomegranate can be used as an adjunct to plaque prevention and may be effective in maintaining daily oral hygiene (53). In a study in children, 15 ml mouthwash prepared from pomegranate extracts was used twice a day for 1 week. At the end of the study, mouthwash obtained from pomegranate extract showed good antibacterial activity against oral *streptococci* (54).

Experiments to test the safety of pomegranate have shown that pomegranate juice and extracts are safe at dosages used in traditional medicine. A dose of 600 mg per kg of body weight was found to cause no side effects (55). It is also stated that daily oral administration weighs 60 mg/kg. Because the activity of rats treated with 60 mg/kg of extract per day was found to be normal. In addition, they found that daily oral administration weighs 60 kg. It does not cause any side effects with 180 mg/kg of punicalagin for 90 days (56). Safety testing for pomegranate seed oil showed no appreciable results for two grams of pomegranate seed oil/kg body weight (57). Repeated applications of the extract did not result in irritation or change in the oral mucosa. These findings demonstrate that pomegranate extract has low toxicity and is recommended because of its medicinal properties (58).

In one study, pomegranate extract was used in the form of chips and gel in patients with periodontitis. As a result, it was stated that it could be complementary to calculus cleaning and root surface planing in the treatment of periodontal pockets (59). Another study conducted in 2023 reported that *Punica granatum* mouthwash was effective in reducing inflammation in patients with periodontitis (60). A wide variety of doses and formulations in the different clinical trials are given in Table 1. As seen in the table, the application method of pomegranate in clinical studies, the application period, the design of the study and the results obtained are available. Others did not indicate concentrations at all. Short research times and small sample sizes are among the drawbacks of the clinical data that has already been collected. In order to prove pomegranate effectiveness for the treatment of periodontal disease, future clinical trials are necessary.

Table 1. Clinical studies showing the pomegranate effectiveness for treatment of periodontal disease.

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Application method	Study design	Duration of study	Outcomes	References
Pomegranate gel	Randomized clinical trial	7 days	Significant reduction in the quantitative bacterial levels Preventing plaque formation	52
30ml of pomegranate juice for 2 minutes	Randomized clinical trial	24 hrs	Reduction in the number of colony forming units of bacteria	35
Pomegranate extract (dissolved in distilled water for an effective concentration of 4 g%)	Randomized controlled trial	4 days	Antiplaque effects	53
The 300 mg/ml concentration of *Punica granatum* extract was used to prepare the mouthrinse. About 18 grams of *Punica granatum* extract was dissolved in 60 ml of distilled water	Randomized controlled trial	Once (short time)	Reduced the salivary count of S. mutans Increased the salivary pH significantly within a short time interval of 10	54

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			min after the mouthrinse Potential as an anti-cariogenic agent	
Pomegranate gel, pomegranate chip and scaling and root planning	Prospective study	During treatment	Advantages to scaling and root planing for remedy of periodontal pockets	59
Punica granatum mouthwash (About 8 grams of *Punica granatum* extract was dissolved in 100 ml of distilled water)	Randomized control trial	Two weeks	Reduced the inflammation	60

SUMMARY / SONUÇ

Resolving periodontal disease is done by reducing inflammation, improving clinical outcomes, and reversing its progression. Restoration of periodontal structure is the recommended goal and can be obtained through regulation of inflammation. Pomegranate can be used as an alternative to mouthwash to reduce inflammation and ROS. Many researchers argue that chemical agents should be used regularly in addition to mechanical treatment. Compared to chemicals used regularly to treat periodontitis, such as chlorhexidine, anti-plaque efficacy is high. However, no significant difference has been found between pomegranate and clorhexidine. In addition, the absence of side effects such as chlorhexidine suggests that it is a natural alternative. It shows that more comprehensive clinical studies should be done on mouthwash or chewing gum containing pomegranate as a standard use alternative. Although this article was prepared for mouthwash, it may also open new horizons and

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enable new experiments to be conducted on the systemic use of pomegranate particles in the pathogenesis of periodontal disease.

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