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Pomegranate: Natural remedy for treating periodontal disease

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Abstract
Pomegranate is one such fruit/ plant which is beneficial with added effect on oral health. This plant has source of polyphenols which has antioxidant properties, meaning they help to protect cells from damage and may lower the inflammation in the body. Apart from this various other components of the pomegranate plant such as flowers are rich source flavonoids. Peel extracts have been demonstrated to have antibacterial and antifungal activity due to the presence of hydrolysable tannins and polyphenols. The stem part is known to have astringent and antihelminthic properties and the leaves have been used for conjunctivitis. Thus, the purpose of this review is to summarize the therapeutic benefits of various extracts derived from the pomegranate plant and its benefits on oral health.

Keywords: Pomegranate, Antiplaque, Antioxidant, Antiinflammatory

Introduction
Gingivitis is the inflammation of the gingiva. Plaque is a requirement for the development of gingivitis [1]. Periodontitis is a polymicrobial disease in which disease expression involves intricate interactions of the plaque biofilm with the host inflammatory response and subsequent alterations in bone and connective tissue metabolism [2]. Mechanical plaque control methods are efficient in maintaining adequate levels of oral hygiene, studies have shown that patient compliance in following these methods are not adequate in a large population [3]. In order to overcome the shortcomings of mechanical plaque control methods, various chemotherapeutic agents have been employed [3].
Herbs have various bioactive components which possess enormous medicinal value with least side effects [4]. Synthetic antimicrobial agents and antibiotics are known to cause antimicrobial resistance, emergence of previously uncommon infections probably due to the inappropriate or widespread overuse of antimicrobials. Natural phytochemicals have proven to be good alternatives to such synthetic agents [5]. Various studies have proven to show excellent medicinal properties of different herbal products in various medical and dental diseases. This review showen pomegranate herbal product, their medicinal properties and their uses in the field of periodontics.

Description
The pomegranate tree typically grows 12−16 feet and has many spiny branches. It can be extremely long lived, as evidenced by trees at Versailles, France, known to be over 200 years old. The leaves are glossy and lance shaped. The bark of the tree turns gray as the tree ages. The flowers are large, red, white, or variegated, and have a tubular calyx that eventually becomes the fruit. The fruit contains many seeds (arils) separated by white, membranous pericarp, and each is surrounded by small amounts of tart, red juice. The pomegranate is native of the Himalayas in northern India to Iran [7].

History
The pomegranate, an ancient, mystical, and highly distinctive fruit, is the predominant member of two species comprising the Punicaceae family. In Ayurvedic medicine the pomegranate is considered “a pharmacy unto itself” and is used as an antiparasitic agent, a “blood tonic,” and to heal aphthae, diarrhoea, and ulcers. However, the name pomegranate originates from the genus ‘Punica’, which was the Roman name for Carthage, where the best pomegranates were known to grow. Pomegranate is known by the French as grenade, the Spanish as Granada, which literally translates to seeded (‘granatus’) apple (‘pomum’) [8, 9].

Phytochemistry
Pomegranate juice contains anthocyanins, glucose, ascorbic acid, ellagic acid, gallic acid, caffeic acid, catechin, Epigallocatechin gallate (EGCG), querticin, rutin, iron, and amino acids. Pomegranate seed oil is composed primarily of punicic acid and sterols. The pericarp (peel, rind) contains punicalgins, flavones, flavonones, and other flavanols. Tannins, including punicalin and punicafolin, and flavone glycosides like luteolin and apigenin, form important constituents of pomegranate leaves. The flowers of pomegranate are composed of ursolic acid, triterpinoids like maslinic acid, and asiatic acid. Ellagitannins and piperidine alkaloids are present in pomegranate roots and bark. However, current research seems to indicate that the most therapeutically beneficial pomegranate constituents include ellagic acid ellagitannins (including punicalagins), punicic acid, flavonoids, anthocyanidins, anthocyanins, and estrogenic flavones.
Pomegranate aril juice provides about 16% of an adult’s daily vitamin C requirement per 100 ml serving, and is a good

source of vitamin B5 (pantothenic acid), potassium, and natural phenols, such as ellagitannins and flavonoids [10].

Functional components of pomegranate parts

The pomegranate fruit could be considered a functional food because it has valuable compounds in different parts of the fruit that display functional and medicinal effects. Pomegranate flowers attenuate agingmediated undesirable skin abnormalities [11], besides possessing potent antioxidant and hepatoprotective properties [12]. Additionally, they also diminish cardiac toxicity [13] and glucose levels [14]. The pomegranate peel has been shown to have anti-inflammatory [15], antimutagenic [16], and antifungal activity [17]. Furthermore, the pomegranate peel extracts also prevents liver fibrosis [18]. Pomegranate juice, which is rich in tannins, possesses anti-atherosclerotic, antihypertensive, anti-aging, and potent anti-oxidative characteristics [19]. Hence, it provides cardioprotective benefits [20]. Pomegranate juice may have cancer-chemopreventive as well as cancer-chemotherapeutic effects against prostate cancer, in humans [21]. Pomegranate seed oil exhibits nephroprotective properties [22]. Pomegranate bark has been seen to have molluscicidal activity [23].

Mechanisms of Action

Although pomegranate's wide-ranging therapeutic benefits may be attributable to several mechanisms, most research has focused on its antioxidant, anticarcinogenic, and anti-inflammatory properties.

A) Antioxidant Mechanisms

An in vitro assay using four separate testing methods demonstrated pomegranate juice and seed extracts have 2-3 times the antioxidant capacity of either red wine or green tea [24]. Pomegranate extracts have been shown to scavenge free radicals and decrease macrophage oxidative stress and lipid peroxidation in animals [25] and increase plasma antioxidant capacity in elderly humans [26].

B) Anticarcinogenic Mechanisms

In vitro assays utilizing three prostate cancer cell lines (DU-145, LNCaP, and PC-3) demonstrated various pomegranate extracts (juice, seed oil, peel) potently inhibit prostate cancer cell invasiveness and proliferation, cause cell cycle disruption, induce apoptosis, and inhibit tumor growth [27, 28].

C) Anti-inflammatory Mechanisms

Cold pressed pomegranate seed oil has inhibited both cyclooxygenase and lipoxygenase enzymes in vitro. Both these are key enzymes in production of various inflammatory mediators [7]. Pomegranate fruit extract has a broad inhibitory effect on matrix metalloproteinaises (MMPs) expression and IL–1β induced tissue destruction [7]. Apart from the above mechanisms, anti-inflammatory effect of pomegranate could be due its immunoregulatory action on macrophages and T and B lymphocytes [29].

Pomegranate extract exhibited anti-inflammatory activity through inhibition of NF-κB (nuclear factor kappa-B) activity and prevention of ERK-1 or ERK-2 (Mitogen activated protein kinase cascades) activation. It also decreased NO (nitric oxide) and PGE2 synthesis in human intestinal Caco-2 cells. Ellagic acid inhibited NF-κB activation through a mechanism independent of Iκ-B (inhibitor of nuclear factor kappa B) phosphorylation [31]. Blocking NF-κB, inflammatory cell signaling pathways that produce various destructive factors may be a potential strategy to prevent inflammation induced bone resorption and a promising mechanism to treat periodontitis [30, 32]. Oral ingestion of polyphenol rich extract of pomegranate fruit extract inhibited COX-1 and COX-2 enzymes. It also inhibited IL-1β induced NO and PGE2 production [33].

D) Other Mechanisms

Numerous in vitro studies [34, 35, 36] and two human trials [37, 38] demonstrate the antimicrobial activity of pomegranate extracts. The growth of Staphylococcus aureus, Streptococcus pyogenes, Diplococcus pneumoniae, Escherichia coli and Candida albicans was inhibited via direct bacteriocidal or fungicidal activity.

General therapeutics of pomegranate

Pomegranate has many potential effects including bactericidal, antifungal, antiviral, immune modulation, vermifuge, stimulant, refrigerant, astringent, stomachic, styptic, laxative, diuretic and antihelminthic. It has also been widely used in treatment of cardiovascular diseases, diabetes, diarrhea, dysentery, asthma, bronchitis, cough, bleeding disorders, fever, inflammation, acquired immune deficiency syndrome, dyspepsia, ulcers, bruises, sores, mouth lesions, skin lesions, malaria, prostate cancer, atherosclerosis, hypertension, hyper lipidemia, denture stomatitis, male infertility, vaginitis, erectile dysfunction, Alzheimer's disease, obesity, and neonatal hypoxic-ischemic brain injury [6, 7, 39, 40].

Therapeutic uses of Punica granatum in oral cavity

Pomegranate Fruit Extract

Pomegranate is fast becoming recognized as an antioxidant power house, possibly beating green tea and red wine. The antioxidants extracted from pomegranate are polyphenols, hydrolysable tannins and anthocyanins. These antioxidants help bind harmful oxygen containing molecules in our body called free radicals and peroxides that otherwise could damage DNA, cell membrane and other cell components. These hydrolysable tannins are used as botanical ingredients in herbal supplements for their antioxidant, antibacterial, anti-inflammatory, anticancer and antiatherosclerotic activities [7].

Pomegranate Juice

According to Guo *et al*, 250 ml of pomegranate juice given daily for 4 weeks to healthy elderly subjects increased plasma antioxidant capacity from 1.33 to 1.46 mmol, while subjects consuming apple juice experienced no significant increase in antioxidant capacity [26].

Pomegranate Gel

Vanconcelos *et al* in 2006, investigated the antimicrobial effect of pomegranate gel against Streptococcus mutans, Streptococcus mitis and Candida albicans and found that pomegranate gel has greater efficiency in inhibiting microbial adherence. Their results suggests that this gel might be used in the control of adherence of different microorganisms in the oral cavity that is responsible for caries periodontal disease and stomatitis [42].

In 2003 Vanconcelos *et al* conducted in vivo studies using pomegranate gel as antifungal agent against candidiasis

associated with denture stomatitis and found that there was a resolution of the symptoms and an improvement in general oral health.38 A gel containing the extract of pomegranate fruit peel, applied to the gums of patients with candidiasis associated with denture stomatitis three times daily for 15 days seems to be as effective as miconazole gel, a topical antifungal agent [43].

Pomegranate-Methanolic Extract (MEPGP)

In vitro study conducted by Abdollahzadeh 2011[2] showed that extract of pomegranate might be used in the control of common oral pathogens responsible for caries stomatitis and periodontal diseases however, their study requires further photochemical studies to determine the type of compounds responsible for the antibacterial effect of pomegranate [41].

Pomegranate Hydroalcoholic Extract as Mouthrinse

The antibacterial effect on dental plaque microorganisms was tested using 15 ml of hydroalcoholic extract of pomegranate (HAEP) solution in comparison with chlorhexidine (CHX) mouthwash. They found that HAEP and CHX were effective against Staphylococcus, Streptococcus, Klebsiella and Proteus species as well as E. coli. The ellagitannin, punicalagin fraction is thought to be responsible for pomegranate antimicrobial activity [37].

Pomegranate Extract

The extracts have been found to work against methicillinsensitive as well as methicillin-resistant Streptococcus aureus, E. coli, Salmonella typhi and some other species of streptococci [41]. Research shows that pomegranate extract suppresses the ability of these microorganisms to adhere to the surface of the tooth. It inhibits common species of streptococcus, preventing it from producing chemicals that create favorable conditions for fungi and other microorganisms to thrive [44]. Plaque may involve four or more different microorganisms combining forces to colonize the surface of the teeth. A biodegradable chip impregnated with pomegranate peel extract, meant for sub-gingival use as an adjunct to scaling in patients with periodontitis, demonstrated decreased plaque build-up, pocket depth size and bacterial attachment in patients compared to those with the placebo chip after a period of six months [45].

Pomegranate Mouthrinse Antiplaque Efficacy

Study conducted by Bhadbhad in 2011 tested the mouth rinse against A. actinomycetemcomitans, P. gingivalis and P. intermedia strains in vitro. The results showed that the extract was effective against these organisms and can be used as an antiplaque agent, but its efficacy as a long-term antiplaque rinse with prophylactic benefits should be further explored [46].

When used regularly in combination with toothpaste that has been reinforced with bioactive botanical extracts, pomegranate containing mouthwash may fight dental plaque and biofilm formation by inhibiting the activities of the microorganisms that causes plaque. Additionally, pomegranate compounds possess anti-inflammatory properties that may help soothe irritated tissues [47]. The addition of pomegranate-polyphenols extract (POMx) to various oral agents, including toothpaste and mouthwash, gave these agents an antimicrobial effect which gives even better results compared to that of white tea and green tea extracts [48].

Ohio state study done to compare the use of pomegranate mouthwash with a placebo mouthrinse used three times daily for 4 weeks, showed that there was a reduction in saliva total protein content which is normally higher in people with gingivitis and may correlate with the plaque forming bacterial count. They also found significant decrease in salivary activity of the enzyme aspartate aminotransferase, an enzyme considered as a reliable indicator of cell injury which is elevated among periodontitis patients. Pomegranate rinse also lowers salivary activity of alphaglucosidase, an enzyme that breaks down sucrose, while it increased activity of ceruloplasmin, an antioxidant enzyme [46].

Safety of pomegranate

Pomegranate and its constituents have been consumed for centuries without adverse effects [7]. Studies of pomegranate constituents in animals at concentrations and levels commonly used in folk and traditional medicine did not indicate any toxic effects [39]. Pomegranate juice, oil or powdered extracts can be consumed by healthy individuals without high risk. No adverse effects on renal or liver function were observed in humans upon administration of up to 1420 mg/day of pomegranate fruit extract tablets [49].

P450 enzymes play a pivotal role in the metabolism of various drugs. Pomegranate inhibited this enzyme resulting in altered drug pharmacokinetics of tolbutamide, carbamazepine and pentobarbital [50-52]. Future studies should be directed with emphasis on bioavailability of compounds, effective and safe doses of pomegranate that can be used in dentistry.

Conclusion

Substantial health benefits of pomegranate has recently become popular among people, unfortunately they are consuming only commercially available pomegranate juice and are missing out many other beneficial parts of the plant, such as leaves, flowers and oil from seeds. Each component of pomegranate works together synergistically to maximize its beneficial effects on our health. Currently, numerous clinical trials are in progress exploring the therapeutic potential of pomegranate extracts. Further, studies are required to find their effects in order to replace synthetic medications with natural remedies. Although, considerable evidence exists regarding the antioxidant, antibacterial, anti-inflammatory and antifungal properties, further human trials are necessary to refute or substantiate these properties.

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