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Review Article

POMEGRANATE AS AN CURATIVE THERAPY IN MEDICAL AND DENTAL SCIENCES: A REVIEW

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ABSTRACT

Pomegranate (*Punica granatum L*), in addition to its ancient historical uses, has been used in several systems of medicine for a variety of ailments. Pomegranate juice is a polyphenol-rich juice with high antioxidant capacity pomegranate consumption possesses a diverse array of biological actions and may be helpful in the prevention of some inflammatory-mediated diseases including cancer. In the past decade, numerous studies on the antioxidant, anticarcinogenic, and anti-inflammatory properties of pomegranate constituents focusing on treatment and prevention of cancer, cardiovascular disease, diabetes, dental conditions. Currently, numerous clinical trials are in progress exploring the therapeutic potential of pomegranate extracts.

Keywords: Alternative therapy, Dentistry, Pomegranate, *Punica granatum.*

INTRODUCTION

Name of the Medicinal Plant: *Punica granatum L.*

Family: Punicaceae

Common name: Pomegranate [1]

Pomegranate (*P. granatum* L.) is considered one of the oldest known edible fruits and is symbolic of abundance and prosperity. For thousands of years, many cultures have believed that pomegranate has beneficiary effects on health, fertility, longevity, and rebirth [2].

The pomegranate tree typically grows 12-16 ft, has many spiny branches and 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, and 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 ripe pomegranate fruit can be up to 5″ wide with a deep red, leathery skin, is grenade-shaped, and crowned by the pointed calyx. 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 from the Himalayas in northern India to Iran but has been cultivated and naturalized since ancient times over the entire Mediterranean region. It is also found in India and more arid regions of Southeast Asia, the East Indies, and tropical Africa. The tree is also cultivated for its fruit in the drier regions of California and Arizona [3].

In addition to, its ancient historical uses, pomegranate is used in several systems of medicine for a variety of ailments. 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, diarrhea, and ulcers. Pomegranate also serves as a remedy for diabetes in the Unani system of medicine practiced in the Middle East and India. The potential therapeutic properties of pomegranate are wide ranging and include treatment and prevention of cancer, cardiovascular disease, diabetes, dental conditions, erectile dysfunction, and protection from ultraviolet radiation. Other potential applications include infant brain ischemia, Alzheimer's disease, male infertility, arthritis, and obesity [1].

CONSTITUENTS [1]

Plant component	Constituents
Pomegranate juice	Anthocyanins; glucose, ascorbic acid, ellagic acid, gallic acid, caffeic acid, catechin, EGCG, quercetin, rutin, numerous minerals, particularly iron, amino acid
Pomegranate seed oil	95% punicic acid, other constituents, including ellagic acid, other fatty acid, sterols
Pomegranate pericarp (peel, rind)	Phenolic punicalagins, gallic acid and other fatty acids, catechin, EGCG, quercetin, rutin and other flavonols, flavones, flavonones, anthocyanidins
Pomegranate leaves	Tannins (punicalin and punicafolin), and flavones glycosides, including luteolin and apigenin
Pomegranate flower	Gallic acid, ursolic acid, triterpenoids, including maslinic and Asiatic acid, other unidentified constituents
Pomegranate roots and bark	Ellagitannins, including punicalin and punicalagin, numerous piperidine alkaloids

EGCG: Epigallocatechin gallate

Commercially available as:

- As mouthwashes
- As toothpaste
- As pomegranate gel.

MEDICAL IMPLICATIONS

Antioxidant mechanisms

An *in vitro* assay using four separate testing methods demonstrated pomegranate juice (PJ) and seed extracts have 2-3 times the antioxidant capacity of either red wine or green tea [4]. Pomegranate extracts have been shown to scavenge free radicals and decrease macrophage

oxidative stress and lipid peroxidation in animals and increase plasma antioxidant capacity in elderly humans [5].

Research in humans has shown a juice made from pomegranate pulp (PPJ) has the superior antioxidant capacity to apple juice. Using the FRAP assay (ferric reducing/antioxidant power), Guo *et al*. found 250 mL PPJ daily for 4 weeks given 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. In addition, subjects consuming the PPJ exhibited significantly decreased plasma carbonyl content (a biomarker for oxidant/antioxidant barrier impairment in various inflammatory diseases) compared to subjects taking apple juice. Plasma Vitamin E, ascorbic acid, and reduced glutathione values did not differ significantly between groups, leading researchers to conclude pomegranate phenolics may be responsible for the observed results [5].

Anticarcinogenic mechanism

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. These studies also demonstrated combinations of pomegranate extracts from different parts of the fruit were more effective than any single extract [1].

In an open-label, phase II clinical trial in 46 men with recurrent prostate cancer, 16 patients (35%) showed a significant decrease in serum prostate-specific antigen (PSA) levels (average=27%) during treatment with eight ounces of PJ. Corresponding *in vitro* assays using patient plasma and serum demonstrated significant decreases in prostate cancer cell line proliferation and increased apoptosis. Nitric oxide preservation via ingestion of pomegranate polyphenols significantly correlated with lower PSA values. These results indicate pomegranate may affect prostate cancer because of antiproliferative, apoptotic, antioxidant, and possibly anti-inflammatory effects [6]. Recent research also indicates pomegranate constituents inhibit angiogenesis via down-regulation of vascular endothelial growth factor in MCF-7 breast cancer and human umbilical vein endothelial cell lines [1].

Anti-inflammatory mechanisms

Cold pressed pomegranate seed oil (CPSO) had been shown to inhibit both cyclooxygenase and lipoxygenase enzymes *in vitro*. Cyclooxygenase, a key enzyme in the conversion of arachidonic acid to prostaglandins (important inflammatory mediators), was inhibited by 37% by a CPSO extract. Lipoxygenase, which catalyzes the conversion of arachidonic acid to leukotrienes also key mediators of inflammation, was inhibited by 75% by the CPSO extract. By comparison, a fermented PJ extract resulted in a 23.8% inhibition of lipoxygenase *in vitro* [1].

Another *in vitro* study that may have far-reaching implications for those suffering from osteoarthritis (OA) demonstrated pomegranate fruit extract (PFE) has a significant and broad inhibitory effect on matrix metalloproteinases (MMPs), a subgroup of collagenase enzymes expressed in high levels in arthritic joints and involved in the turnover, degradation, and catabolism of extracellular joint matrix. In pretreated human femoral OA chondrocytes, PFE inhibited interleukin-1β (IL-1β)-induced destruction of proteoglycan, expression of MMPs at the cellular level, and phosphorylation and activation of mitogen-activated protein kinases (signal transduction molecules involved in MMP expression). The suppression of MMP expression in OA chondrocyte cultures by PFE suggests pomegranate constituents prevent collagen degradation and may inhibit joint destruction in OA patients [7].

HYPERTENSION

A small clinical trial demonstrated PJ inhibits serum angiotensin converting enzyme (ACE) and reduces systolic blood pressure in hypertensive patients. 10 hypertensive subjects (ages 62-77; seven men and three women) were given 50 mL/day PJ containing 1.5 mmol total polyphenols for 2 weeks. Two of seven patients were also diabetic and two were hyperlipidemic. 7 of 10 subjects (70%) experienced a 36% average decrease in serum ACE activity and a small, but significant, 5% decrease in systolic blood pressure [8].

MYOCARDIAL PERFUSION

In a double-blind, randomized, placebo-controlled trial, 39 patients were given either 240 mL PJ (polyphenol content not specified) (n=23) or a sports beverage of similar color, flavor, and caloric content daily for 3 months (n=16). Although both control and treatment patients demonstrated similar levels of stress-induced ischemia at baseline, at 3 months stress-induced ischemia increased in the placebo group (from 5.9±4.3 to 7.1±5.5) but decreased in the treatment group (from 4.5±3.1 to 3.7±3.7). In addition, angina episodes increased 38% in the placebo group but decreased 50% in the treatment group (a net change of 88%). These results demonstrate a reduction in myocardial ischemia and improved myocardial perfusion (as measured by stress-induced ischemia) in patients consuming PJ [9].

DIABETES

In an animal model of diabetes, Huang *et al*. demonstrated the favorable effect of Pomegranate flower extract (PFLE) on lipid profiles and cardiac fibrosis of Zucker fatty diabetic rats. Rosenblat *et al*. investigated the effect of 50 mL/day PJ for 3 months on oxidative stress, blood sugar, and lipid profiles in 10 type 2 diabetic patients (history of diabetes for 4-10 years) and 10 healthy controls (ages 35-71) [10].

In diabetic patients, triglyceride levels were 2.8 times greater; high-density lipoprotein (HDL) cholesterol was 28% lower, and hemoglobin A1C (HbA1c) values were 59% higher than in control patients. Insulin was only slightly lower in patients than controls, and C-peptide (a proinsulin metabolite marker for endogenously secreted insulin) was slightly higher in diabetic patients than in healthy controls at baseline (indicating slight hyperinsulinemia). Consuming PJ for 3 months did not significantly affect triglyceride, HDL cholesterol, HbA1C, glucose, or insulin values, but did lower serum C-peptide values by 23% compared to baseline in diabetic patients – a sign of improved insulin sensitivity.

PJ consumption also significantly reduced oxidative stress in the diabetic patients as evidenced by a 56% reduction in lipid peroxides and a 28% reduction in thiobarbituric reactive substances compared to baseline serum levels. In addition, a 39% decrease in uptake of oxidized low-density lipoprotein by human monocyte-derived macrophages (an early development in foam cell formation and atherogenesis) was observed in diabetic patients after PJ consumption. Researchers concluded that despite the sugars naturally present in PJ, consumption did not adversely affect diabetic parameters but had a significant effect on atherogenesis via reduced oxidative stress [10].

ALZHEIMER'S DISEASE

The neuroprotective properties of pomegranate polyphenols were evaluated in an animal model of Alzheimer's disease. Transgenic mice with Alzheimer's - like pathology treated with PJ had 50% less accumulation of soluble amyloid-beta and less hippocampal amyloid deposition than mice consuming sugar water, suggesting PJ may be neuroprotective. Animals also exhibited improved learning of water maze tasks and swam faster than control animals [1].

OBESITY

PFLE (400 or 800 mg/kg/day) given to obese hyperlipidemic mice for 5 weeks caused significant decreases in body weight, the percentage of adipose pad weights, energy intake, and serum cholesterol, triglyceride, glucose, and total cholesterol/HDL ratios. Decreased appetite and intestinal fat absorption were also observed, improvements mediated in part by inhibition of pancreatic lipase activity [1].

BACTERIAL INFECTIONS

The only human trials examining the antibacterial properties of pomegranate extracts have focused on oral bacteria. However, several *in vitro* assays demonstrate its bactericidal activity against several highly pathogenic and sometimes antibiotic-resistant organisms. Brazilian researchers evaluated the synergistic effect of a *P. granatum* methanolic extract with five antibiotics on 30 clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *S. aureus*. 75 Antibiotics tested were chloramphenicol, gentamicin, ampicillin, tetracycline, and oxacillin. Although synergistic activity between the pomegranate extract and all five antibiotics was noted in the *S. aureus* isolates, synergy with ampicillin was the most pronounced. A combination of the two increased the lag time to bacterial growth by 3 hrs (over that of ampicillin alone) and was also bactericidal as evidenced by a 72.5% reduction in methicillin-sensitive organisms and a 99.9% reduction in MRSA. Based on earlier research 76 and the results of this study, the ellagitannin, punicalagin, is thought to be the primary constituent responsible for the observed antibacterial effects. Another organism that can cause significant disease in humans is entero-hemorrhagic *Escherichia coli* (*E. coli* O157:H7), which can present with diarrhea, hemorrhagic colitis, thrombocytopenic purpura, and hemolytic uremic syndrome. *P. granatum* and seven other Thai medicinal plant extracts were tested for *in vitro* activity against *E. coli* O157:H7. An ethanolic PPE, one of the two most effective extracts against *E. coli* O157:H7, was shown to be both bacteriostatic and bactericidal, indicating PPE may be an effective adjunct treatment for *E. coli* O157:H7 infection [11].

DENTAL IMPLICATIONS

Topical applications of pomegranate preparations have been found to be particularly effective for controlling oral inflammation, as well as bacterial and fungal counts in periodontal disease and *Candida*-associated denture stomatitis [1].

DENTAL PLAQUE

A hydroalcoholic extract of *P. granatum* fruit (HAEP) was investigated for antibacterial effect on dental plaque microorganisms. 60 healthy patients (33 females/27 males; ages 9-25) with fixed orthodontic appliances were randomized to three groups of 20: (1) Control group who rinsed with 15 mL distilled water; (2) a group who rinsed with 15 mL chlorhexidine, a standard antiplaque mouth rinse; and (3) a group who rinsed with a 15 mL HAEP solution. Rinsing duration was 1 minute, and dental plaque material was collected from each patient before and after rinsing. Samples were diluted and plated on Mueller-Hinton agar and incubated at 37°C for 48 hrs. HAEP decreased the number of colonies forming units of dental plaque bacteria 84%, comparable to chlorhexidine (79% inhibition) but significantly better than the control rinse (11% inhibition). Both HAEP and chlorhexidine were effective against *Staphylococcus*, *Streptococcus*, *Klebsiella*, and *Proteus* species as well as *E. coli*. The ellagitannin, punicalagin, is thought to be the fraction responsible for pomegranate's antibacterial activity [12].

CLINICAL STUDIES ON GINGIVITIS

Gingivitis is an inflammation of the gums in response to bacterial plaque biofilms adhering to tooth surfaces. If left untreated, gingivitis may progress to periodontal disease and subsequent tooth loss. There is an incentive to use alternative plant-based preparations as an adjunctive to mechanical therapy in the prevention and treatment of gingivitis, due to the health risks imposed by the long-term use of chemical and pharmaceutical preparations and the lack of available dental care in lesser-developed countries. Results of a randomized, clinical study of 40 patients with chronic gingivitis showed that significant improvements were obtained in the group that used a pomegranate extract gel along with mechanical debridement for 7 days when compared with patients using only control gel or mechanical debridement for the 7-day test period [13]. Another placebo-controlled human clinical trial of 32 young adults examined salivary measures relevant to oral health and gingivitis after using a pomegranate extract mouth rinse three times per day for 4 weeks or a placebo rinse [14]. Compared to the control group, those participants using the pomegranate rinse had reduced total protein associated with the presence of plaque forming bacteria, reduced activities related to cell injury, reduced levels of the sucrose-degrading enzyme alpha-glucosidase, and increased activity of the enzyme ceruloplasmin, which protects against oral oxidative stress. Based on these results, the authors suggest the possibility of using pomegranate extracts in oral health products such as toothpaste and mouthwashes [15].

PERIODONTAL DISEASE

A preliminary and follow-up study by a group of Thai researchers investigated the effect of biodegradable chips impregnated with *Centella asiatica* and *P. granatum* pericarp on periodontal disease in 20 patients with gum pocket depths of 5-8 mm. A baseline exam was performed and followed by root planning and scaling of target teeth. Subgingival placement of the medicated chips (treatment group) and non-medicated chips (placebo/control group) followed, and pocket depth, attachment level, bleeding, and gingival and plaque indexes were measured at baseline and after three and 6 months. All treatment sites demonstrated a trend toward decreasing plaque and significant improvements were noted in pocket depth and attachment level at 3 months compared to placebo [16].

In the follow-up study, 15 patients who had completed standard periodontal therapy but still had pocket depths of 5-8 mm were implanted with the same medicated chips. The same parameters were measured again at baseline and after three and 6 months, but researchers also measured inflammatory markers IL-1β and IL-6. Significant improvement was noted in all re-measured parameters and confirmed by significant decreases in IL-1β and IL-6 at three and 6 months compared to baseline [17].

DENTURE STOMATITIS

The primary etiologic factors for denture stomatitis are poor oral hygiene, inflammation from ill-fitting dentures, and *Candida* infection which manifest as swelling, pain, burning in the mouth, and aphthous ulcers. In a randomized, double-blind study of 60 subjects (ages 19-62) with candidiasis confirmed via mycological examination, the effect of a gel-based *P. granatum* bark extract (GPBE) was evaluated for its effect on healing of oral lesions and direct fungicidal effect. Patients were randomized into two groups of 30: One received miconazole oral gel (standard therapy) and the other used GPBE, both three times daily for 15 days. Gels were applied to oral surfaces; dentures were removed and cleaned nightly and then brushed with the corresponding oral gels. All subjects reported an improvement in symptoms and general oral health. Clinical symptoms of those using miconazole were slightly better (27/30 satisfactory improvement) compared to GPBE (21/30 satisfactory improvement). Clearing of *Candida* infection was approximately the same in both groups (25/30 in the miconazole group and 23/30 in the GPBE group) [18].

Interestingly, despite randomized subject placement, there were three times more subjects with good oral hygiene scores in the miconazole group compared to the GPBE group, possibly accounting for the superior results observed by miconazole therapy. Furthermore, because the initial step in the development of *Candida* denture stomatitis is adherence of organisms to dentures and the miconazole gel was stickier than GPBE, contact duration of miconazole was longer. A stickier GPBE might result in improved clinical response [18].

SAFETY

No adverse effects have been reported on consuming pomegranate and its constituents, since time immemorial. In addition, animal studies have failed to report any toxicities at doses conventionally used in the

conventional system of medicine. Even the histopathological analyzes of pomegranate extract punicalagin were devoid of any toxic findings. Human trials using doses of PFEs up to 1420 mg/day (870 mg gallic acid equivalents), for 28 days, did not report any adverse changes in blood or urine laboratory values. Another study in 10 patients with carotid artery stenosis demonstrated that PJ consumption (121 mg/L EA equivalents) for up to 3 years had no toxic effect on the blood chemistry analysis for kidney, liver, and heart function [3].

CONCLUSION

An explosion of interest in the numerous therapeutic properties of *P. granatum* over the last decade has led to numerous *in vitro*, animal, and clinical trials. Pomegranate is a potent antioxidant, superior to red wine, and equal to or better than green tea. In addition, anticarcinogenic and anti-inflammatory properties suggest its possible use as a therapy or adjunct for prevention and treatment of several types of cancer and cardiovascular disease. Because of pomegranate's antimicrobial properties, it may aid in preventing infection by dental pathogens, pathogenic *E. coli* O157:H7, and antibiotic-resistant organisms.

Pomegranate's effect on bacterial pathogens has only been tested *in vitro*, however, necessitating human trials to refute or substantiate any clinical effect. The possibility that pomegranate extracts may also have an effect on several other disease processes, such as Alzheimer's disease, OA, neonatal brain injury, male infertility, and obesity, underscores the need for more clinical research. Currently, numerous clinical trials are in progress exploring the therapeutic potential of pomegranate extracts.

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