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Punica Granatum L - A Nutraceutical functional food

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ABSTRACT

Pomegranate is a widely used plant having medicinal properties. Pomegranates and their extracts may serve as natural alternatives due to their potency against a wide range of bacterial and viral pathogens. The synergistic action of the pomegranate constituents appears to be superior to that of single constituents. Pomegranate provides health benefits, that is, a nutraceutical food. It is used in dentistry as an active ingredient such as mouth rinse for plaque control, treatment of various oral lesions, storage media for avulsed teeth, wound healing. This paper describes the uses of pomegranate, its mechanism and various therapeutic and dental applications.

Key words: Pomegranate, Phytochemicals, Antioxidant, Functional food, Nutraceutical.

INTRODUCTION

In Ayurvedic medicine pomegranate is considered as “a pharmacy unto itself”^[1] because of its role in folk medicine, for eliminating parasites, as an antihelmintic and vermifuge, and to treat and cure aphtae ulcers, diarrhea, acidosis, dysentery, hemorrhage, microbial infections and respiratory pathologies. It was also used as an antipyretic.^[2] The use of pomegranate fruit dates back to Biblical times and reports of its therapeutic qualities have echoed throughout the millennia.^[3] The Babylonians regarded pomegranate seeds as an agent of resurrection; the

Persians believed the seeds conferred invincibility on the battle fields, while for the ancient Chinese the seeds symbolized longevity and immortality.^[4] Since ancient times, the pomegranate has been regarded as a “healing food” with numerous beneficial effects in several diseases.^[5]

Modern applications include hormone replacement therapy in the treatment of immune suppression and cardiovascular complications. It is affectionately known as the “jewel of winter”, pomegranate is receiving growing acclamation for its disease-fighting abilities, largely due to its staggering antioxidant potency.^[6] It is a nutrient dense fruit rich in phytochemical compounds.^[7] It could be considered a functional food because it has valuable compounds in different parts of the fruit that display functional and medicinal effects.^[8] Each and every part of pomegranate provides health benefits, that is, a nutraceutical food. These substances provide essential nutrients often beyond quantities necessary for normal maintenance, growth and development and other biologically active components that impart health benefits or desirable physiological effects.

Pomegranate, *Punicagranatum* L is a highly distinctive fruit, categorized as a berry but it belongs to its own botanical family, *Punicaceae*. The only genus is *Punica*,

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with one predominant species called *P. granatum*. It is a long-lived and drought-tolerant plant. Pomegranate fruit conforms to this definition in several ways, although the establishment of any function would involve identifying the bioactive components to help specify their possible beneficial effects on health.

Pomegranate Fruit Parts and Constituents

The chemical composition of the fruits differs depending on the cultivar, growing region, maturity, cultivation practice, climate and storage circumstances. It contains different kinds of polyphenolic antioxidants. Commercially available pomegranate juice has been shown to possess antioxidant activity three times higher than those of red wine and green tea. The strongest antibacterial activity is the skin, followed by juice and the least is the seeds (red seeds are stronger than white). About 50% of the total fruit weight corresponds to the peel, which is an important source of bioactive compounds.^[9] The edible part of 50% pomegranate fruit consists of 40% arils and 10% seeds. Arils contain 85% water, 10% total sugars, mainly fructose and glucose, and 1.5% pectin, organic acid, such as ascorbic acid, citric acid and malic acid and bioactive compounds such as phenolic and flavonoids, principally anthocyanin's. (Table 1)

Table 1: Principal constituents of different parts of pomegranate tree and fruit.^[10]

Plant Component	Constituents
Pomegranate peel	Gallic acid, Ellagic acid, Punicalin, Punicalagin, Caffeic acid, Ellagitannins, Pelletierin, Alkaloids, Luteolin, Kaempferol, Quercetin
Pomegranate juice	Simple sugars, Aliphatic organic acids, Gallic acid, Ellagic acid (EA), Quinic acid, Flavonols, Amino acids, Minerals, EGCG, Ascorbic acid
Pomegranate root and bark	Ellagitannins, Piperidine, Alkaloids, Pyrrolidine Alkaloid, Pelletierine, alkaloids
Pomegranate	Gallic acids, Ursolic acid,

flower	Triterpenoids, Fatty acids
Pomegranate leaves	Carbohydrates, Reducing sugars, Sterols, Saponins, Flavanoids, Tannins, Piperidine Alkaloids, Flavone, Glycoside, Ellagitannin
Pomegranate seed	Punicic acid, Oleic acid Palmitic acid, Stearic acid, Linoleic acid, Sterols, Tocopherols, Sex steroids.

Mechanism of Action

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

Anti-inflammatory activity

Inflammation the first physiological defense system in human body can protect against injuries caused by physical wounds, poison, etc. The inflammatory process is triggered by several chemical and/or biological aspects that include pro-inflammatory enzymes and cytokines, low molecular weight compounds such as eicosanoids, or the enzymatic degradation of tissue. Cyclooxygenase (COX) which has two isoforms, COX-1 and COX-2 is the enzyme that catalyzes the rate-limiting step in prostaglandin synthesis. COX-1 and COX-2 enzymes and IL-1 β (Interleukin-1 β) activity can be inhibited by pomegranate fruit extract. COX-2 is responsible for catalyzing arachidonic acid to prostaglandin while COX-1 regulates homeostasis. Cold Pressed Pomegranate Seed (CPSO) has been shown to inhibit both cyclooxygenase and lipoxygenase enzymes in vitro. Lipoxygenase enzyme which catalyzes the conversion of arachidonic acid to leukotrienes is also a key mediators of inflammation, was inhibited by 75 percent by a CPSO extract. By comparison, a Fermented Pomegranate Juice (FPJ) extract resulted in a 23.8% inhibition of lipoxygenase in vitro.^[11]

Punicic acid, a conjugated fatty acid present in pomegranate seed oil has an invivoanti-inflammatory effect by limiting neutrophil activation and lipid peroxidation consequences.^[12] Tannins, punicalagin, punicalin, strictinin A, and granatin B, isolated from pomegranate by bioassay-guided fractionation

displayed a dose-dependent and significant inhibitory effect on nitric oxide production.^[13] According to Romier-Crouzet et al 2009 pomegranate extract has an promising effect on dietary prevention of inflammation due to the action of the Ellagic acid (EA) present in pomegranate.^[14] The extract supplementations of pomegranate decreases prostaglandin E2 (PGE2) levels in the colon mucosa by down-regulating the over-expressed COX-2 and prostaglandin E synthase (PTGES) levels due to the action of EA.^[5]

Antioxidant mechanism

The antioxidant activity of pomegranate components may be related to the diverse phenolic compounds. Reducing properties are generally associated with the presence of reductones. Antioxidative action of reductones is based on the breaking of the free radical chain by the donation of a hydrogen atom.^[15] Reductones also react with certain precursors of peroxides, thus preventing peroxide formation.^[16]

Negi and Jayaprakasha 2003 reported a significant increase in the reducing power of pomegranate peel extracts with increase in concentration from 50 to 400 ppm.^[17] In vitro assay of a Fermented Pomegranate Juice (FPJ) extract and a cold pressed seed oil (CPSO) extract found the antioxidant capacity of both are superior to red wine and similar to green tea extract.^[18] Homogenates prepared from the whole fruit exhibited an approximately 20-fold higher antioxidant activity than the level found in the aril juice.^[19]

Research in humans has shown a juice made from Pomegranate pulp Juice (PPJ) has superior antioxidant capacity to apple juice. 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.^[20]

Anticarcinogenic mechanism

Pomegranate constituents efficiently inhibited angiogenesis, invasiveness, growth and induced apoptosis. Its anti-invasive, anti-proliferative and anti-

metastatic effects were attributed to the modulation of Bcl-2 proteins, upregulation of p27 and p21 and downregulation of cyclin-cdk network.^[21]

Pomegranate fruit extract was revealed to inhibit ultraviolet B (UVB) mediated phosphorylation of mitogen-activated protein kinase (MAPK) and nuclear factor NF- κ B activation.^[20] Pomegranate juice almost down regulated the TNF α induced Akt (protein kinase B) activation required for NF- κ B activity.^[22] Koyama et. al. examined the effects of pomegranate extract (POMx) on the IGF (Insulin like growth factor) system and found out cell growth inhibition and apoptosis. POMx treatment reduced mTOR (mammalian target of rapamycin) phosphorylation at Ser2448 and Ser2481, whereas IGFBP-3 (Insulin-like growth factor binding protein 3) increased phosphorylation at those sites. These results suggested that POMx decreased prostate cancer cell survival by inhibiting IGF1 expression.^[23]

Prostate cancer cell proliferation, invasion and phospholipase A-2 expression were inhibited from extracts of pomegranate compartments (peels, juice, and seeds).^[24]

Antimicrobial activity

Pomegranate by products and punicalagins inhibit the growth of certain pathogenic Clostridia species, Staphylococcus aureus and Pseudomonas aeruginosa but increase the growth of Bifidobacterium breve and Bifidobacterium infantis as well as the production of short chain fatty acids, which have been shown to elicit beneficial effects. The growth of Staphylococcus aureus, Streptococcus pyogenes, Diplococcus pneumoniae, Escherichia coli O157:H7 and Candida albicans was inhibited via direct bacteriocidal or fungicidal activity.

The hydrolyzable tannins and anthocyanins are the main compounds associated with the beneficial effects of pomegranate consumption on other health effects "including antibacterial", and may be responsible for the antiviral activity.^[25]

Antibacterial Activity

Hydroalcoholic extract of *P. granatum* had a significant antibacterial effect on common oral

bacteria, namely, *S. sanguinis*, *S. mutans*, *S. salivarius*, *S. sobrinus* and *E. faecalis* with maximum effect on *S. mutans*, which is the main microorganism responsible for dental plaque and caries.^[26] The effects of three different concentrations of a methanolic pomegranate peel extract was compared at 4 mg/mL, 8 mg/mL and 12 mg/mL on growth of dental bacteria using the disc diffusion method. Results showed that pomegranate gel might be useful in the control of adherence of different bacteria in the oral cavity.^[27] In other in vitro studies, pomegranate extract also inhibited strains of periodontal bacteria, *Aggregatibacter actinomycetemcomitans*, *P. gingivalis*, *Prevotellaintermedia*, *Klebsiella*, *E. coli* and *Proteus* species.^{[27],[28]} In a study done by Dilshad Umar et. al. (2016) the effect of pomegranate mouth rinse was compared with 0.2% chlorhexidine mouthrinse on *Streptococcus mutans* count and salivary pH and reported that PPE mouthrinse significantly reduced the salivary count of *S. mutans* count in the subjects as compared to the standard chlorhexidine mouthwash. The herbal mouth rinse also increased the salivary pH significantly within a short-time interval of 10 min after the mouth rinse; thereby proving its potential as an anti-cariogenic agent.^[29]

Antiviral Activity

The fruit's antiviral effects have been reported against clinically relevant influenza virus, herpes virus, poxviruses and human immunodeficiency (HIV-1) virus.^[30]

S. G. Kasimsetty compared four flavonoid compounds associated with pomegranates (ellagic acid, caffeic acid, luteolin, and punicalagin) and reported that only punicalagin was shown to have inhibitory effects on influenza virus.^[31] Natural antimicrobials from plant extracts have become increasingly popular for use as alternative antivirals.^[32]

Antifungal activity

Simone R Foss et. al., 2014 reported that crude pomegranate extract inhibited the growth of *T. rubrum*, *T. mentagrophytes*, *M. canis* and *M. gypseum*. Spectroscopic analyses revealed punicalagin as an active substance. Also, cytotoxicity assay showed that punicalagin was more selective for fungal

than mammal cells, indicating its probable best use in clinical applications. This activity indicates that pomegranate is a good target for study due to its potential future use as a new therapeutic alternative against dermatophytosis.^[33]

Pericarp and peel extracts upon the morphological structure of *C. albicans* and *C. krusei* was studied and bioactive compounds (tannins) present in the pericarp and peel showed antifungal activity. These bioactive compounds could be responsible for changes in cell morphology, inhibiting growth, producing viscous material and rupturing the cells.^[34]

Antidiabetic activity

Pomegranate has been used in the various traditional and the folk systems of medicine to treat diabetes. Scientific studies carried out in the past one decade have also shown that the extract of pomegranate flower, seed, seed oil, seed hull and the phytochemicals like ellagic acid, gallic acid, quercetin and punicalagins possess antidiabetic effects in various preclinical animal models of study. Additionally the seed juice is shown to ameliorate the diabetes induced hyperlipidemia and to prevent the various secondary complications of diabetes.

The main compounds that present antidiabetic properties are polyphenols, which may affect glycemia through different mechanisms, including the inhibition of glucose absorption in the gut or of its uptake by peripheral tissues.^[35]

Improves cardiovascular health

Evidence suggested that polyphenolic antioxidants contained in pomegranate juice can cause reduction of oxidative stress and atherogenesis through the activation of redox-sensitive genes ELK-1 and p-JUN and increased eNOS (Endothelial nitric oxide synthase) expression. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduced common blood pressure, LDL oxidation and carotid intima-media thickness.^[36]

A pilot study in Type 2 diabetic patients with hyperlipidemia found that concentrated pomegranate juice decreased cholesterol absorption, increased faecal excretion of cholesterol, had a favorable effect

on enzymes concerned in cholesterol metabolism, drastically reduced LDL cholesterol, improved LDL/HDL cholesterol and total/HDL ratios.^[37] Aviram et. al. analyzed atherosclerotic lesion size, antioxidant activity, blood sugar, peritoneal macrophages, oxidative status and lipid profiles for 3 months after giving 6 different pomegranate preparations with varying amounts of total polyphenols and gallic acid content in atherosclerotic apolipoprotein-E deficient mice and they found that pomegranate phenolics and pomegranate unique complexed sugars could mimic the antiatherogenic effects of pomegranate extracts.^[38]

One year of pomegranate juice consumption, reduced systolic blood pressure by 21%, was believed to be related to the particularly potent antioxidant properties of pomegranate polyphenols.^[36] Pomegranate juice exerts a direct effect on macrophage cholesterol metabolism by reducing cellular uptake of oxidized LDL and inhibiting cellular cholesterol biosynthesis. Both of these processes eventually lead to a reduction in macrophage cholesterol accumulation and foam cell formation and attenuation of atherosclerosis development.^[39] Pomegranate juice reverts the potent down-regulation of the expression of nitric-oxide synthase (NOSIII) induced by oxidized low-density lipoprotein (oxLDL) in human coronary endothelial cells. Hence Pomegranate juice(PJ) can exert beneficial effects on evolution of clinical vascular complication, coronary heart disease and atherogenesis in humans.^[40] An investigation on effects of PJ for its capacity to protect nitric oxide against oxidative destruction and enhance the biologic action of nitric oxide was done. The results showed that PJ is a potent inhibitor of superoxide anion-mediated disappearance of nitric oxide.^[41]

Improves skin health

Prolonged exposure to ultraviolet (UV) radiation has been identified as a cause of serious adverse effects to human skin, including oxidative stress, premature skin aging, sunburn, immunosuppression, and skin cancer.^[42] The protective effects of pomegranate polyphenolics against UVA (Ultraviolet A) and UVB(

Ultraviolet B) -induced cell death of human skin fibroblasts may be attributed to reduced generation of intracellular ROS (Reactive Oxygen Species) and increased intracellular antioxidant capacity. Pomegranate aqueous extracts (especially of pomegranate peel) promotes regeneration of dermis and pomegranate seed oil promotes regeneration of epidermis.^[43] Pomegranate extract has a whitening effect on the skin after oral administration. This effect was probably due to inhibition of the proliferation of melanocytes and melanin synthesis by tyrosinase in the melanocytes.^[44]

Afaq et. al. suggested that pomegranate derived products may be useful against UVB-induced damage to human skin due to these products inhibited UVB-induced MMP-2 (Matrix metalloproteinase-2) and MMP-9 (Matrix metalloproteinase-9) activities and also caused decrease in UVB-induced protein expression of c-Fos and phosphorylation of c-Jun.^[45] Pomegranate extract can protect against UVA mediated cellular damage that occurs primarily through the release of ROS and is responsible for immunosuppression, photodermatoses, photoaging and photocarcinogenesis due to its extract is an effective agent for ameliorating UVA-mediated damages by modulating cellular pathways and merits further evaluation as a photochemopreventive agent.^[46]

Application in Dentistry

Dental plaque

Dental plaque is a biofilm which is comprised of a population of bacteria growing on the tooth surface enmeshed in a polysaccharide matrix. The researchers have shown that antioxidants can inhibit the formation of the plaque polysaccharide matrix, block the adherence of bacteria, prevent acid formation and reduce acid tolerance of cariogenic microorganisms.^[47]

In a study by Shastravaha, treatment with the extract of *Punica granatum* was found to significantly improve clinical signs of chronic periodontitis.^[47] Trivedi and Kazmi 1979, using extracts of fruit barks have observed an antibacterial activity of pomegranate extract against *Bacillus anthracis* and *Vibrio*

cholerae,^[48] while Machado et. al. showed similar effect against *Staphylococcus aureus*.^[49] Pomegranate mouth rinse was very effective to reduce dental plaque compared to chlorhexidine and distilled water in fixed orthodontic patients. Menezes et. al. studied the effect of the hydroalcoholic extract from pomegranate fruits on dental plaque microorganisms. It was reported that the hydroalcoholic extract was very effective against dental plaque microorganisms, decreasing the CFU/mL by 84% (CFU × 10^[5]) and it may be a possible alternative for the treatment of dental plaque bacteria.^[50] Di Silvestro et. al. 2009 have concluded that rinsing the mouth for 1 min with a mouthwash containing pomegranate extract effectively reduced the amount of microorganisms cultured from dental plaque.^[51]

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. *P. granatum* has great potential for preventing and fighting various diseases, highlighting its anti-inflammatory and antimicrobial properties. The use of pomegranate and particularly its fruit is relatively easily, without compromising its therapeutic properties.^[52]

A clinical study on 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.^[53] 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 concluded that those participants using the pomegranate rinse had reduced total protein associated with 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.^[51] Badria

and Zidan 2004 reported that pomegranate flavonoids have shown modest antibacterial action in vitro for strains relevant to gingivitis.^[54]

Periodontitis

The effects of pomegranate fruit and peel extracts on proliferation and differentiation of osteoblasts significantly improved the pocket depth, level of attached gingiva and bleeding on probing in gingival pockets.

Sastravaha et. al. 2005, implanted pomegranate chips or placebo chips in 20 patients with gum pocket depths of 5-8 mm. Level of bacterial attachment, bleeding and gingival and plaque indexes were initially measured and again at 3 and 6 months. After 3 months, the pomegranate treatments resulted in decreased plaque and significant decreases in pocket depth and bacterial attachment compared to placebo.^[47] Mouth-rinsing with pomegranate extracts lowered saliva activities of aspartate aminotransferase, an indicator of cell injury that shows high values with periodontal disease.^[55] A gel containing extracts of *Centellaasiatica* and *Punicagranatum* was effective as adjunctive periodontal therapy.^[47]

Avulsion of teeth

Avulsion is a traumatic dental injury which leads to detachment of periodontal ligament (PDL) from alveolar socket. The treatment of choice for avulsion is immediate replantation of the tooth. Maintenance of PDL vitality until provision of dental treatment is of high importance for a good prognosis. The prognosis depends on two factors: the interim transport medium and extra-alveolar time. The capacity of storage medium to prevent cell vitality is considered more critical than the extra-alveolar time in prevention of inflammation and replacement root resorption.^[56]

Buttke and Trope suggested that the storage of avulsed teeth in a medium containing one or more antioxidant components may improve the prognosis of replantation.^[57] Pomegranate as an ancient fruit is attracting tremendous attention due to its strong antioxidant properties.^[58] The potent antioxidant

activity of PJ is attributed to its polyphenols including punicalagin, the major fruit ellagitannin and ellagic acid. Punicalagin is the major antioxidant polyphenol ingredient in PJ. Thus, it is assumed to be effective for maintaining PDL cell viability.

A study conducted by Thring et al 2009 evaluated anti-collagenase, anti-elastase and anti-oxidant activities of extracts from 21 plants, it was reported that pomegranate showed 15% anti-elastase and 11% anti-collagenase activity. Strong attachment of cells may occur as a result of serine protease inhibitor components of PJ which deactivate enzymes such as trypsin and collagenase.^[59] Kwak et. al. 2005 suggested that pomegranate contains components such as ellagic acid and punicalagin that are specific inhibitors of beta-secretase (BACE1) and have an inhibitory effect on alpha-secretase (TACE) and other serine proteases such as chymotrypsin, trypsin, and elastase.^[60] Sara et. al. 2011, evaluated the capacity of pomegranate juice as a storage medium for retaining avulsed teeth and it was concluded that pomegranate juice promotes viability and induce proliferation of periodontal ligament cells.^[61]

Effect on wound healing

Pomegranate skin preparations hold promise in increasing the rate of wound healing. Pomegranate peel (5% methanolic extract) prepared as an ointment was applied to guinea pig wounds daily for 12 days. The treatment significantly enhanced wound healing by increasing collagen, DNA and protein synthesis as well as contraction rate and tensile strength. The extract exhibited significant antibacterial activity against wound bacteria, including strains of *Pseudomonas aeruginosa*, *S. aureus*, *E. coli*, *Klebsiella pneumoniae* (K. pneumoniae), *Salmonella Anatum*, *S. Typhimurium* and *Streptococcus pneumoniae*. There were no toxic effects noted from use of the skin ointment.^[62]

Pomegranate Safety and Drug Interactions

Pomegranate and its constituents have been safely consumed by humans for several millennia. Nevertheless, several animal studies and human clinical trials have investigated the toxicity of pomegranate. No adverse side effects have been

noted in any of these studies, therefore considering safe to consume the fresh fruit or pomegranate juice in general. No toxic effects were seen after the repeated consumption of the polyphenol antioxidant punicalagin by rats, which were confirmed by histopathological analyses of their organs.^[63]

However, due to the presence of alkaloids in its composition, some precautions regarding poisoning should be considered since its use may produce nausea, dizziness and vision problems and is contraindicated in pregnancy, lactation, children under 5 years, gastritis cases and gastroduodenal ulcer.^[64]

CONCLUSION

Pomegranate is slowly gathering interest as an exciting new oral hygiene product. It has been shown to improve oral hygiene considerably, by means of destroying plaque and suppressing the adherence of microorganisms to the surface of the tooth. It is additionally, a rich source of natural anti-oxidants, useful in reducing the inflammatory signs in cases of established chronic periodontitis. Pomegranate is therefore a true functional food.

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