

Pomegranate uses in biomedicine: a review

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Abstract

All components of Punicagranatum L(Pomegranate) namely the flowers, leaves, bark of young shoots and roots and fruit peel have been traditionally used for the treatment of various ailments. Pomegranate has got an unique biochemical profile with more than 124 phytochemicals. It is a good source of vitamins, namely vitamin A, C, E, and folic acid which are responsible for the broad range of anti-oxidant, antiinflammatoy, antibacterial anti-viral and anti-tumor properties. The compounds present in Pomegranate namely punicalagin and punicic acid is reported to provide potent health benefits. The antioxidants present in pomegranates is three times higher than wine or green tea. Daily consumption of pomegranates fruit or juice can prevent atherosclerosis thus it is cardio tonic, it can boost the immunity, fight Type-2 diabetes, maintains blood pressure, improves digestion, prevents arthritis, oseoporosis, strengthen bone, improves memory, acts as natural fertility booster, promotes wound healing, prevents oxidative stress, lower psychological stress, reduces dental plaque formation, and provides a healthy skin.The healing properties and health benefits of pomegranate have been evaluated for the last two decades This review discusses the findings of studies that explored the health benefits of pomegranate fruit and its fractions.

Key words; Pomegranate, *Punica granatum* L, Antioxidant, Antibacterial, Anti-inflammatory, Phytonutrients, Polyphenols

Introduction

Pomegranate (Punica granatum L.) is the fruit of a shrub cultivated predominantly in west Asia and around the Mediterranean terrains [1]. The pomegranate belongs to the Punicaceae family and two species exist viz. Punica granatum and Punica protopunica. The first written document on the genus Punica dates back to 1753 and belongs to C. Linnaeus. The current scientific name Punica granatum means "seeded apple" (Punica—apple; granatum—grainy) [2,3]. In Sanskrit it is known as Dadim, Aacharya charak has placed Dadim in the Hridya mahakashay [4] and Aacharya Vagbhata has placed it in

Amla gana in Sutrasthana chapter 10/25, 26. [5,6]. (Ashtanga hridaya)

The Mediterranean climate is ideal for the growth of pomegranate. [1] The fruitbearing plant grows up to 12–16 feet. The fruit is round or grenade-shaped with an average diameter of 10 cm, and a crownshaped calyx on the top. The exocarp is leathery and it encloses clusters of delicious arils separated by pale white spongy mesocarp [7]. The edible portions of the fruit are the arils. The exocarp, that is the pomegranate peel, makes around 50% of the whole fruit, and the edible portion has 40% arils and 10% seeds [8]. Pomegranate and its juice have an intense color which is mainly due to the presence of bioactive compounds namely anthocyanins, the difference in color among the variants is mainly due to the different concentrations of these compounds. The fruit is traditionally used as an ethnic medicine for various health disorders [9].

The fruit is richly cultivated in Iran, Afghanistan, India, Pakistan, and China. Among the oldest cultivated fruits researchers have placed pomegranate in five positions the first [10,11]. Pomegranate was thought to be an auspicious symbol in many religions designating luck, abundance and fertility. The fruit is consumed as fresh or dried arils, fresh or fermented juice, powdered extracts, capsules, rind powder tablets, soft gels, and extracts-based ointments and decoctions [12,]. Pomegranate fruit waste including peel and seeds are reservoirs of phytonutrients and is proved to have antioxidant, antimicrobal and astringent The flower buds are properties.[13]. powdered and used in the treatment of bronchitis. The seeds are considered to help in digestion and the pulp is cardio protective and stomachic. The green leaves are made into a paste and applied in conjunctivitis [14,15]. The biological activities,[16] - antibacterial, antifungal [17,18] anthelmintic [19] and antifertility [20] - of the various extracts of different parts of this plant have also been reported. The extracts of root of Pgranatum [21]and rind of this plant have been reported to exert some sugar lowering action in animals. [22]

In the last two decades numerous studies were carried out highlighting the health benefits and healing properties of pomegranate and itsfractions. This review comprehensively discusses the recent findings of studies that explored the health benefits of pomegranate fruit and its fractions, the capability of this miracle fruit in preventive and therapeutic aspects against certain acute and chronic ailments is also discussed

Biochemical composition of Pomegranate

Biochemical profile of Pomegranate is unique with more than 124 phytochemicals which are responsible for the broad range of antioxidant, anti-inflammatory, and antimutagenic properties [23]. Pomegranate fruit and its fractions like flower, peel, juicy sacs, and seeds are considered as reservoirs of high molecular weight hydrolysable tannins, i.e.. ellagitannins, wide range of а anthocyanins, which are protective degenerative towards diseases. hydroxybenzoic acids, hydroxycinnamic acids, minerals, essential lipids, and complex polysaccharides [24-27]. It has low pH value usually <4.0, sugar content mainly glucose and fructose 70-180 g/L. The biochemical composition depends on the soil condition, the cultivar, climate, ripening stage, cultivation techniques, processing and storage conditions.[28] Peel of fruit is rich in phenolics, minerals and complex polysaccharides. The edible part of fruit contains 85% water, sugars, pectin, organic acids, phenolics, and flavonoids-primarily anthocyanins. Seeds contain proteins, vitamins, minerals, oils, crude fibers, polyphenols, isoflavones,

pectin, and sugars. Oils such as linolenic

and linoleic acids, other lipids such as

punicic acid, oleic acid, stearic acid, and

palmitic acid are also present in seed oil

[29]. Hydrolysable tannins present are,

ellagitannins and gallotannins, which are

hydrolyzed into ellagic and gallic acid,

respectively. Ellagitannins are present in

the pericarp, seeds, flowers, and bark. Gallotannins are present in the leaves. Antioxidant effect of pomegranate juice is mainly due to punicalagin, a member of ellagitannins family . Ellagitannins are converted by the intestinal flora into urolithins. Pomegranate juice also contain phenolic acids, mainly gallic acid and ellagic acid belonging to hydroxybenzoic acids, as well as caffeic acid, chlorogenic acid, and p-coumaric acid belonging to hydroxycinnamic acids.

Constituent that gives antioxidant, antiand antiproliferative inflammatory properties is anthocyanins. It is a watersoluble plant pigment belonging to the family of flavonoids and gives the color to the fruit and its juice. . Flavonoids, namely anthocyanins and phenolic flavonols, acids, are found in the peel and juice. The main phenolic compounds in pomegranate juice are anthocyanins, and the main phenolic compounds in the mesocarp and pericarp are hydrolysable tannins [30]. It is reported that the pomegranate peel has a higher concentration of phenolic compounds than the arils and seeds making it a potent source of bioactive compounds that provide antioxidant capacity [31,32].

Applications in traditional medicine

All components of Punica granatum L namely the flowers, leaves, bark of young shoots and roots and fruit peel have been traditionally used.[27]. The presence of abundant tannins gives a strong astringent effect. Decoctions of the plant flowers was used to treat simple diarrhoea, dysentery, vaginal discharge and stomach disorders. Pomegranate extract along with pomegranate peel was used to relieve inflammation of the pancreas. Juice of Punica granatum L fruit is recommended for gallbladder diseases. The fruit contains strong tannin which is considered as nutrient. Tannin content of pomegranate seed, is used to treat vaginal discharge and wound healing. Fresh or dried root barks or ethanol extracts of pomegranate are used to remove intestinal parasites because of the alkaloid substances. It is also used in traditional medicine making use of the antibacterial and anti-inflammatory properties.[32]

Anti-inflammatory Activity

Inflammation is the first physiological defence system of human body. It can destroy infectious microorganisms, eliminates irritants and maintains normal physiologic functions. Several chemical and biological factors trigger the inflammatory process. These factors include pro-inflammatory enzymes and cytokines, low-molecular-weight compounds such as eicosanoids, or the enzymatic degradation of tissues. [31]. Cyclooxigenase-2 (COX-2) an isoform of cyclooxigenase (COX) has been related to the inflammatory process.[32]

anti-inflammatory properties The of compounds in pomegranate fruit namely hydrolyzable tannins, punicalagin, punicalin, strictinin A, and granatin B, have a significant dose-dependent on nitric oxide inhibitory effect production in invitro studies. Granatin B inhibited PGE2 production and COX-2 expression to a greater extent than the others. The components of pomegranate juice appear to synergistically suppress inflammatory cytokine expression. [33] Pomegranate extract supplementation's decreased the prostaglandin E2 (PGE2) levels in the colon mucosa by downregulating the over-expressed COX-2 and prostaglandin E synthase (PTGES) levels due to the action of a phenolic acid namely ellagic acid [34]. Conjugated fatty acid called punicic acid in pomegranate seed oil has an antiinflammatory effect by limiting neutrophil activation and lipid peroxidation consequence invivo .[35] Whole pomegranate methanol extract inhibited, the production and expression of tumor necrosis factor TNFα in microglial cells, in which inflammation was induced by lipopolysaccharide in a dose-dependent manner [36].

Pomegranate fruit extract have different antiinflammatory effect in disease models and protected chondrocytes against IL-1-induced expression of matrix metalloproteinases by inhibiting the activation of kinases and NF-kB in human chondrocytes in vitro. [37] Obese rats when fed with atherogenic diet and pomegranate juice or pomegranate fruit extract showed a significant decrease in the expression of vascular inflammation markers, thrombospondin (TSP), and cytokine-transforming growth factor-β1 (TGF- β1). Arterial endothelial-nitric oxide synthase (eNOS) expression was significantly increased in comparison to controls. [38] Pomegranate extract prevents inflammation by inhibiting cytokine IL-8, prostaglandin PGE2, and nitric oxide secretion, due to the action of the ellgic acid present in pomegranate. [39]

Antimicrobial activity

The antimicrobial effect of pomegranate against several highly pathogenic or antibiotic-resistant organisms were demonstrated. Pomegranate extracts inhibit or delay Staphylococcus aureus growth and production of enterotoxin due to the antibacterial effect[40] Methanolic extracts of Punica granatum fruit rind was active against S. aureus, Proteus vulgaris, E. coli, Klebsiella neumoniae, Bacillus subtilis, and Salmonella typhi. [41]

Chloroform, ethanol and water extract of pomegranate showed high antibacterial against strains of E. coli activity O157:H7, verocytotoxin inhibition was marked. This was thought to be due to the interference of active compounds in with transcriptional and/or pomegrnate translational steps [42]. Antibacterial effects of different types of extracts viz water. ethanolic. butanolic extracts. methanolic extract of pomegranate peels, methanol, ethanol, acetone, and water extracts of pomegranate were reported by authors.[43-48] Antimicrobial activity of pomegranate peel ethanol extract against 16 strains of Salmonella were reported and it was inferred that pomegranate peel ethanol extract can be used effectively for the treatment of salmonellosis [49]. Alcohol extracts of Pomegranate enhanced the activity of all antibiotics tested, a synergistic activity was detected between pomegranate extract and the antibiotics[50]

Phytonutrients present in pomegranate including polyphenols, flavonoids, tannins, terpenoids. and phytosterols are extensively tested for their potential antimicrobial activity[51,52] the inhibitory effects of the pomegranate extracts on various microorganisms could be due to the phenolic, anthocyanin, and tannin contents of fruits. Structural components of Ellagitannins ETs (ellagic acid and gallic acid) were tested for antimicrobial activity against Salmonella enterica; ellagic acid did not inhibit the growth, but gallic acid caused strong inhibition [53,54,] .The antimicrobials target the cell wall, cell membrane,

metabolic enzymes, protein synthesis, and genetic systems. A specific action site is difficult to identify many interacting reactions that take place simultaneously.[55,56] Tannins are considered to be toxic to microorganisms. Tannins create stable complexes with proteins and, carbohydrates and decreases the cell wall permeability thereby reducing the transport of substrates into the cell. Tannins also decrease metal ion availability to bacteria. Metal depletion may adversely affect the activity of metalloenzymes in microbial cell. These findings clearly demonstrate and confirm the effectiveness of pomegranate fruit in inhibiting microbial activity. Probable targets in the microbial cell are surface exposed adhesions, cell wall polypeptides, and membrane-bound enzymes. Phenols may also render substrates unavailable to microorganisms.

Polyphenols namely punicalagin, catechin, epigallocatechin and are potential antifungal agents. They induce precipitation of microbial cell membrane proteins and cause intercellular leakage causing change in composition of cytoplasm and outer cell membranes this inhibits fungal growth [57,58 1. Hydroalcoholic extracts of Pomegranate antiviral activity against human have immunodefificiency virus type 1, herpes simplex virus 1, influenza A, adenovirus, and hepatitis C virus. The possible mechanism behind viral cell damage is caused by formation of complex between condensed tannins and viral glycoprotein that affect viral attachment with host cell, suppresses viral transcription/translation and prevents viral replication [59,60,61]

Applications in general health Cancer Prevention The second leading cause of death is cancer. It is reported that the number of new cancer cases will increase by 70% by 2030 worldwide.[62,63]Pomegranate fruits contain very high concentrations of cancer chemopreventive and therapeutic biomolecules which include ellagitannins, flavonoids, and anthocyanins. Purified fruit extracts or fruit juice contain polyphenols which possess anticancer activities of inducing apoptosis, cell cycle antiangiogenesis, arrest. and antimutagenesis activities [64]. Pomegranate juice enhances three times higher antioxidant properties and inhibits the production of DNA oxidation products, reactive nitrogen species, lipid peroxidation, and in scavenging reactive oxygen species [65,66,67].

Pre-cancerous tumor initiation was done in mouse mammary organ culture (MMOC),via exposure to chemical carcinogen 7,12-dimethylenz[*a*]anthracene (DMBA),and fermented pomegranate juice (W) produced a 46% decrease in tumor occurrence [68] Where as cold-pressed Pomegranate seed oil isolated from fermented pomegranate juice (W) resulted in 87% reduction in tumor occurrence. [69]. The supply of oxygen and nutrients for tumor growth and metastasis is attained though angiogenesis. Research indicates that pomegranates possess the ability to inhibit the development of new blood vessels and inhibition of tumor blood vessel formation and it is a non-toxic therapeutic approach of tumor[70]. in the treatment Angiogenesis in chicken chorio allantoic membrane (CAM) in vivo was significantly suppressed by fermented pomegranate juice (W) but not by Pomegranate peel extract (P). [71]

Pro-angiogenic vascular endothelial growth factor (VEGF) was potently down regulated in MCF-7 estrogen dependent breast cancer cells. The anti-angiogenic migration inhibitory factor (MIF) was potently unregulated in MDA-MB-231cells by pomegranate juice (W) and supercritical CO2-extracted pomegranate seed oil; (SESCO), which also moderately suppressed human umbilical vein endothelial cell (HUVEC) proliferation and tubule formation. Conversely, P and W potently inhibited human myometrial fibroblast proliferation suggesting inhibition of cellular proliferation[72,73]. Pomegranate peel extracts have shown to retard proliferation of cells in several different human cancer cell lines.[74]

It was reported that in human prostate cells. DU-145 cancer androgen independent cells were more sensitive to W and P than to cold-pressedpomegranate seed oil (PSO), normal prostate epithelial cells hPrEC were found to be considerably less affected by either W or P than the androgen sensitive cancer cells LNCaP .[75] When equal amounts of any two of W, P or PSO were combined synergistic effect was obtained and the combination resulted in a 90% suppression of invasion. When all three were equally combined as exceeded the suppression 99%[82]. Inflammation is one of the cancer initiation factor. It activates cancer cells, induces DNA damage and causes epigenetic changes. Pomegranate juice, fruit extracts, and biomolecules exert significant impact expression of inflammatory on cell signaling protein in cancer cells .[76]

Pomegranate juice, pomegranate tannins, and punicalagin significantly reduced the expression of cyclooxygenase – 2 (COX-2). COX-2 proteins are responsible for production of prostanoids that induce inflammation [77]. Ellagic acid, a metabolite of pomegranate ellagitannins, inhibited intestinal inflammation by down regulating certain inflammation-mediating compounds such as COX-2 and iNOS and blocking cell signaling pathways including NF-kB, p38 MAPK, IL6, and STAT3 in tissues of the colon [78].

Local invasion of tumour and metastases are clinically the most relevant and most difficult to target. Majority of cancer deaths are due to the metastatic spread of primary tumours. Series of researches are conducted to know the chemopreventive and therapeutic properties of pomegranate against different types of cancers. However, the tolerable doses of combined extracts and individual compounds capable of giving chemopreventive and therapeutic effects and the underlying anticancer mechanism needs further exploration.

Cardiac Health

Pomegranate fruit is a rich source of natural phenolics which can reduce the risk of cardiovascular diseases[79]. The presence of alkaloids, flavonoids, phenolic compounds, tannins, lignins, fats and oils, inulin, cardiac glycosides and carbohydrates povide antioxidant and free radical scavenging effect. Polyphenol-rich pomegranate fruit consumption cause modulatory effect and improves cardiac muscle tone, mitigates oxidative stressmediated arterial hardening, and attenuates atherosclerosis.[80] Healthy heart features attributed predominantly are by the pomegranate ellagitannins especially punical gin isomers α and β . Pomegranate hydrolyzable ellagitannin are converted to ellagic acid and then metabolized to urolithins by intestinal microbiota and reduces cardiac complications.[81]

Lipid accumulation is encouraged by low-density lipoprotein (LDL) cholesterol oxidation leading to atherosclerosis. Dyslipidemic obese patients administered with 500 mg pomegranate rind extract demonstrated a significant reduction in systolic blood pressure and improved lipid profile proving its antiatherogenicity. [82]. Administration of pomegranate juice in addition to medical treatment in patients with myocardial ischemia and unstable angina, caused a significant reduction in serum level of malondialdehyde and troponin, intensity of angina pectoris, and reperfusion injury [83].

Pomegranate fruit and peel extracts have ameliorative role in an vascular inflammation. oxidative stress. and elevated cardiac enzymes markers. Pomegranate supplements when given to hyperlipidemic animal models prevented coronary endothelial dysfunction. It also inhibited vascular inflammation and stressmediated coronary DNA damage and stimulating Akt/endothelial nitric oxidesynthase pathway and favorably counteracted vascular inflammation and oxidative damage[84]. Pomegranate fruit extracts have been found to present an ameliorative effect in isoproterenoltoxicated myocardial infarction by attenuating oxidative stress and level of cardiac enzymes markers, i.e., CK-MB and troponin [85]. These findings suggest that pomegranate fruit juice, seeds, rind extracts, and other derived products offer cardio protective and therapeutic properties.

Antidiabetic properties

Pomegranate fruit, flowers and leaves were traditionally used for the treatment of diabetes [86] Damage to the pancreatic β cells by oxidative stress causes the onset of type 2 diabetes. Free radical scavenging properties of pomegranate safeguard pancreatic β -cells from injury through neutralising the effect of free radicals [87,88]. Pomegranate fruit juice and derived products have a preventive role in the onset of diabetes. [89,90].Pomegranate peel powder when supplemented orally, substantially improved the serum level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutathione and superoxide dismutase (SOD) contents. It also improved hepatic glucose-6 phosphate dehydrogenase activity, and caused regeneration of pancreatic β -cells in streptozotocin-induced diabetic animal model [91,92,]. Fruit extracts and individual components like punicalagin, punicalin, ellagic acid, and gallic acid exhibited anti-glycation properties. [93]. Ellagitannins bind the active site of α glucosidase surface and make it inactive and delay carbohydrate digestion and lowers glucose absorption [94,95]. The fruit also exhibits healing effect in treating diabetic nephropathy via improving blood glucose level, kidney hypertrophy index, strengthening glomeruli tubules. increasing basement membrane thickness, and reducing renal disease markers [96-100].

Hepatoprotective Role

Liver is considered as the metabolic powerhouse of the body. It is responsible for nutrient metabolism and detoxification. The pathogenesis and progression of chronic liver disease is due to oxidative stress. Pomegranate fruit prevents progression of liver illnesses. Oral feeding of pomegranate protects sepsis-mediated acute liver injury. Free radical scavenging properties and anti-inflammatory activities of the fruit phenolics was considered as the

fundamental protection mechanism. Phenolics can protect and allay the risks of acute liver injury. Pomegranate phenolics consumed in the form of juice or extracts activate superoxide dismutase (SOD) and glutathione activity and reduce serum malondialdehyde contents that further help in mediating TLR4 and NF-kB inflammatory pathways [101,102]. Pomegranate peel when extracts administered to animals with signs of fatty liver showed considerable protective effect on hepatic morphology, inhibited lipogenesis in cytoplasm of hepatocytes, and improved liver enzymes [103]. Ellagic acid. attenuates alcohol-induced hepatotoxicity by reducing expressions of pro-fibrogenic and pro-inflammatory cytokines like interleukins, TNF- α , and TGF- β which are reported to increase in alcohol-induced liver fibrosis and inflammation [104-105]

Effect on Brain

Fruits like pomegranate having free radical quenching properties, can act as a natural neuro protective agent. A study conducted in transgenic amyloid precursor protein (APP) of mutated mice models revealed that the cognitive performance of the animal models were boosted with diet enriched with 4% pomegranate juice. It also reduced the anxiety level, improved the learning ability, memory and motor coordination when compared to the mice fed with standard diet[106] Memory assessments on older adults with mild complaints memory showed that individuals who consumed pomegranate iuice experienced significant improvements on memory performance. fMRI studies of memory-impaired subjects revealed that the pomegranate juice intervention activated memory-related brain regions. The findings support the hypothesis that in older adults with mild memory complaints, preexisting pomegranate juice can increase brain activation and improve memory ability[107]. Pomegranate peel extracts hadgamma secretase modulatory and acetylcholinesterase inhibitory effect and it reduced pathogenesis of Alzheimer's diseases. Human trials also revealed that intake of pomegranate juice boosted the and brain functionality memory by strengthening brain antioxidants pool [108].

Effect on bone

Botanical extracts from pomegranate are potent carrier of antioxidants and antiinflammatory compounds that can be utilized for restoring bone health. Rheumatoid arthritis is an autoimmune disease affecting about 0.5-1% world population. It is characterized by synovial inflammation infiltration and of cells inflammatory in synovial fluid causing irreversible cartilage and bone damage[109]. Consumption of pomegranate extract prevented the development of collagen induced arthritis (CIA) in mice by selectively inhibiting a spectrum of signal transduction pathways and cytokines. These are critical to the development of inflammation in rheumatoid arthritis (RA)[110]. Dietary pomegranate peel extract can improve bone mass and micro architecture of bone tissue during osteoporosis. [111].

Pomegranate fruit extract acts against osteoarthritis by improving cartilage stiffness and physical fitness. It also decreases level of cartilage catabolizing enzymes and strengthens antioxidative defence system [112]. In osteoporosis during the remodelling phase there is structural deterioration of the micro architecture of leading to bone bone fragility and bone loss. Pomegranate peel extract-enriched diet improves bone mineralization by increasing osteogenic transcription factors and stimulating activity of bone maker protein, i.e., alkaline phosphatase (ALP) [113]. Identification of the components of Pomegrnate extracts will open new avenues for the development of preventive effective therapies against arthritis. The antioxidants and antiinflammatory features compounds bearing of pomegranate fruit can be suggested as functional food to prevent bone loss, prevention of inflammatory arthritis and associated disorders.

Other Properties

Scientific literature gives ample evidence regarding the benefits of pomegranate for heart, diabetes, skin, teeth, cancer etc. Other health promoting effects of the pomegranate on human body have also been reported but more conclusive studies are needed to confirm these effects, because, related references are very few to substantiate these effects.

Antidiarrheal properties: Consumption of aqueous and alcohol extracts of pomegranate fruit rind by albino rats showed a significant reduction in faecal output when compared to loperamide hydrochloride, a standard antidiarrheal drug[114]. Extract of pomegranate peels when consumed by rats exhibited a concentration-dependent inhibition of the spontaneous movement of the ileum and attenuated acetylcholine-induced contractions[115]. Pomegranate peel extract also decreased the number of defecation and the weight of faeces[116] Gut microbiota

Consumption of pomegranate products leads to a significant accumulation of Ellagitanins. In the large intestine they interact with the complex gut microflora and can affect the growth of various species of human gut bacteria.[117] The growth of Bifidobacterium animalis ssp. lactis was slightly inhibited by punicalagins, punicalins, and ellagic acid and significantly enhanced the growth of Bifidobacterium breve and Bifidobacterium infantis. Punicalagins inhibited the growth of pathogenic and Staphyloccocus aureus. clostridia Probiotic lactobacilli and bifidobacteria were generally not affected by ellagitanins, [118]

Sperm quality

Consumption of Pomegranate juice, can increase epididymal sperm concentration, sperm motility, spermatogenic cell density, diameter of seminiferous tubules and germinal cell layer thickness. It also decreased the abnormal sperm count. An improvement in antioxidant enzyme activity in both rat plasma and sperm was also noted [119]. Ellagic acid has a protective effect against testicular and toxicity spermatozoal induced bv cyclosporine A. This protective effect of ellagic acid (EA) seems to be closely involved with the suppression of oxidative stress. [120]

Erectile dysfunction

Use of pomegranate juice for the treatment of mild-to-moderate erectile dysfunction showed improved scores[121]. Long term pomegranate juice intake in a rabbit model increased intracavernous blood flow and improved erectile response and smooth muscle relaxation erectile dysfunction. in Pomegranate juice intake prevented erectile tissue fibrosis .

Obesity

According to the World Health Org., there currently are more than 1billion overweight adults, 300 million of whom are obese. Consumption of pomegranate extract in female rats significantly decreased the feed intake and body weight of the animals. Pomegranate leaf extract when given to mouse model with high-fat diet-induced obesity, showed inhibition in development of obesitv and hyperlipidemia. [122]

Wound Healing Properties

Pomegranate pericarp and epicarp extracts can be recommended as a natural remedy in wound healing. They contain bioactive ingredients that aid in skin epithelialization and regeneration. Pomegranate pericarp and epicarp were used in folk medicines in various ailments including excised and incised wound healing. Biochemical and histological examination revealed that pomegranate comprises tremendous antimicrobial and antioxidant features that aid in epithelialization and production of hydroxyproline to regenerate wounds [123,124]. Topical application of pomegranate polyphenols and lipophilic fractions-based ointments on cutaneous wounds resulted in significant wound recovery notably in diabetic patients [125,126]. Topical administration of pomegranate extracts to incised wounds in experimental animals reduced the wound area to 95% as compared to 85% in control petroleum jelly-based ointment. Topical application of Pomegranate extracts to burn wounds significantly reduced the period of epithelialization compared to standard drugs [127,128]. Pomegranate and Oral Health

Oral dental health is affected by plaqueformaion and cariogenic bacteria. Flavonoids, tannins, vitamins, and minerals-rich fractions of pomegranate have anticariogenic and anti-plaque formulations. Pomegranate natural polyphenols inhibited growth of plaqueforming bacteria including Streptococcus sanguis and Pseudomonas aeruginosa [129,130]. Use of pomegranate mouthwash effectively reduced gingivitis and periodontitis in comparison with 0.2% chlorhexidine mouth rinse [131].Topical application of oral gel containing 10% pomegranate extracts relieved pain and reduced time for wound healing in aphthous stomatitis. Pomegranate fruit extracts efficiently reduced production of bacterial secondary metabolites, sucrose α-glucosidase catabolizing enzyme activity, aspartate aminotransferase activity, and upregulation of ceruloplasmin inhibited oral oxidative that stress [132,133]. The results of application of pomeganate extracts against various orodental is encouraging. distresses Therefore the use of natural oral care formulations based on pomegranate extract may be preferred to synthetic and chemotherapeutic products.

Conclusion

All parts of pomeganate including the peel, airls, flower, rind, the root, and stem bark have been reported to be effective in the treatment of a wide variety of diseases. Consumption of pomegranate is reported to improve the defence mechanism of the body[134]. Compared to other fruits of same class, pomeganate has got a wider range of applications against serious ailments. Pomegranate juice and the compounds derived from it has been focused in many in vitro and in vivo studies which revealed their antioxidative, antimicrobial, anti-inflammatory, antimutagenic, hepatoprotective, cardio

protective, antidiabetic and neuro protective properties. It has got an unique biochemical profile with more than 124 phytochemicals responsible for a broad range of applications. [27] Therefore exploitation of pomegranate and derived bioactive compounds as therapeutic agent either alone or in combination calls for careful experimentation to rule out genotoxic response of the plant material.

Reference

- Panagiotis Kandylis, Evangelos Kokkinomagoulos, Food Applications and Potential Health Benefits of Pomegranate and its Derivatives Foods 2020, 9, 122
- Akhtar S, Ismail T, Fraternale D, Sestili P (2015) Pomegranate peel and peel extracts: chemistry and food features. Food Chem 174:417– 425.https://doi.org/10.1016/j. foodchem.2014.11.035
- Rana, T.S.; Narzary, D.; Ranade, S.A. Systematics and taxonomic disposition of the genus Punica L.Pomegranate. Fruit Veg. Cereal Sci. Biotechnol. 2010, 4, 19–25.
- 4. Pansare tabassum arif , Borokar archana ajabrao, Dodke pranita chandu A critical review on hridya (cardiotonic) action of dadim (punica granatum linn.) with special reference to ayurvedic and modern aspect : IJAPR | December 2017 | Vol 5 | Issue 12
- Dr. Brahmanand Tripathi and Dr. Ganga Sahay Pandey. Caraka-Chandrika Hindi Commentary Caraca Samhita -1 (Hindi Translation). Varanasi; Chaukhamba Surbharati Prakashan. Reprint 2017: p. 80.
- 6. Dr. Bramhananda Tripathi. Astanga Hrdayam of Srimadvagbhata. Nirmala

Hindi Commentary (Hindi Translation). Delhi: Chaukhamba Sanskrit Pratishthan; reprinted 2017, p.155.

- Julie Jurenka, MT (ASCP)Therapeutic Applications of Pomegranate (Punica granatum L.): A Review :Altern Med Rev 2008;13(2):128-144)
- 8. Sreeja Sreekumar, Hima Sithul. Parvathy Muraleedharan, Juberiya and Sreeia Mohammed Azeez. Sreeharshan;Pomegranate Fruit as a Rich Source of Biologically Active Compounds : Hindawi Publishing Research Corporation .BioMed International Volume 2014, Article ID 686921, 12 pages,
- Saeed Akhtar, Tariq Ismail, and Anam Layla,Pomegranate Bioactive Molecules and Health Benefits. Springer Nature Switzerland AG 2019 J.-M. Mérillon, K. G. Ramawat (eds.), Bioactive Molecules in Food, Reference Series in Phytochemistry,
- 10. Lansky EP, Newman RA (2007) Punica granatum (pomegranate) and its potential for prevention and treatment of inflflammation and cancer. J Ethnopharmacol 109:177–206.
- 11. Kumari A, Dora J, Kumar A, Kumar A(2012) Pomegranate (Punica granatum)overview. Int J Pharm Chem Biol Sci1:1218–1222
- 12. Zhao X, Yuan Z, Fang Y, Yin Y, Feng L (2013) Characterization and evaluation of major anthocyanins in pomegranate (Punica granatum L.) peel of different cultivars and their development phases. Eur Food Res Technol 236:109–117. https://doi.org/10.1007/s00217-012-1869-6
- 13. Qu W, Breksa AP III, Pan Z, Ma H, Mchugh TH (2012) Storage stability of

sterilized liquid extracts from pomegranate peel. J Food Sci 77:765– 772.

- 14. M.A. Jafri a, M. Aslam a , Kalim Javed a , Surender Singh b, Effect of Punica granatum Linn. (flowers) on blood glucose level in normal and alloxan-induced diabetic rats M.A. Jafri et al. / Journal of Ethnopharmacology 70 (2000) 309–314
- Anonymous, 1969. Wealth of India, vol. VIII. Publication and Information Directorate (CSIR), New Delhi, pp. 317–324.
- Chopra, C.L., Bhatia, M.C., Chopra, I.C., 1960. In vitro antibacterial activity of oils from Indian medicinal plants. J. Am. Pharm. Assoc. (Sci. Ed.) 49, 780
- Janardhanan, K.K., Ganguly, D., Baruah, J.N., Rao, P.R., 1963. Fungitoxicity of extracts from tanninbearing plants. Curr. Sci. 32, 226.
- Charya, M.A.S., Reddy, S.M., Kumar, B.P., Reddy, S.R., 1979. Laboratory evaluation of some medicinal plant extracts against two pathogenic fungi. New Botany 6, 171.
- Prakash, V., Singhal, K.C., Gupta, R.R., 1980. Anthelmintic activity of Punica granatum and Artemesia si6ersiana. Ind. J. Pharmacol. 12, 62.
- Dhawan, B.N., Saxena, P.N., 1958. Evaluation of some indigenous drugs for stimulant effect on the rat uterus: a preliminary report. Indian J. Med. Res. 46, 808.
- Carraz, G.L.M., Willemot, J., Demenge P., 1978. Penta-O-galloyl-bglucose is useful as an hypoglycaemic agent. Fr. Demande 1978. 2, 380, 299 (C1CO 7H 13/08) 08 Sept. 1978, Appl

77/3, 610, 09 Feb. 1977, 11 pp./Chem. Abstr. 91: 1978 P5441h.)

- 22. Nogueira, D.G., Pereira, N.A., 1984. Activity of Punica granatum L. extract in hyperglycemic mice treated with propranolol. Rev. Bras. Farm. 65, 46– 51,
- 23. Heber D (2011) Pomegranate ellagitannins. In: Benzie IFF, Wachtel-Galor S (eds) Herbal medicine: biomolecular and clinical aspects, 2nd edn. CRC Press, Boca Raton
- 24. Neyrinck AM, Van Hée VF, Bindels LB, De Backer F, Cani PD, Delzenne NM (2012) Polyphenol-rich extract of pomegranate peel alleviates tissue inflflammation and hypercholesterolaemia in high-fat dietinduced obese mice: potential implication of the gut microbiota. Br J Nutr 7:1-8. https://doi.org/10.1017/S00071145120 02206
- 25. Syed DN, Chamcheu JC, Adham MV, Η (2013) Pomegranate Mukhtar extracts and cancer prevention: and cellular activities. molecular Anticancer Agents Med Chem (Formerly CurrMed Chem Anticancer Agents) 13:1149–1161
- 26. Orgil O, Schwartz E, Baruch L, Matityahu I, Mahajna J, Amir R (2014) The antioxidative and anti-proliferative potential of non-edible organs of the pomegranate fruit and tree. LWT-Food Sci Technol 58:571– 577.<u>https://doi.org/10.1016/j.lwt.2014.</u> 03.030
- Viuda-Martos, M.; Fernández-López, J.; Pérez-Álvarez, J.A. Pomegranate and its many functional components as related to human health: A review. Compr. Rev. Food Sci. Food Saf. 2010, 9, 635–654.

- Turrini, E.; Ferruzzi, L.; Fimognari, C. Potential effffects of pomegranate polyphenols in cancer prevention and therapy. Oxid. Med. Cell. Longev. 2015, 2015, 1–19.
- 29. Williamson, G. The role of polyphenols in modern nutrition. Nutr. Bull. 2017, 42, 226–235. [PubMed]
- Bonesi, M.; Tundis, R.; Sicari, V.; Loizzo, M.R. The juice of pomegranate (Punica granatum L.): Recent studies on its bioactivities. In Quality Control in the Beverage Industry; Grumezescu, A.M., Holban, A.M., Eds.; Academic Press: New York, NY, USA, 2019; Volume 17, pp. 459–489.
- 31. Dao TT, Chi YS, Kim J, Kim HP, Kimb S, Parka H. 2004. Synthesis and inhibitory activity against COX-2 catalyzed prostaglandin production of chrysin derivatives. Bioorg Med Chem Lett 14:1165–7.
- 32. Cho H, Yun CW, Park WK, Kong JY, Kim KS, Park Y, Lee S, Kim BK. 2004. Modulation of the activity of pro-inflflammatory enzymes, COX-2 and iNOS, by chrysin derivatives. Pharcacol Res 49:37–43.
- 33. Lee CJ, Chen LG, Liang WL, Wanga CC. 2010. Anti-inflammatory effects of Punica granatum Linne in vitro and in vivo. Food Chem 118:315–22.
- 34. Larrosa M. Gonzalez-Sarrias A. Yanez-Gascon MJ. Selma MV. Azor'ın-Ortu no M, Toti S, Tom'as-Barber´an F, Dolara P, Espina JC. 2010.Anti-inflflammatory properties of a pomegranate extract and its metabolite urolithin-A in a colitis rat model and the effect of colon inflflammation phenolic on metabolism. J Nut Biochem 21(8):717-25.

- 35. Boussetta T, Raad H, Letteron P, Gougerot-Pocidalo MA, Marie JC, Driss F, El-Benna J. 2009. Punicic acid, a conjugated linolenic acid, inhibits TNF α -induced neutrophil hyperactivation and protects from experimental colon inflflammation in rats. PLoS One 4(7):6458. Available from:
- 36. Suppressive effect of Punica granatum on the production of tumor necrosis factor (Tnf) in BV2 microglial cells. Biol Pharm Bull 29:1258–61.
- 37. Ahmed S, Wang N, Hafeez BB, Cheruvu VK, Haqii TM.
 2005.PunicagranatumL.extract inhibits IL-1beta-induced expression of matrix metalloproteinases by inhibiting the activation of MAP kinases and NFkappaB in human chondrocytes in vitro. J Nutr 135:2098–102
- 38. De Nigris F, Balestrieri ML, Williams-Ignarro S, D'Armiento FP, Fiorito C, Ignarro LJ, Napoli C. 2007. The inflfluence of pomegranate fruit extract in comparison to regular pomegranate juice and seed oil on nitric oxide and arterial function in obese Zucker rats. Nitric Oxide 17:50–4.
- 39. Romier-Crouzet B, Walle JV, During A, Joly A, Rousseau C, Henry O,Larondelle Y, Schneider YJ. 2009. Inhibition of inflammatory mediators by polyphenolic plant extracts in human intestinal Caco-2 cells. Food ChemToxicol 47:1221–30
- 40. Braga LC, Shupp JW, Cummings C, Jett M, Takahaski JA, Carmo LS, Chartone-Souza E, Nascimento AMA. 2005a. Pomegranate extract inhibits Staphylococcus aureus growth and subsequent enterotoxin production. J Ethnopharmacol 96:335–9.

- Prashanth DJ, Asha MK, Amit A. 2001. Antibacterial activity of Punicagranatum. Fitoterapia 72:171–3.
- 42. Voravuthikunchai SP. Sririrak T, Limsuwan S, Supawita T, Iida T, Honda T.2005. Inhibitory effects of active compounds from Punica granatum pericarp on verocytotoxin production by enterohemorrhagic Escherichia coli O157:H7. J Health Sci 51(5):590–6.
- 43. Salgado L, Melgarejo P, Meseguer I, S´anchez M. 2009. Antimicrobial activity of crude extracts from pomegranate (Punica granatum L.). Acta Hort 818:257–64.
- 44. [44] Reddy MK, Gupta SK, Jacob MR, Khan SI, Ferreira D. 2007. Antioxidant,antimalarial and antimicrobial activities of tannin-rich fractions, ellagitannins and phenolic acids from Punica granatum L. Planta Med 73:461–7.
- 45. Al-Zoreky NS. 2009. Antimicrobial activity of pomegranate (Punica granatum L.) fruit peels. Int J Food Microbiol 134:244–8.
- 46. Mathabe MC, Nikolova RV, Lall N, Nyazema NZ. 2005. Antibacterial activities of medicinal plants used for the treatment of diarrhoea in Limpopo Province, South Africa. J Ethnopharmacol 105:286–93.
- 47. Braga LC, Leite AA, Xavier KG, Takahashi JA, Bemquerer MP, Chartone-Souza E, Nascimento AM. 2005b. Synergistic interaction between pomegrante extract and antibiotics against Staphylococcus aureus. Can J Microbiol 51:541–7.
- 48. Melendez PA, Capriles VA. 2006. Antibacterial properties of tropical plants from Puerto Rico. Phytomed 13:272–6.

- 49. Choi JG, Kang OH, Lee YS, Chae HS, Oh YC, Brice OO, Kim MS, Sohn DH, Kim HS, Park H, Shin DW, Rho JR, Kwon DY. 2009. In vitro and in vivo antibacterial activity of Punica granatum peels ethanol extract against salmonella. Evid Based Compl Alter Med 17:1–8.
- 50. Ahmad I, Beg AZ. 2001. Antimicrobial and phytochemical studies on 45Indianmedicinal plants against multi-drug and resistant human pathogens.J Ethnopharmacol 74:113– 23.
- 51. Naz S, Siddiqi R, Ahmad S, Rasool SA, Sayeed SA (2007) Antibacterial activity directed isolation of compounds from Punica granatum. J Food Sci 72:M341–M345.
- 52. Howell AB, D'Souza DH (2013) The pomegranate: effects on bacteria and viruses that influence human health. Evid Based Complement Alternat Med 2013:606212.
- 53. Puupponen-Pimia R, Nohynek L, Hartmann-Schmidlin S, Kahkonen M, Heinonen M, Maatta-Riihinen K, Oksman-Caldentey KM. 2005. Berry phenolics selectively inhibit the growth of intestinal pathogens. J Appl Microbiol 98:991–1000.
- 54. Puupponen-Pimia R, Nohynek L, Meier C, Kahkonen M, Heinonen M, Hopia A, Oksman-Caldentey KM. 2001. Antimicrobial properties of phenolic compounds from berries. J Appl Microbiol 90:494–507.
- 55. Veldhuizen EJ, Tjeerdsma-van Bokhoven JL, Zweijtzer C, Burt SA, Haagsman HP. 2006. Structural requirements for the antimicrobial activity of carvacrol. J Agric Food Chem 54:1874–9.

- 56. Naz S, Siddiqi R, Ahmad S, Rasool S, Sayeed S. 2007. Antibacterial activity directed isolation of compounds from Punica granatum. J Food Sci 72:341–5.
- 57. Foss SR, Nakamura CV, Ueda-Nakamura T, Cortez DA, Endo EH, Dias Filho BP 2014 Antifungal activity of pomegranate peel extract and isolated compound punicalagin against dermatophytes. Ann Clin Microbiol Antimicrob 13:32. https://doi.org/10.1186/s12941-014-0032-6
- 58. Dahham SS, Ali MN, Tabassum H, Khan M (2010) Studies on antibacterial and antifungal activity of pomegranate (Punica granatum L.). Am Eurasian J Agric Environ Sci 9:273–281
- 59. Cheng HY, Lin TC, Yang CM, Wang KC, Lin CC (2004) Mechanism of action of the suppression of herpes simplex virus type 2 replication by pterocarnin A. Microbes Infect6:738–744.

https://doi.org/10.1016/j.micinf.2004.0 3.009

- 60. Reddy BU, Mullick R, Kumar A, Sudha G, Srinivasan N, Das S (2014) Small molecule inhibitors of HCV replication from pomegranate. Sci Rep 4:5411. https://doi.org/10.1038/ srep0541
- 61. Moradi MT, Karimi A, Alidadi S, Saedi-Marghmaleki M (2015) In vitro anti-adenovirus activity of pomegranate (Punica granatum L.) peel extract. Adv Herb Med 1:1–8
- 62. Eleonora Turrini, Lorenzo Ferruzzi, And Carmela Fimognari:Potential Effects Of Pomegranate Polyphenols In Cancer Prevention And Therapy :Hindawi Publishing Corporation Oxidative Medicine And Cellular

Longevity Volume 2015, Article Id 938475,

- 63. Rebecca Siegel, Elizabeth Ward, Otis Brawley, Ahmedin Jemal,The Impact Of Eliminating Socioeconomic And Racial Disparities On Premature Cancer Deaths A Cancer Journal For Clinicians volume 61 _ Number 4 _ July/August 2011
- 64. Gil MI, Tomás-Barberán FA, Hess-Pierce B, Holcroft DM, Kader AA (2000) Antioxidantactivity of pomegranate juice and its relationship with phenolic composition and processing. J Agric Food Chem 48:4581–4589.
- 65. Seeram NP, Adams LS, Henning SM, Niu Y, Zhang Y, Nair MG, Heber D (2005) In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. J Nutr Biochem 16:360–367.
- 66. Kulkarni AP, Mahal HS, Kapoor S, Aradhya SM (2007) In vitro studies on the binding, antioxidant, and cytotoxic actions of punicalagin. J Agric Food Chem 55:1491–1500.
- 67. Aqil F, Munagala R, Vadhanam MV, Kausar H, Jeyabalan J, Schultz DJ, Gupta RC (2012) Anti-proliferative activity and protection against oxidative DNA damage by punicalagin isolated from pomegranate husk. Food Res Int 49:345–353.
- 68. Kim ND, Mehta R, Yu W, et al. (2002). Chemopreventive and adjuvant therapeutic potential of pomegranate (Punica granatum) for human breast cancer. Breast Cancer Res Treat 71: 203–217.

- 69. R Mehta1 and E P Lansky Breast cancer chemopreventive properties of pomegranate (Punica granatum) fruit extracts in a mouse mammary organ culture European Journal of Cancer Prevention 2004, Vol 13 No 4
- 70. Ephraim P. Lansky, Robert A. Newman Punica granatum (pomegranate) and its potential for prevention and treatment of inflammation and cancer Journal of Ethnopharmacology 109 (2007) 177– 206
- 71. Ghulam Jilany Khan1 , Muhammad Ovais Omer2 , Muhammad Ash:Effect of punica granatum (pomegranate) fruit extract on angiogenesis J App Pharm 04(02): 764-780; April, 2013
- 72. Toi, M., Bando, H., Ramachandran, C., Melnick, S.J., Imai, A., Fife, R.S., Carr, R.E., Oikawa, T., Lansky, E.P., 2003. Preliminary studies on the antiangiogenic potential of pomegranate fractions in vitro and in vivo. Angiogenesis 6, 121–128.
- 73. Kim, M.M., Kim, S., 2002. Composition for improving oral hygiene containing Punica granatum Korean L. extract. Patent: KR 2002066042
- 74. Albrecht, M., Jiang, W., Kumi-Diaka, J., Lansky, E.P., Gommersall, L.M., Patel, A., Mansel, R.E., Neeman, I., Geldof, A.A., Campbell, M.J., 2004. Pomegranate extracts potently suppress proliferation, xenograft growth, and invasion of human prostate cancer cells. Journal of Medicinal Food 7, 274–28
- 75. Lansky et al., 2005 Lansky, E.P., Jiang, W., Mo, H., Bravo, L., Froom, P., Yu, W., Harris, N.M,Neeman, I., Campbell, M.J., 2005a. Possible synergistic prostate cancer suppression

by anatomically discrete pomegranate fractions. Investigational New Drugs 23, 11–20.

- 76. Pohl C, Hombach A, Kruis W (2000) Chronic inflammatory bowel disease and cancer. Hepatogastroenterology 47:57–70
- 77. Adams, L.S., Seeram, N.P., Aggarwal,
 B.B., Takada, Y., Sand, D., Heber,
 D.,2006. Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflflammatory cell signaling in colon cancer cells. Journal of Agricultural and Food Chemistry 54, 980–985.
- 78. Marín M, Giner RM, Ríos JL, Recio MC (2013) Intestinal antiinflflammatory activity of ellagicacid in the acute and chronic dextrane sulfate sodium models of mice colitis.J Ethnopharmacol 150:925–934. https://doi.org/10.1016/j.jep.2013.09.0 30
- 79. Taghadosi M, Gilasy HR (2008) The general and specific quality of life in patients with ischemia in Kashan. Iran J Nurs Res 3:39–46
- 80. Vilahur G, Padró T, Casaní L, Mendieta G, López JA, Streitenberger S, Badimon L (2015) Polyphenolenriched diet prevents coronary endothelial dysfunction by activating the Akt/ eNOS pathway. Rev Esp Cardiol 68:216–225.
- 81. Aloutaibi GT, Gashlan H, Moselhy SS, Al-Malki AL, Khan JA (2017) Possible cardioprotective action of pomegranate juice punica granatum and propolis against myocardial infarction induced in rats. AJTCAM 14:138–146.
- 82. Espín JC, Larrosa M, García-Conesa MT, Tomás-Barberán F (2013) Biological signifificance of urolithins,

the gut microbial ellagic acid-derived metabolites: the evidence so far. Evid Based Complement Alternat Med 2013:270418.

- 83. Haghighian MK. Rafraf M. Moghaddam A, Hemmati S, Jafarabadi MA, Gargari BP (2016) Pomegranate (Punica granatum L.) peel hydro alcoholic extract ameliorates cardiovascular risk factors in obese women with dyslipidemia: a double blind, randomized, placebo controlled EuJIM pilot study. 8:676-682.https://doi.org/10.1016/j.eujim.201 6.06.010
- 84. Razani Z, Dastani M, Kazerani HR (2017) Cardioprotective effects of pomegranate (Punica granatum) juice in patients with ischemic heart disease. Phytother Res 31:1731–1738. https:// doi.org/10.1002/ptr.5901
- 85. [85]Vilahur G, Padró T, Casaní L, Mendieta G, López JA, Streitenberger S, Badimon L (2015) Polyphenolenriched diet prevents coronary endothelial dysfunction by activating the Akt/ eNOS pathway. Rev Esp Cardiol 68:216–225. https://doi.org/10.1016/j.rec.2014.04.0 21
- 86. Xu KZY, Zhu C, Kim MS, Yamahara J, Li Y (2009) Pomegranate flower ameliorates fatty liver in an animal model of type 2 diabetes and obesity. J Ethnopharmacol 123:280–287.
- 87. Hunt JV, Smith CC, Wolff SP (1990) Autoxidative glycosylation and possible involvement of peroxides and free radicals in LDL modifification by glucose. Diabetes 39:1420–1424. https://

doi.org/10.2337/diab.39.11.1420

88. Tzulker R, Glazer I, Bar-Ilan I, Holl D, Aviram M, Amir R (2007) Antioxidant activity, polyphenol content and related compounds in different fruit juices and homogenates prepared from 29 different pomegranate accessions. J Agric Food Chem 55:9559–9570. https://doi.org/ 10.1021/jf071413n

89. Rock W, Rosenblat M, Miller-Lotan R, Levy AP, Elias M, Aviram M (2008) Consumption of wonderful variety pomegranate juice and extract by diabetic patients increases paraoxonase association with high-density 1 lipoprotein and stimulates its catalytic activities. J Agric Food Chem 56:8704-

8713.<u>https://doi.org/10.1021/jf801756x</u>

90. Rosenblat M, Hayek T, Aviram M (2006) Anti-oxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and on macrophages. Atherosclerosis 187:363–371.
https://doi.org/10.1016/i.atherosclerosi

https://doi.org/10.1016/j.atherosclerosi s.2005.09.006

- *91.* Saad EA, Hassanien MM, El-Hagrasy MA, Radwan KH (2015) Antidiabetic, hypolipidemic and antioxidant activities and protective effects of Punica granatum peels powder against pancreatic and hepatic tissues injuries in streptozotocin induced IDDM in rats. Int J PharmPharm Sci 7:397–402
- 92. Hasona Qumani NASA, MA. Alghassab TA, Alghassab MA. Alghabban AA (2017) Ameliorative properties of Iranian Trigonella foenum-graecum L. seeds and Punica L. granatum peel extracts in streptozotocin-induced experimental diabetic guinea pigs. Asian Pac J Trop Biomed 7:234-239. https://doi.org/10.1016/j.apjtb.2016.12. 004

- 93. Kumagai Y, Nakatani S, Onodera H, Nagatomo A, Nishida N, Matsuura Y, Wada M (2015) Anti-glycation effects of pomegranate (Punica granatum L.) fruit extract and its components in vivo and in vitro. J Agric Food Chem 63:7760–7764.
- 94. Bekir J, Cazaux S, Mars M, Bouajila J (2016) In vitro anti-cholinesterase and anti-hyperglycemic activities of flflowers extracts from seven pomegranate varieties. Ind Crop Prod 81:176–179. https://doi.org/10.1016/j.indcrop.2015.

11.066

95. Çam M, İçyer NC (2015) Phenolics of pomegranate peels: extraction optimization by central composite design and alpha glucosidase inhibition potentials. J Food Sci Technol 52:1489–1497. https://doi.org/10.1007/s13197-013-

1148-y

- 96. Ankita P, Deepti B, Nilam M (2015) Flavonoid rich fraction of Punica granatum improves early diabetic nephropathy by ameliorating proteinuria and disturbed glucose homeostasis in experimental animals. Pharm Biol 53:61–71.
- 97. Mestry SN, Dhodi JB, Kumbhar SB, Juvekar AR (2017) Attenuation of diabetic nephropathy in streptozotocininduced diabetic rats by Punica granatum Linn. leaves extract. JTCM 7:273–280.

https://doi.org/10.1016/j.jtcme.2016.06 .008

98. Mira Rosenblat a, Tony Hayek a,b, Michael Aviram : Anti-oxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and on macrophages:Atherosclerosis 187 (2006) 363–371

- 99. Julie Jurenka, Therapeutic Applications of Pomegranate (Punica granatum L.):A Review Alternative Medicine Review Volume 13, Number 2 2008
- 100. Sumner MD, Elliott-Eller M, Weidner G, et al. Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease. Am J Cardiol 2005;96:810-814
- 101. Makled MN, El-Awady MS, Abdelaziz RR, Atwan N, Guns ET, Gameil NM et al (2016) Pomegranate protects liver against cecal ligation and puncture-induced oxidative stress and inflammation in rats through TLR 4/NF-κB pathway inhibition. Environ Toxicol Pharmacol 43:182–192. https://doi.org/10.1016/j.etap.2016.03. 011
- 102. Al-Shaaibi SN, Waly MI, Al-Subhi L, Tageldin MH, Al-Balushi NM, Rahman MS (2016) Ameliorative effects of pomegranate peel extract against dietary-induced nonalcoholic fatty liver in rats. Prev Nutr Food Sci 21:14–23. https://doi.org/10.3746/pnf.2016.21.1.1

https://doi.org/10.3746/pnf.2016.21.1.1 4

103. García-Nino WR, Zazueta C (2015)
Ellagic acid: pharmacological activities and molecular mechanisms involved in liver protection. Pharmacol Res 97:84– 103. https://doi.org/10.1016/j. phrs.2015.04.008

104. Mandrekar P, Szabo G (2009) Signalling pathways in alcoholinduced liver inflammation. J Hepatol 50:1258–1266.

https://doi.org/10.1016/j.jhep.2009.03. 007

- 105. Wei XL, Fang RT, Yang YH, Bi XY, Ren GX, Luo AL, Zhao M, Zang WJ (2015) Protective effects of extracts from pomegranate peels and seeds on liver fibrosis induced by carbon tetrachloride in BMC rats. Altern Med Complement 15:389. https://doi.org/10.1186/s12906-015-0916-9
- 106. Subash S, Braidy N, Essa MM, Zayana AB, Ragini V, Al-Adawi S, Guillemin GJ (2015)Long-term dietary supplementation with pomegranates from Oman attenuates cognitive and behavioral deficits in a transgenic mice model of Alzheimer's disease. Nutrition 31:223-229. https://doi.org/10.1016/j.nut.2014.06.0 04
- 107. Susan Y. Bookheimer, Brian A. Renner, Arne Ekstrom, Zhaoping Li, Susanne M.Henning, Jesse A. Brown, Mike Jones, Teena Moody, and Gary W. Small1,Pomegranate Juice Augments Memory and fMRI Activity in Middle-Aged and Older Adults with Mild Memory Complaints Evid Based Complement Alternat Med 2013:946298.

https://doi.org/10.1155/2013/946298

- 108. Vasudev P, Shreedhara CS, Chandrashekar KS, Yamini D (2015) Neuroprotective action of Gmelina arborea (bark) and Punica granatum (peel) extracts. Asian J Pharm.
- 109. Allam G, Mahdi EA, Alzahrani AM, Abuelsaad AS (2016) Ellagic acid alleviates adjuvant induced arthritis by modulation of pro-and antiinflammatory cytokines. Cent Eur J Immunol

41:339.<u>https://doi.org/10.5114/ceji.201</u> 6.65132

- 110. Meenakshi Shukla, Kalpana Gupta, Zafar Rasheed, Khursheed A. Khan, and Tariq M. Haqqi:Consumption of hydrolyzable tannins-rich pomegranate extract suppresses inflammation and joint damage in rheumatoid arthritis;Nutrition 24 (2008) 733–743
- 111. Mélanie Spilmont, Laurent Léotoing, Marie-Jeanne Davicco. Patrice Lebecque, Elisabeth Miot-Noirault, Paul Pilet, Laurent Rios. Yohann Wittrant, Véronique Coxam.Pomegranate Peel Extract Prevents Bone Loss in a Preclinical Model of Osteoporosis and Stimulates Osteoblastic Differentiation in Vitro Nutrients 2015, 7, 9265-9284; doi:10.3390/nu7115465
- 112.N. Karandish M. Mowla K. Haghighizadeh MH, Jalali MT (2016) The effect of pomegranate juice on clinical signs, matrix metalloproteinases and antioxidant with status in patients knee J Sci osteoarthritis. Food Agric 96:4377-4381.
- 113. Spilmont M, Léotoing L, Davicco MJ, Lebecque P, Mercier S, Miot-Noirault E, Pilet P, Rios L, Wittrant Y, Coxam V (2013) Pomegranate seed oil prevents bone loss in a mice model of osteoporosis, through osteoblastic stimulation, osteoclastic inhibition and decreased inflammatory status. J Nutr Biochem 24:1840–1848.
- 114. Pillai NR. 1992. Anti-diarrhoeal activity of Punica granatum in experimental animals. Int J Pharmaco 30(3):201–4.
- 115. Qnais EY, Elokda AS, Abu-Ghalyun YY, Abdulla FA. 2007. Antidiarrheal activity of the aqueous extract of Punica granatum (pomegranate) peels.Pharma Biol 5(9):715–20

- 116. Olapour S, Mousavi E, Sheikhzade M, Hoseininezhad O, Najafzadeh H.2009. Evaluation antidiarrheal effects of pomegranate peel extract. J Iran Chem Soc 6(Nov):115–43.
- 117. Seeram NP, Henning SM, Zhang Y, Suchard M, Li Z, Heber D.
 2006.Pomegranate juice ellagitannin metabolites are present in human plasma and some persist in urine for up to 48 h. J Nutr 136:2481–5
- Kasimsetty 118. Bialonska D. SG. Schrader KK, Ferreira D. 2009. The pomegranate effect of (Punica granatum L.) by products and ellagitanins on the growth of human gut bacteria. J Agric Food Chem 57:8344-9
- 119. T[•]urk G, S[•]onmez M, Aydin M, Yuce A, G[•]ur S, Yuksel M, Aksu EH, Aksoy H. 2008. Effects of pomegranate juice consumption on sperm quality, spermatogenic cell density, antioxidant activity and testosterone level in male rats. Clin Nut 27(2):289–96.
- 120. T[°]urk G, S[°]onmez M, C_s eribasi AO, Yuce A, Atessahin A. 2010. Attenuation of cyclosporine A-induced testicular and spermatozoal damages associated with oxidative stress by ellagic acid. Int Immunopharmacol 10(2):177–82.
- 121. Forest CP, Padma-Nathan H, Liker HR. 2007. Efficacy and safety of pomegranate juice on improvement of erectile dysfunction in male patients with mild to moderate erectile dysfunction: a randomized, placebocontrolled, double-blind crossover study. Int J Impot Res 19(6):564–7.
- 122. Lei F, Zhang XN, Wang W, Xing DM, Xie WD, Su H, Du LJ. 2007.Evidence of anti-obesity effects of pomegranate leaf extract in high-fat-

diet-induced obese mice. Int J Obes 31(6):1023–9.

123. Hayouni EA, Miled K, Boubaker S, Bellasfar Z, Abedrabba M, Iwaski H et al (2011) Hydroalcoholic extract based-ointment from Punica granatum L. peels with enhanced in vivo healing potential on dermal wounds. Phytomedicine 18:976–984. https://doi.org/

10.1016/j.phymed.2011.02.011

- 124. Adiga S, Tomar P, Rajput RR (2010) Effect of Punica granatum peel aqueous extract on normal and dexamethasone suppressed wound healing in wistar rats. Int J Pharm Sci Rev Res5:34–37. Available online at<u>www.globalresearchonline.net</u>
- 125. Yan H, Peng KJ, Wang QL, Gu ZY, Lu YQ, Zhao J et al (2013) Effect of pomegranate peel polyphenol gel on cutaneous wound healing in alloxaninduced diabetic rats. Chin Med J 126:1700–1706
- 126. Klein M (2008) Pomegranate-derived products for the treatment of skin sores & lesions. US Patent Appl 12:676–957
- 127. Nayak SB, Rodrigues V, Maharaj S, Bhogadi VS (2013) Wound healing activity of the fruit skin of Punica granatum. J Med Food 16:857–861. ttps://doi.org/10.1089/jmf.2012.0229
- 128. Rajput R, Sagar VS, Adiga S (2011) Effect of punica granatum peel extract on burn wound healing in albino wistar rats. Int J Appl Biol Pharm 2:353–357
- 129. Menezes SM, Cordeiro LN, Viana GS (2006) Punica granatum (pomegranate) extract is active against dental plaque. J Herb Pharmacother 6:79–92.
- 130. Umar D, Dilshad B, Farhan M, Ali A, Baroudi K (2016) The effect of pomegranate mouthrinse on Streptococcus mutans count and

salivary pH: an in vivo study. J Adv Pharma Tech Res7:13– 16.<u>https://doi.org/10.4103/2231-</u> 4040.173266

- 131. Sedigh-Rahimabadi M, Fani M. Rostami-chijan M, Zarshenas MM, Μ Shams (2017)А traditional mouthwash (Punica granatum var pleniflflora) for controlling gingivitis of diabetic patients: a double-blind randomized controlled clinical trial. J Evid Based Complementary Altern 22:59-Med 67.https://doi.org/10.1177/2156587216 633370
- 132. Ghalayani P, Zolfaghary B, Farhad AR, Tavangar A, Soleymani B (2013) The efficacy of Punica granatum extract in the management of recurrent aphthous stomatitis. JRPP 2:88–92
- 133. DiSilvestro RA, DiSilvestro DJ, DiSilvestro DJ (2009) Pomegranate extract mouth rinsing effects on saliva measures relevant to gingivitis risk. Phytother Res 23:1123–1127. https://doi.org/10.1002/ptr.2759
- 134. Times of India article,<u>https://timesofindia.indiatimes.c</u> om/life-style/healthfitness/diet/pomegranatebenefits/articleshow/60114168.cms, Apr 6, 2022, 10:17 IST