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Review Article

A review on potential therapeutic properties of Pomegranate (*Punica granatum* L.)

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Abstract

Pomegranate (*Punica granatum* L. formerly in Punicaceae family) considered to be super food worldwide, belongs to the family Lythraceae. It is primarily cultivated in the Middle East, north and tropical Africa, the Indian subcontinent, Asia and Latin America. The medicinal potential of pomegranate is extensively mentioned in the ancient literature and also used in different system of medicines for a variety of ailments. The chemical constituents of pomegranate have increased the research concern of this fruit in the current years. It includes a variety of bioactive compounds such as quercetin, ellagic acid, punicalagin, pedunculagin, tannic acid, anthocyanins, rutin, catechin and polyphenols. These components of pomegranate possess antioxidant, neuroprotective, anti-inflammatory, anti-angiogenic, anticancerous, anti-mutagenic, cytoprotective, cardiovascular protective, anti-diabetic, anti-ulcerogenic, hepatoprotective, antibacterial and antifungal potentials. It can enhance the male fertility and also protect from the UV induced skin damage. Furthermore, it also illustrate the inhibitory effects on vital metabolic enzymes, stimulate cell differentiation and toxicological properties. The pomegranate also impedes with numerous signalling pathways, which include Bax, Bcl-X, Bad, ERK1/2, JNK, PI3K/AKT, mTOR, PI3K, MAPK and P38. The present review will extensively discuss the above properties of pomegranate and its extracts, supporting the rich nutritive and healthy advantages of the fruit belonging to the monogeneric family.

Keywords: Anticancer; Antioxidant; Cytoprotective; Therapeutic

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Introduction

Pomegranate (*Punica granatum*) is a fruit bearing deciduous shrub or small tree which grows between 15 to 28ft tall (1). Pomegranate is believed to have been originated from the modern day Iran, though the fruit has been cultivated since time immemorial in the Northern India and Mediterranean region (2). Globally it's been cultivated in the Caucasus region and Middle East, Tropical and North Africa, Central Asia and Indian subcontinent. In America it`s been cultivated in Arizona and California, also commercially available

in the markets of Europe (3). The shrubs or the small trees are particularly long lived with several anatomical differentiation including seed, peel, leaf, bark, flower and root, each having medicinal benefits (4). The ripe fruit is a berry, ranging about 5-12 cm in diameter which is round in shape and the skin is thick and reddish. The number of seeds in the pomegranate fruit range from 200 to 1400, each surrounded by water laden pulp (5), which varies in colour from white to deep red or purple. The seeds have no arils unlike some other species in the order, Myrtales. The sarcotesta of the seeds are made of epidermis cells derived from the integument (6).

The fruit has been mentioned in the Old Testament of the Holy Bible, the Babylonian Talmud and the Jewish Torah as a revered fruit conferring strength of fertility, abundance and good luck (7). It is also found in the Egyptian and Greek mythology and was the emblem of the Roman Emperor, Maximilian. Pomegranate gets its name from the ancient city of Granada in Spain, which is their symbol of victory. Pomegranate has been widely used in the alternative and traditional medicine. In Ayurveda, the pomegranate is famously known as “a pharmacy unto itself” and is used as an antiparasitic (8), diarrhoea, ulcers (9) and considered as “blood tonic” (10). Pomegranate is also a remedy for diabetes in the Unani system of medicine, practiced particularly in India (11).

The interest in the pomegranate research worldwide has been evidenced by the pubmed search from 2005 to 2019, showing 998 articles associated with its beneficial effects, however between 1950 and 1999 only 25 articles pertaining to pomegranate were found (7, 12). The potential of whole pomegranate fruit also significantly showed antioxidant (13, 14), anti-inflammatory (15), anti-diabetic (16), anticancer (17), hepatoprotective (18), anti-ulcerogenic (19), neuroprotective (20) and cardioprotective (21) properties.It was also demonstrated to treat erectile dysfunction (22), to enhance male fertility (23), to treat oral diseases (24) and for many other medicinal properties. Pomegranate seeds also exhibit properties against microbial infections, helminth infection and haemorrhage (25). Other potential applications comprise arthritis, obesity, Alzheimer`s disease, infant brain ischemia and UV induced skin damage (26, 27).

Chemical constituents

The chemical composition depends on the region where the fruits are grown, soil composition, cultivation type and other conditions (28). Considerable alterations in the chemical components have been reported over the decade of research (29). However most of the medicinal properties of the fruit are attributed to the particular secondary metabolites like ellagitannins, ellagic acid, punicic acid, anthocyanins like delphinidin, cyanidin and pelargonidin, anthocyanidines, flavonoids and flavones, and condensed tannins (30, 31).The peel of the pomegranate is a good source of minerals, polysaccharides, flavonoids, ellagitanins and phenolic compounds (32). The edible portion of the pomegranate contains mainly water, seeds, phenolic compounds, anthocyanins, pectins, malate, ascorbate, citrate and sugars, mainly glucose and fructose in it (33). The oil extracted from the seeds is rich in ω-3 fatty acids. It also contains palmitate, stearic acid, oleic acid, punicic acid, vitamins, proteins, sugars, fibres, polyphenols and minerals (34). Primary chemical constituents of pomegranate are listed in the Table 1.

Table 1. Primary chemical constituents of *Punica granatum*

Constituent	Formula	Molecular weight	Pomegranate Plant Parts
Anthocyanins Delphinidin (35)	$C_{15}H_{11}O_7$	303.24	Juice
Ascorbic acid (36)	$C_6H_8O_6$	176.12	Juice
Ellagic acid	$C_{14}H_6O_8$	302.19	Juice, seed oil (37) pericarp, flower
Gallic acid	$C_7H_6O_5$	170.12	Juice, pericarp, flower
Caffeic acid (36)	C_9H8O_4	180.16	Juice, seed oil, pericarp
Catechin	$C_{15}H_{14}O_6$	290.27	Juice, pericarp
EGCG (38)	$C_{40}H_{30}O_{24}$	894.65	Juice, pericarp
Quercitin	$C_{15}H_{10}O_7$	302.04	Juice, pericarp
Rutin (39)	$C_{27}H_{31}O_{15}$	595.53	Juice, pericarp
Iron (40)	Fe	55.85	Juice
Amino acids	$C_6H_9N_3O_2$	155.15	Juice
Punicic acid (41)	$C_{18}H_{30}O_2$	278.43	Pericarp, flower, root and bark
Sterols (42) Asiatic acid	$C_{30}H4_8O_5$	488.7	Seed oil
Punicalagens (43)	$C_{48}H_{28}O_{30}$	1084.7	Pericarp, leaves, roots and bark
Flavanones, flavones (44) Apigenin-4'-O-*β*-D-glucoside	$C_{21}H_{20}O_{11}$	448.32	Pericarp, leaves
Anthocyanidins (45) Cyanidin	$C_{15}H_{11}O_6$	287.24	Leaves
Tannins (punicalin and punicafolin)	$C_{34}H_{22}O_{22}$	782.53	Leaves, roots and barks
Glycosides (44) (Luteolin and Apigenin)	$C_{15}H_{10}O_6$	286.24	Juice, leaves
Ursolic acid (46)	$C_{30}H_{48}O_3$	456.70	Flower
Terpenoids (47) (Triterpenoids) Estradiol	$C_{18}H_{24}O_2$	272.38	Flower, roots and bark
Piperidine alkaloids (48) 2,3,4,5-tetrahydro-6-propenyl-pyridine	$C_8H_{13}N$	123.20	Roots and barks

Synergic potential of pomegranate

Most of the studies on pomegranate have been to investigate the therapeutic potentials of bioactive constituents. The most generally found bioactive molecule is ellagic acid, which is found to exhibit potential anticancer (49) and antioxidant properties (50) thus highlighting its role as the most significant bioactive molecule in pomegranate. However, research on quercetin (51, 52) has made to divert on the above findings. In fact research studies confirm the synergistic potential of whole pomegranate is superior to ellagic acid in suppressing prostate cancer (53, 54). Thus, the whole pomegranate extracts have found to be more beneficial when compared to particular bioactive molecules as such.

Very less is known about the biochemistry and bioavailability of ellagitannins from the food sources. There is strong evidence that ellagic acid is absorbed by blood plasma (55). A human study has investigated the metabolism, absorption, bioavailability, and antioxidant effects of pomegranate extracts. In a clinical trial, three pomegranate juice metabolites were identified in the plasma – urolithin A, urolithin B, and an unidentified small metabolite; urinalysis revealed six metabolites – the above three found in the plasma and an aglycone metabolite analogous to each of three plasma metabolites. Maximum excretion rates were observed 3-4 days after juice consumption. Important variability of urinary metabolite concentrations was reported among subjects and may be correlated to differences in the microflora of colonic system, where the ellagitannins are believed to be metabolized (56).The determination of urolithin A and B in the urine may suggest for pomegranate's prolonged antioxidant properties, relatively to the polyphenols in the juice.

Mechanism of action and health benefits

Human gut contains about hundred trillion microorganisms (57). The bacteria supply the host with colonization resistance against pathogens, excite the host immune system, avert allergies and tumors, generate vitamins, metabolize cholesterol, and boost mineral bioavailability (58, 59). Nevertheless, the overgrowth of these usually beneficial bacteria can lead to intestinal diseases and also been related with cancer, obesity and other related ailments (60). Ellagitannins present in pomegranate juice act together with the microflora of the gut. Punicalagins are known to inhibit the growth of pathogenic microorganisms like Clostridia species, *Pseudomonas aeruginosa*and *Staphylococcus aureus*, but are beneficial for the growth ofmicroorganism like bifido bacterium species including generation of short chain fatty acids (61, 62) which are reported to exhibit positive effects by activation of peroxisome proliferator-activated receptors (PPARs).

PPARs are the receptors for endogenous lipid molecules and targets for drugs against type 2 diabetes (63, 64) and are also reported to be promising molecules for prevention of inflammatory disorders (65). PPARs are transcription factors which belong to the nuclear hormone receptor family with more than 40 members recognized in the human genome. They control gene expression by binding to Retinoid X Receptor (RXR) as a heterodimeric partner to specific DNA sequence elements known as Peroxisome proliferator response element (PPRE) (66). PPARs are the major regulator of lipid and carbohydrate metabolism, inflammation and immunity (67).

PPAR have three known isoforms: α, β or δ, and γ, of which PPARα is vital in the clearance of circulating or cellular lipids through the control of gene expression during lipid metabolism. PPAR β/δ plays an important role in lipid oxidation, cell proliferation and PPARγ is reported to promote adipocyte differentiation to increase the blood glucose uptake (68). The molecular expression and activation is reported to be controlled by varied forms of natural and synthetic molecules, including nutrients, micro and macro element, and drugs like thiazolidinediones (TZD) (69). However, TZD class of antidiabetic drugs are likely to be rejected by physicians due to followed ill effects (70) including hepatotoxicity, obesity, edema, and congestive heart failure (71). Consequently, the use of natural molecules which are able to activate PPARs can be safer alternative to synthesized drugs.

Antioxidant mechanism

An earlier study have reported that pomegranate extracts have 2-3 times the antioxidant potential to that of either red wine or green tea (72). In another investigation pomegranate extracts have exhibited free radicals scavenging activity and decreased macrophage oxidative stress and lipid peroxidation in laboratory animal models (73) and enhance the plasma antioxidant capacity in humans (74). Studies on animal models revealed the antioxidant potentials of pomegranate extracts prepared from whole fruit sans the juice, exhibiting a 20-percent reduction in oxidative stress in mouse peritoneal macrophages (MPM), and a 53-percent increase in reduced glutathione levels (73). Fermented pomegranate juice extract has exhibited higher antioxidant capacity compared to red wine and green tea extract (75). Another study on rats with carbon tetra chloride induced liver damage with pre-treated pomegranate peel extract increased the free-radical scavenging activity of the catalase and super oxide dismutase which resulted in 50-percent decreased lipid peroxidation compared to standards (76).

A report on human trails that were made to consume PPJ has exhibited increased

antioxidant potential compared to the apple juice. Another investigation found that daily consumption of 250 ml PPJ for four weeks given to healthy subjects resulted in enhanced plasma antioxidant capacity from 1.33 mmol to 1.46 mmol, whereas subjects consuming apple juice showed no considerable increase in antioxidant property. Concentration of vitamin E, Vitamin C and reduced glutathione values did not change remarkably across different groups. This results extensively indicated pomegranate secondary metabolites, may be responsible for the significant observations.

Antiproliferative mechanisms

Various studies have revealed that pomegranate extracts (juice, peel) significantly inhibit cancer cells and proliferation by disrupting cell cycle thus inducing apoptosis, finally suppressing growth of tumor (77). Investigation on prostate cancer cell lines DU-145, LNCaP, and PC-3 have exhibited antiproliferative activity, thereby shown different combinations of pomegranate extracts were more effective than any single extract (78). Investigation on animal models against prostate cancer PC-3 cell line resulted in pomegranate extracts inhibiting cell proliferation and induces apoptosis through regulation of proteins which control apoptosis (79).

Many studies have revealed the association between increased cell proliferation and cyclooxygenase 2 (COX-2) expressions (80). **C**OX-2 is a vital enzyme for the conversion of arachidonic acid to prostaglandins, which are important inflammatory mediators. PME and punicalagin decreased COX-2 expression in HT-29 cells in a dose-dependent approach, which are most possibly due to remarkable interactions with other bioactive secondary metabolites for instance anthocyanins. Another study has reported that COX-2 expression in HT-29 cells is NF-κB dependent. These studies indicate that pomegranate juice extracts have reduced COX-2 expression by inhibiting phosphatidylinositide 3-kinases (PI3K) and protein kinase B which is essential for NF-κB activation (81).

Pomegranate extracts were also reported to decrease lipoxygenase, an enzyme which catalyzes the change of arachidonic acid to leukotrienes, which are known vital inflammatory mediators (75), consequently, pomegranate consumption changes eicosanoid biosynthesis. Flavonoids present in pomegranate juice extracts have shown 20–30% inhibition of soybean lipoxygenase although no remarkable inhibition of sheep cyclooxygenase was found. Pomegranate juice is also known to restrain inflammatory cytokine expression (82) and also inhibit matrix metalloproteinases (MMPs) in colon cancer condition (83).

NF-κB, a pro-inflammatory pathway is also known to be downregulated by pomegranate juice injestion and activation of NF-κB has been reported in a number of cancer cell lines (84), consequently leading to inflammation and cell proliferation through upregulation of collagenase, and pro-inflammatory cytokines like TNF-α (tumor necrosis factor), IL-1 (interleukin), IL-2, IL-6, and IL-8 (85). Therapeutic properties of pomegranate fruit extracts have potential anti-inflammatory property and anticancer potential, as they have been reported to diminish the generation of IL-6 and IL-8 and thus inhibit NF-κB in mast cells and basophils. Pomegranate extracts on action with urolithin A is known to decrease few pro-inflammatory markers such as iNOS, COX-2, and prostaglandin E2 in a colon cancer cells (86).

Current investigations have reported that pomegranate juice extracts reduce angiogenesis by down regulating vascular endothelial growth factor in MCF-7 breast cancer cell lines. Another study exhibited how the pretreatment with dietary pomegranate oil reduced the occurrence and increase of colonic adenocarcinomas in azoxymethane-induced colorectal cancer cells (87). Remarkably, the inhibition of tumor occurrence correlated with improved expression of PPARγ protein in the nontumormucosa. In a clinical phase II study, in vitro assays using patient plasma and serum demonstrated remarkable reduction in prostate cancer cell line proliferation and increased apoptosis. Administration of pomegranate polyphenols significantly correlated nitric oxide preservation with decreased PSA values. These results demonstrate pomegranate juice extracts may affect prostate cancer cells because of antiproliferative, apoptotic, antioxidant, and anti-inflammatory effects (88).

Conclusion

The present researchers are focussing on natural sources with a range of medicinal properties with selective targets and minimal side effects. Pomegranate has been found to be one of the excellent sources with diverse biological activities including antioxidant, anti-inflammatory, anti-diabetic, anticancer, hepatoprotective, cardioprotective, neuroprotective and anti-ulcerogenic properties. Clinical trials are in advancement to investigate the beneficial effects of the pomegranate extracts. A number of applications of pomegranate in pharmaceuticals have been patented from many scientists across the world which reflects the scope of the pomegranate in the pharmaceutical industries (89, 90).

Authors' contributions

Both the authors have contributed to the manuscript and approved the final version.

Conflict of Interest

Authors declare no conflict of Interest.

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