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Toxicological, Pharmacological and Cellular properties of Pomegranate (*Punica granatum* L.): A Review

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Abstract
Pomegranate (*Punica granatum* L.) is an ancient fruit that is widely consumed as fresh fruit and juice. The use of pomegranate fruit dates back from ancient times and reports of its therapeutic qualities have echoed throughout the ages. They also show inhibitory effects on invasion/motility, cell cycle, apoptosis, and vital enzymes such as cyclooxygenase (COX), lipooxygenase (LOX), cytochrome P450 (CYP450), phospholipase A2 (PLA2), ornithine decarboxylase (ODC), carbonic anhydrase (CA), 17beta-hydroxysteroid dehydrogenase (17β-HSDs) and serine protease (SP). Furthermore, they can stimulate cell differentiation and possess anti-mutagenic effects. Pomegranate can also interfere with several signalling pathways including PI3K/AKT, mTOR, PI3K, Bcl-X, Bax, Bad, MAPK, ERK1/2, P38, JNK, and caspase. However, the exact mechanisms for its pharmacological and toxicological properties remain to be unclear and need further evaluation. These properties strongly suggest a wide range use of pomegranate for clinical applications. This review will discuss the areas for which pomegranate has shown therapeutic properties in different mechanisms.

Keywords: Pomegranate, antioxidants, free radicals, ellagic acid, value addition

Introduction
Punica granatum (Pomegranate) is a small tree which measures between five and eight meters tall and mainly found in Iran, the Himalayas in northern India, China, USA and throughout the Mediterranean region (Facciola, 1990) [6]. The Pomegranate can be also divided into several anatomical compartments including seed, juice, peel, leaf, flower, bark, and root with each possessing interesting pharmacological and toxicological activities. The edible fruit is a berry which is about 5-12 cm in diameter with a rounded hexagonal shape, thick reddish skin and around 600 seeds, each surrounded by a water laden pulp (aril) ranging in color from white to deep red or purple, the aril is the edible part of the fruit.In Chinese the seeds symbolized longevity and immortality. Science from the ancient times pomegranate has been regarded as a "healing food" with numerous beneficial effects in several diseases (Vidal *et al*., 2003) [16]. Indeed, the pomegranate was commonly used in folk medicine, for eliminating parasites, as an antihelmintic and vermifuge, and to treat and cure ulcers, diarrhoea, acidosis, dysentery, hemorrhage, microbial infections, and respiratory pathologies. It was also used as an antipyretic (Larrosa *et al*., 2010) [8]. Recent years have seen increased interest on the part of consumers, researchers, and the food industry into how food products can help maintain health; and the role that diet plays in the prevention and treatment of many illnesses has become widely accepted (Viuda-Martos, 2010) [17]. At the present time, considerable importance is given to functional foods, apart from their basic nutritional functions, provide physiological benefits and play an important role in disease prevention or slow the progress of chronic diseases (Viuda-Martos, 2010) [17]. There has been a virtual explosion of interest in the pomegranate as a medicinal and nutritional product because of its multifunctionality and its great benefit in the human diet as it contains several groups of substances that are useful in disease risk reduction. The fruit of the pomegranate has extensively been used as a traditional remedy against acidosis, dysentery, microbial infections, diarrhea, helminth infection, hemorrhage and respiratory pathologies and the seeds have also been shown to contain the estrogenic compounds, estrone and estradiol. Furthermore, the dried pericarp and the juice of the fruit are considered beneficial for treatment of colic, colitis, menorrhagia, oxyuriasis, headache, diuretic, acne, piles, allergic dermatitis. The aim of this review was to present an overview of the functional, medical, and physiological properties of the pomegranate. The aim of this review was to present an overview of the functional, medical, and physiological properties of the pomegranate.

The Metabolites of Punica granatum

About 50% of the total fruit weight corresponds to the peel, which is an important source of bioactive compounds such as phenolics, flavonoids, ellagitannins (ETs), and proanthocyanidin compounds. The edible part of the pomegranate fruit (50%) 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 ascorbicacid, citricacid, malicacid, and bioactive compounds. The seeds are a rich source of total lipids; pomegranate seed oil comprises 12% to 20% of total seed weight. The oil is characterized by a high content of polyunsaturated (n-3) fatty acids such as linolenic, linoleic, and other lipids such as punicic acid, oleic acid, stearic acid, and palmitic acid. The seeds also contain protein, crude fibers, vitamins, minerals, pectin, sugars, polyphenols, isoflavones (mainly genistein), the phytoestrogen coumestrol, and the sex steroid, estrone.

Application of Pomegranate in Traditional Medicine

All components of Pomegranate fruit with abundant tannins show relatively strong astringent effects. Several infusions or decoctions of the plant flowers have been used in traditional medicine to treat simple diarrhea, vaginal discharge, and also this extract accompanied with pomegranate peel have usually been gurgled to relieve pancreas inflammation of the pancreas. Refreshing juice of the fruit is recommended to heal gallbladder diseases. Its decoction appears to be helpful for treating diseases such as ordinary diarrhea, dysentery, and stomach disorders. Tannin content of pomegranate seed, however, is not remarkable and it is usually used to treat women vaginal discharge and wound healing. Fresh or dried root barks or ethanol extracts of pomegranate are used to remove intestinal parasites due to the alkaloid substances. It is also used in traditional medicine because of the antibacterial and anti-inflammatory properties.

Pharmacological Properties of Pomegranate

Flavonoids and tannins of pomegranate juice can prevent the growth of cancer cells. Flavonoids observed in the watery extract and fruit peel have shown estrogenic activity. In addition, luteolin and naringenin have indicated an activity similar to the hormone usually secreted prior to pregnancy in women. Polyphenols of fermented extract of pomegranate fruit potentially appear to have antioxidant activity and pericarp tannins may increases antioxidant potential of fruit extract. The stronger activities in polyphenols of fermented extract than nonfermented extract is likely due to the breakdown of flavonoids sugar complexes during fermentation that the final products will contain high concentrations of free polyphenols (with high biological activity).Ellagic acid and gallic acid are among the constituents observed in pomegranate peels, and the former is a dimeric derivative of gallic acid and is found mostly in higher plants, such as fruits and nuts. Ellagic acid shows antimutant, antiviral, antioxidant, and skin-bleaching activity and has already been added to food as an antioxidant in Japan. Antioxidant capacity of extracts derived from pomegranate peel in producing phospholipid complex has been measured. Antioxidant capacity of extracts from pomegranate peels is due to the presence of the phenols such as ellagic tannins, ellagic acid, and gallic acid. Antimutagenic and anticarcinogenic properties of the extracts were examined against the azide sodium by the Ames test. The experiment showed that juice extract of pomegranate peel can inhibit mutation and cancer using azide sodium in 2 species of salmonella.

More recent studies have shown that the pomegranate fruit are enriched with a strong antioxidant called punicalagin that controls superoxide and free radicals of DPPH (1,1-diphenyl-2-picrylhydrazyl). The best extraction and separation way is done by methanol. Punicalagin is capable to regulate the activity of superoxide and DPPH radicals. In an additional research, the blood plasma derived from person who had taken pomegranate juice containing ellagic acid (25 mg) and ellagitannins (318 mg, especially punicalagin) was analyzed. The main purpose of the earlier study was to assess the amount and time duration of ellagic acid bioavailability in plasma following consumption. According to the results, the highest ratio of ellagic acid in the blood plasma was measured at 0.5, 1, 2, 3, 4, 5, and 6 hours after taking pomegranate juice. The highest and lowest ratios were observed at 1 hour and 4, 5, and 6 hours after consumption, respectively. The presence of the free ellagic acid in the blood plasma is induced by its breakdown under biologic pH of stomach. Thus, it can be used as a biologic marker in bioavailability studies confirming the consumption of ellagic acid from food resources. Polyphenols of oil prohibit the activity of eicosanoid and cyclooxygenase enzymes. 18C Trans fatty acids known as conjugated linoleic acid, structurally related to punicic acid, possess cancer arresting properties.

Punic acid acts as an inhibitor of prostaglandin biosynthesis as well as a cytotoxin for cancer w2a cells; such activity is possibly due to the inhibitory effect against fat peroxidation. Punic acid of pomegranate seed oil inhibits prostaglandin biosynthesis (promote ornithine decarboxylase enzyme activity at lower concentration). Also this oil can prevent DMBA- and TPA-induced skin cancer. Inhibitory activities of prostaglandin as well as antioxidant activity of polyphenols extracted from both pomegranate seed oil and its fermented extract have widely been reported for prevention from human breast cancer. Inhibitory impact of the watery and oily parts of the fruit has been reported on breast cancer cells in vivo. Such parts prohibit the activity of enzymes responsible for active estrogen biosynthesis (17-b-estradiol) (Simmons, 2005) [14]. Since the watery and oily parts of the fruit are chemically different, they probably active different mechanisms in the prevention of cancer. Pomegranate seed oil is considered as biosynthesis inhibitor E2 (17-b-estradiol) catalyzed by 17-b-hydroxysteroid enzyme. It also prevents invasion of cancer cells and also can strengthen and encourage apoptosis. Extracted polyphenols of pomegranate seed oil can potentially prevent cyclooxygenase activity. Inactivation of the mentioned enzyme prevents the proliferation of breast cancer cells. Punicalagin is capable to regulate the activity of superoxide and DPPH radicals. In an additional research, the blood plasma derived from person who had taken pomegranate juice containing ellagic acid. Ellagic acid and gallic acid are among the constituents observed in pomegranate peels, and the former is a dimeric derivative of gallic acid and is found mostly in higher plants, such as fruits and nuts. Ellagic acid shows antimutant, antiviral, antioxidant, and skin-bleaching activity and has already been added to food as an antioxidant in Japan. Luteolin and naringenin have indicated an activity similar to the hormone usually secreted prior to pregnancy in women.

Table 1: Constituents of pomegranate (*Punica granatum* L)

Plant component	Constituents
Pomegranatejuice	Anthocyanins, glucose, organicacid, ascorbic acid, EA, ETs, gallic acid, caffeicacid, catechin, quercetin, rutin, minerals.
Pomegranate seedoil	Conjugated linolenic acid, linoleicacid, oleicacid, stearic acid, eleostearic acid, catalpic acid
Pomegranatepeel	Luteolin, quercetin, kaempferol, gallagic, EA glycosides, EA, punicalagin, punicalin, pedunculagin
Pomegranate leaves	EA;fattyacids
Pomegranate flower	Polyphenols, punicalaginpunicalin, EA
Pomegranate rootsandbark	Alkaloids, ETs

Despite these high beneficial compounds towards human health, a number of processed products manufactured and preserved for future time satisfying the consumer perception of a high nutritional quality and convenience produce. Potentiality for processing into value added products having extended shelf life, yielding potential, better keeping quality and higher nutraceutical value, popularity of pomegranate is increasing among the growers and consumers throughout the world.

Antioxidant properties

Oxidative stress (OS) produces toxic metabolites which can initiate and promote cancers. Consumption of polyphenoles and flavonoids are beneficial for the prevention of cardiovascular, inflammatory, and other diseases by preventing OS that induces lipid peroxidation in arterial macrophages and in lipoproteins. The presence of antioxidants has been reported in pomegranate juice. pomegranate contains some species of flavonoids and anthocyanidins (delphinidin, cyaniding and pelargonidin) in its seed oil and juice and shows antioxidant activity three times greater than green tea extract (Seeram, 2006) [19]. The fruit extracts exhibit scavenging activity against hydroxyl radicals and superoxide anions, which could be related to anthocyanidins. The antioxidant action of Pomegrante is observed, not only through its scavenging reactions, but also by its ability to form metal chelates. Studies have indicated that methanolic extracts from the peel of pomegranate has a broad spectrum of antioxidant activities which were evaluated by 1,1-diphenyl 2-picrylhydrazyl (DPPH) free radical scavenging, phosphomolybdenum, Ferric(Fe3+) Reducing Antioxidant Power (FRAP), and Cupric (Cu2+) Reducing Anti-oxidanrt Capacity (CUPRAC) assays. Studies have looked at the beneficial effects of pomegranates antioxidant activity in-vivo and in-vitro and have shown that Pomegrante juice consumption causes a decrease in procarcinogen activation through CYP activity/expression (CYP1A2 and CYP3A), protection of rat gastric mucosa from ethanol or aspirin toxicity, protection of neonatal rat brain from hypoxia reduction of hepatic OS, reversal of proatherogenic effects which are induced by perturbed shear stress, protective effects against UVA- and UVB-induced cell damage and the potential use of pomegranate polyphenolics in topical applications(Eatock, 2000) [5]. Other studies have also shown the protective effects of pomegranate on the cardiovascular system, including reduction of LDL and cholesterol, anti-hypertension action by combating OS induced by diabetes and angiotensin II, reduction of carotid arterial stenosis and increase of endothelial nitric oxide (NO) syntheses and suggests the pomegranate as part of a heart-healthy diet through inhibiting of OS mechanism.

Anti-inflammatory effect acute inflammation is a beneficial host response for prevention of tissue injury, but it may also cause immune-associated diseases such as rheumatoid arthritis, inflammatory bowel disease and cancer. Interestingly, pomegranate has been shown to inhibit inflammation by different mechanisms. Cyclooxygenase (COX) and lipooxygenase (LOX), which are key enzymes in the conversion of arachidonic acid to prostaglandins and leukotrienes (important inflammatory mediators), respectively, are inhibited by pomegranate (Sturgeon, 2010) [13]. Non-steroidal anti-inflammatory drugs (NSAIDs) have more adverse effects on cardiovascular function by inhibiting COX and suppressing PGI2 (prostacyclin) in comparison to pomegranate. Ahmed *et al*. have shown that pomegranate has a significant inhibitory effect on osteoarthritis (OA) by suppressing the expression of matrix metalloproteinases (MMPs) in OA chondrocyte cultures and preventing collagen degradation. It may also inhibit joint destruction in OA patients (Ahmed, 2005) [1]. Pro-inflammatory cytokines such as IL-1β play an important role in OA pathogenesis. IL-1β induces the expression of MMPs, especially MMP-1 and MMP13, which are associated to the irreversible breakdown of cartilage matrix through digestion of type-II collagen and the consequent release of matrix proteoglycan from the cartilage. Furthermore, pomegranate has shown anti-inflammatory effects in a colitis rat model. However, studies have shown the inhibitory effect of pomegranate on production of pro-inflammatory cytokines. These studies demonstrate that pomegranate inhibits the p38-mitogen-activated protein kinase (p38MAPK) pathway and transcription factor, NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells). Activation of p38-MAPK and NF-kB are associated with increased gene expression of TNF-α, IL-1β, MCP1, iNOS, and COX-2 agents which are critical mediators of inflammation. Studies have also shown that administration of 50 mg/kg of Pg extract for 28 days causes a decrease in malondialdehyde (MDA), TNF-α, and IL-1β levels in rats with liver fibroses (Toklu, 2007) [15].

Carcinogenesis

Pomegranate possesses inhibitory effects on different type of cancers such as prostate, breast, colon, and lung cancers. Different mechanisms have been outlined for pomegranates anti-cancer activities in these studies. Pomegranate inhibits NF-k Band cell viability of prostate cancer cell lines in a dose-dependent manner in the LAPC4 xenograft model, in-vitro. Pomegranate polyphenols, ellagitannin-rich extract and whole juice extract inhibited gene expression of HSD3B2 (3betahydroxysteroid dehydrogenase type 2), AKR1C3 (aldo-ketoreductase family 1 member C3) and SRD5A1 (steroid 5alpha reductase type 1), which are key androgen-synthesizing enzymes in LNCaP, LNCaP-AR, and DU-145 human prostate cancer cells (Seeram, 2007) [9]. Because Pomegranate inhibits CYP activity/ expression which is necessary for activation of procarcinogens, it may have anti-carcinogenesis effects. Some metabolites of pomegranates chemical components such as 3, 8-dihydroxy 6H-dibenzo[b, d]pyran-6-one (urolithin A, UA) which is produced from Ellagitannins (ETs) may also possess anti-cancer effects.

Treatment with (50-150 μg/mL) pomegranate fruit extract (PFE) for 72 h was found to result in a significant inhibition of lung cancer, with dose- dependent arrest of cells in G0/G1 phase of the cell cycle, induction of WAF1/p21 and KIP1/p27, decrease in the protein expressions of cyclins D1, D2, and E, decrease in cyclin-dependent kinase (cdk) 2, cdk4 and cdk6 expression, phosphorylation of MAPK proteins, inhibition of PI3K, phosphorylation of Akt at Thr308, NF-kB and IKK (inhibitor of kappa kinase) alpha, degradation and phosphorylation of IκB, Ki-67 and PCNA (Khan, 2007)[7]. Also, the levels of Bax and Bcl-2 were altered by PE in PC-3 cell line.

Punica granatum effects on vital enzymes

Enzymes are proteins that catalyze biochemical/chemical reactions. Pomegranate has been shown to inhibit different enzymes including phospholipase A2 (PLA2) (that catalytically hydrolyzes the bond releasing arachidonic acid and lysophospholipids), cyclooxygenase (COX), lipooxygenase (LOX), cytochrome P450 and ornithine decarboxylase (ODC) which plays a role in the urea cycle and catalyzes the decarboxylation of ornithine to polyamines such as putrescine (Balkwill, 2005) [2]. Polyamines regulate growth processes and stimulate the growth of cancer. Carbonic anhydrase (CA) that catalyzes the hydration of carbon dioxide to form bicarbonate (HCO3-) is also inhibited. CA inhibitors such as pomegranate have been shown to inhibit cancer cell growth in vitro and in-vivo (Schubert, 2002) [10]. Aromatase is enzyme responsible for a key step in the biosynthesis of estrogens and catalyzes the formation of estrone and estradiol, which is inhibited by pomegranate. One of the possible mechanisms in which pomegranate can inhibit breast cancer is its inhibitory effect on aromatase and 17 beta-hydroxysteroid dehydrogenase enzymes (17β-HSDs), as well as its anti-estrogenic activity. Furthermore, ellagitannins (ET) and urolithin B (UB), which are found in relatively high quantities in Pomegranate, have been shown to most effectively inhibit aromatase activity in a live cell assay. Serine protease (SP) is another enzyme which is inhibited by pomegranate. SP is enzymes in which one of the amino acids in the active site is serine. Protease plays an essential role in modulating the turnover of extracellular matrix (EC), which provides morphological support for cell growth and differentiation. Furthermore, protease has a verity of important functions including angiogenesis, vasculogenesis, apoptosis, and cell migration/invasion (Basu, 2009) [3]. Ellagic acid and punicalagin, from pomegranate, have shown lower inhibitory effects on alpha-secretase (TACE) and other serine proteases such as chymotrypsin, trypsin, and elastase, thus indicating that they are relatively specific inhibitors of beta-secretase (BACE1) (Saito, 2002) [11]. Other studies have shown that catechin and epicatechin (epigallocatechin-3gallate), which are present in pomegranate, can inhibit SP.

Anti-mutagenicity

A mutagen is a physical orchemical agent that alters the genetic material of an organism, usually DNA, permanently and thus increases the frequency of mutations above the natural background level Mutagenicity is the capacity of a chemical or physical agent to cause such permanent change. It has been shown that pomegranate peel fractions, especially methanol, has anti-mutagenic activities as was detected by the Ames Salmonella/microsome assay against sodium azide (NaN3), methyl methane sulphonate (MMS), 2-aminofluorene (2AF), and benzo(a)pyrene (B(a)P) induced mutagenicity in Salmonella typhimurium (TA97a, TA98, TA100 and TA102) tester strains (Zahin, 2010) [18]. Methanolic extract of Pg (15 mg/plate) shows the highest anti-mutagenic activity in TA 100 cells.

Cell cycle arrest

The cell cycle is a series of events which takes place in a cell, leading to its division and duplication. It consists of four distinct phases; G1 phase, S phase (synthesis), G2 phase (collectively known as interphase) and M phase (mitosis) (Dai, 2010) [4]. Multiple checkpoints have been identified to verify whether the processes at each phase of the cell cycle have been accurately completed before progression into the next phase. Cell cycle may be altered following exposure to pomegranate. Previous studies have suggested several mechanisms for these effects, such as modulation of cell signaling molecules in the cell cycle machinery. Punica granatum extract (PE) inhibited the proliferation of mouse mammary cancer cell line (WA4), derived from mouse MMTV-Wnt-1 mammary tumors in a time and concentration-dependent manner through an arrest of cell cycle progression in the G0/G1 phase 1]. Ellagitannins, derived from pomegranate juice, and their metabolites, urolithins exhibit dose and time-dependent decreases in cell proliferation and clonogenic efficiency of HT-29 cells through cell cycle arrest in the G0/ G1 and G2/M stages of the cell cycle followed by induction of apoptosis.

Conclusion

The consumption of pomegranate has grown tremendously due to its reported health benefits. Pomegranate and derivates, such as juice, peel, and seeds, are rich sources of several high-value compounds with potential beneficial physiological activities. The rich bioactive profile of pomegranate makes it a highly nutritious and desirable fruit crop. Accumulating research offers ample evidence that routine supplementation with pomegranate juice or extract may protect against and even improve several diseases, including diabetes and cardiovascular disease; it may even help to prevent and arrest the development of certain cancers, in addition to protecting the health of the mouth and skin. Side effects are very rare. Using concentrated, low-cost pomegranate juice or standardized pomegranate extract capsules offers consumers a way of reaping the broad spectrum of health benefits of this fruit.

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