

Review of Characteristic Components, Traditional and Pharmacological Properties of *Punica granatum*

Tabbassum Zehra¹, Shadab Ahmed^{1,*}, Sadaf Zehra²

¹ Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan

² Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan

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*Address of Correspondence Author:
a_shadab@uok.edu.pk

ABSTRACT

Punica granatum belonging to genus *Punica* family Punicaceae is considered as a wonder fruit for its ample pharmacological activities. It is generally well-known as pomegranate (Anar) inherent to central regions of Asia from Turkmenistan to Northern India and Iran. Various components of pomegranate are medicinally significant like fruit, peel, leaves, seeds, flower, root and bark. A pronounced variety of nutritive compounds like organic acid, fatty acids, sterols, minerals and vitamins have been found in pomegranate. However, phytochemical researches have shown the bioactive constituents including alkaloids, anthocyanin, ellagic acid, tannins, flavonoids and other phenolic compounds depending on the cultivars. Numerous studies revealed promising health benefits of *P. granatum* particularly anti-inflammatory, anti-bacterial, antioxidant, antidiabetic, antimicrobial, anti-hypertensive and anti-proliferative activities which are receiving great interest from researchers and pharmaceutical concerns. The current review embraces some recent findings underlining the pharmacological properties of *Punica granatum* that can be useful for motivating further research and for promoting its consumption as significant and safe medicinal food for human health.

Keywords: *P. granatum*, bioactive constituents, traditional uses, biological actions.

INTRODUCTION

P. granatum generally known as Anar (pomegranate) is a well-known specie of *Punica* genus which is fruit-bearing deciduous shrub with 5 to 8-meter height belonging to the family of Punicaceae. Pomegranate is an ancient fruit intuitive to different Asian countries extending from Iran and Afghanistan to Northern part of India. Nevertheless, is predominantly grown in Egypt, Argentina, Tunisia, USA, Spain, Morocco, South Africa and Turkey [1, 2]. Different parts of pomegranate are medicinally significant like fruits, peel, leaves, seeds, flower, root and bark. The grenade shaped pomegranate fruit contains several profound red pigment juicy arils packed in a tough

pericarp capped with a tenacious calyx. Various studies revealed that pomegranate flower might be useful in diabetes. In addition, its derived products got beneficial effects in cardiovascular diseases [3, 4], hormone replacement therapy [5] and as an additive therapy during systematic imaging by improving the bioavailability of radioactive dyes [6].

Pomegranate extracts had previously used to treat various medical conditions including diarrhea, hemorrhage, ulcer and different parasitic infections [7]. However, *P. granatum* and its bioactive constituents also exhibit different activities which includes antiplatelet [8], anti-inflammatory [9, 10], anti-bacterial [11, 12], anti-diabetic [13], antioxidant [14], antimicrobial [15], antifungal [16], anti-

hypertensive [17] and anticancer activities [18]. Moreover, pre-clinical studies have shown neurodegenerative disorders [19], memory enhancement [20] and hepatic protection [21].

Hartman, Shah [22] reported the valuable effects of pomegranate intake in Alzheimer model to lower amyloid deposition. In addition, the mortality rate due to lymphocystis may be reduced by single intraperitoneal injection of pomegranate leaf extract in fishes [23]. Furthermore, *P. granatum* pericarps comprises of seven extremely active and four weakly active inhibitors of carbonic anhydrase (CA) enzyme. Extremely active inhibitors are tannins including punicalin, punicalagin, gallagyl-dilactone, pedunculagin and tellimagrandin. However, less active inhibitors include gallic acid, ellagic acid and its derivatives, granatin A and corilagin. *P. granatum* oral extract is enriched with ellagic acid effective in reducing UV induced skin pigmentation [24]. Moreover, Raheema [25] investigated the ameliorative effects of *P. granatum* upon various histopathological and biochemical markers in mice infective with *Staphylococcus aureus*.

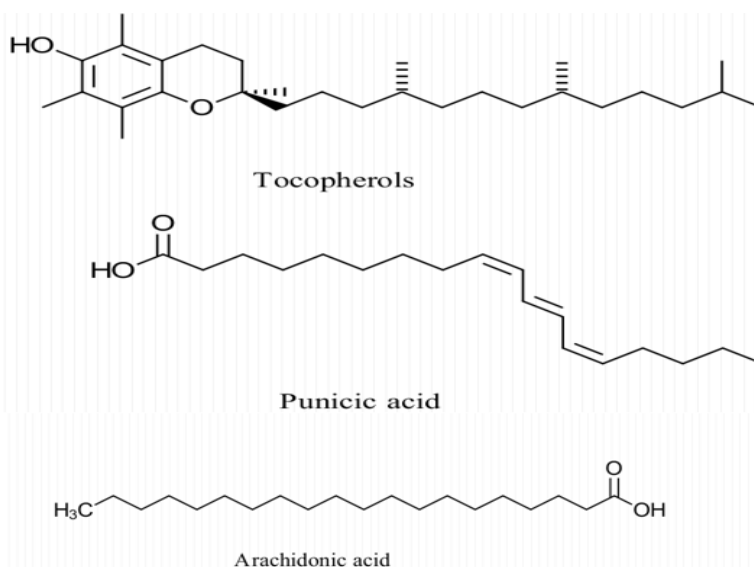
Other uses of *P. granatum* may include cosmetic remodeling [26], oral hygiene [27], erectile dysfunction [28] and management of acquired immune deficiency syndrome [29]. The present review deals with the therapeutic role and various pharmacological and clinical studies of pomegranate on *in vitro* and *in vivo* studies. We hope that this work would provide a valuable reference source for future researches in this area.

Bioactive Constituents

P. granatum is a vital source of various important phytochemicals such as polyphenols (flavonoids, and phenolic acids), hydrolysable tannins, ellagic acid, saccharides, terpenoids, fatty acids and vitamins [30-32]. Arapitsas [33] revealed that ellagitannins and gallotannins with in *P. granatum* disintegrated into ellagic acid, gallic acid and glucose. Moreover, anthocyanins mainly comprise of delphinidin glucose and derivatives, malvidin glycosides, vitisin A, pelargonidin glucoside and derivatives, cyanidin glucoside and derivatives [34-36].

Pomegranate seeds are enriched with fatty acids especially punicic acid [37-41]. However, seed residue also contains essential phenolic components like hydrolysable tannins, flavonoid glycosides and phenolic acids [42]. Whereas, the most represented flavonoid found in pomegranate peel is kaempferol-3-O-glucoside in addition to gallic acid as major phenolic component respectively [43]. A study conducted by Fu, Zhang [44] described the presence of ursolic acid as well as oleanolic acid in *P. granatum* flower.

Vidal, Fallarero [45] investigated the presence of pelletierine, ellagitannins as well as punicacortein A, B, C and D in pomegranate root and bark. Moreover, punicalagin and Punicalin α and β are the important phytochemicals found in the leaves of pomegranate [16, 46]. Chemical structures of some bioactive constituents of pomegranate are summarized in Figure 1 and 2.



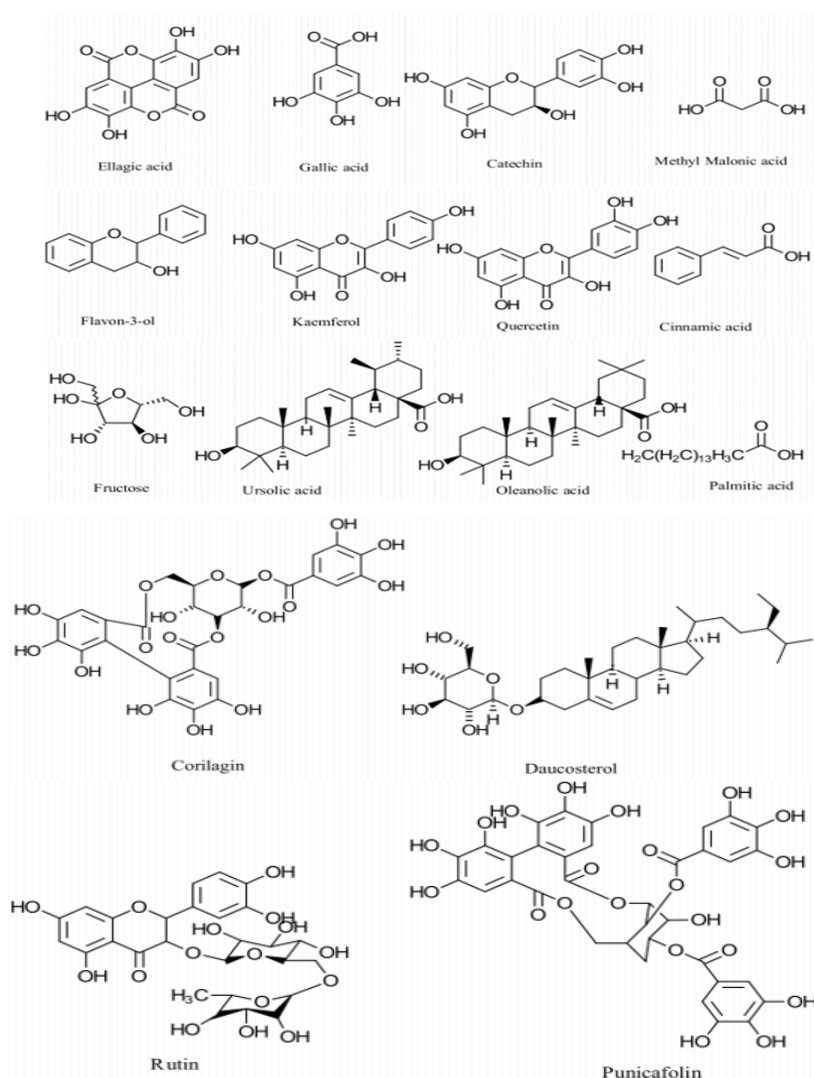


Figure 1. Chemical structures of some polyphenol compounds in *P. granatum*.

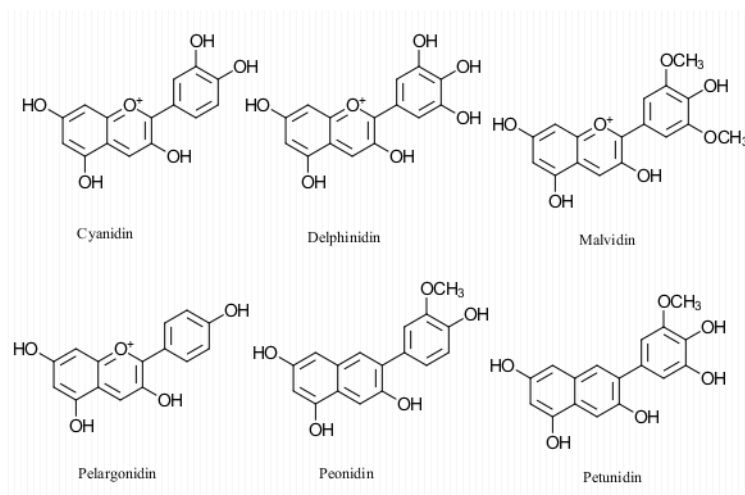


Figure 2. Chemical structures of anthocyanin in some *P. granatum* fruit.

Table 1. Pharmacological properties of *P. granatum*.

Plant Component	Bioactive Constituents	Pharmacological Activity	Extract Used	Observation	Reference
Fruit	Anthocyanins Ellagitannins Tannins	Anti-cancer	Acetone + water	Pomegranate extract inhibit the lung cancer A549 cell line and tumor growth.	[47]
	Anthocyanidins (Delphinidin, Cyanidin, and Pelargonidin)	Antioxidant	Acetone	<i>P. granatum</i> extract showed scavenging activity against O ₂ and OH.	[48]
		Anti-depressant	Methanol	Pomegranate pulp extract at a concentration of 25 mg/kg give significant decreased in duration of immobility time during tail suspension test.	[49]
Juice	Ellagitannin, Punicalagin	Anti-cancer	Juice	In human colon cancer HT-29 cell line affects inflammatory cell signaling proteins.	[9]
	Polyphenols Flavonoids	Antioxidant	Juice	In atherosclerotic mice, protection of LDL against oxidation.	[3]
	Anthocyanin Hydrolysable Tannins Vitamin C	Augmentation of Sperm Motility	Juice	Increase in epididymal sperm concentration, spermatogenic cell density and sperm motility after consumption of pomegranate juice	[50]
		Improvement of Erectile Dysfunction	Juice	Improved penile erection and intracavernous blood flow in rabbits administered with <i>P. granatum</i> juice.	[51]
Peel	Phenolic Flavonoids	Anti-microbial	Methanol	Potent inhibitor of <i>Yersinia enterocolitica</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i> and <i>S. aureus</i> .	[52]
	Gallic Acid Catechin	Wound Healing	Methanol	Explore the wound healing property against the omission of skin lesion.	[53]
	Tannins Alkaloid	Anthelmintic	Aqueous	75% peel extract of pomegranate showed significant effect against <i>Ascaris suum</i> females.	[54]
	Punicalagin	Antifungal	Ethanol	Potent antimicrobial effects against yeast cells of <i>Candida</i> spp.	[16]
Flower	Ellagic Acid Punicatannins	Nephroprotection	Hydro alcoholic	Pomegranate extract ameliorate nephrotoxicity in rats treated with gentamicin 25 mg/kg.	[55]
	Flavonoids	Memory Enhancement	Flower powder mixed with feed	Flavonoids have direct role in enhancing the memory and learning capability by means of increased blood flow to brain.	[56]
	Polyphenols	Anti-diabetic	Ethanol	Pomegranate flower extract has significant anti-diabetic activity in NIDDM rats by enhancing the insulin sensitivity.	[57]
Seed		Antioxidant	Methanol	Seed extract displayed antioxidant activity at 100 ppm using the DPPH and beta-carotene-linoleate oxidative stress test.	[58]
	Punicic acid	Anti-cancer	Seed oil	Pomegranate seed oil (5%) significantly reduced tumor prevalence, multiplicity of skin and ornithine decarboxylase activity during skin carcinomas.	[59]

Traditional Uses

Pomegranates are broadly consumed for the management of infections caused by various protozoa and fungi, in stomatitis, diarrhea and dysentery. Jurenka [60] revealed the significant importance of pomegranate root extract in the prevention of gynecological and infertility complications. However, it is also efficacious in burns, snakebites as well as in the treatment of leprosy. Additionally, the early civilization of Chinese pays special attention to *P. granatum* and considered it as a soul concentrate containing similar properties like that of human blood and having anti-aging action.

Biological Actions of Pomegranate

Different bioactive elements of pomegranate are a great source of important nutrients with therapeutic

and health-promoting abilities however; the entire fruit might be utilized for several therapeutic purposes as mentioned in Table 1. Two types of pomegranate have come into view in which one type contain more sweetness than other and may involve in mild laxative properties. On the other hand, less sweet type has ability to decrease gastritis and heart pain. *Punica granatum* deliberated to be therapeutically significant from ancient eras and has permitted its capability in improving insulin resistance, hypertension, cancers, hyperlipidemia, hyperglycemia, oxidative stress, chronic inflammatory conditions like ulcerative colitis, cardiovascular diseases, obesity and it also serve as healing agent [61-63]. Schematic presentation of biological actions has been shown in Figure 3.

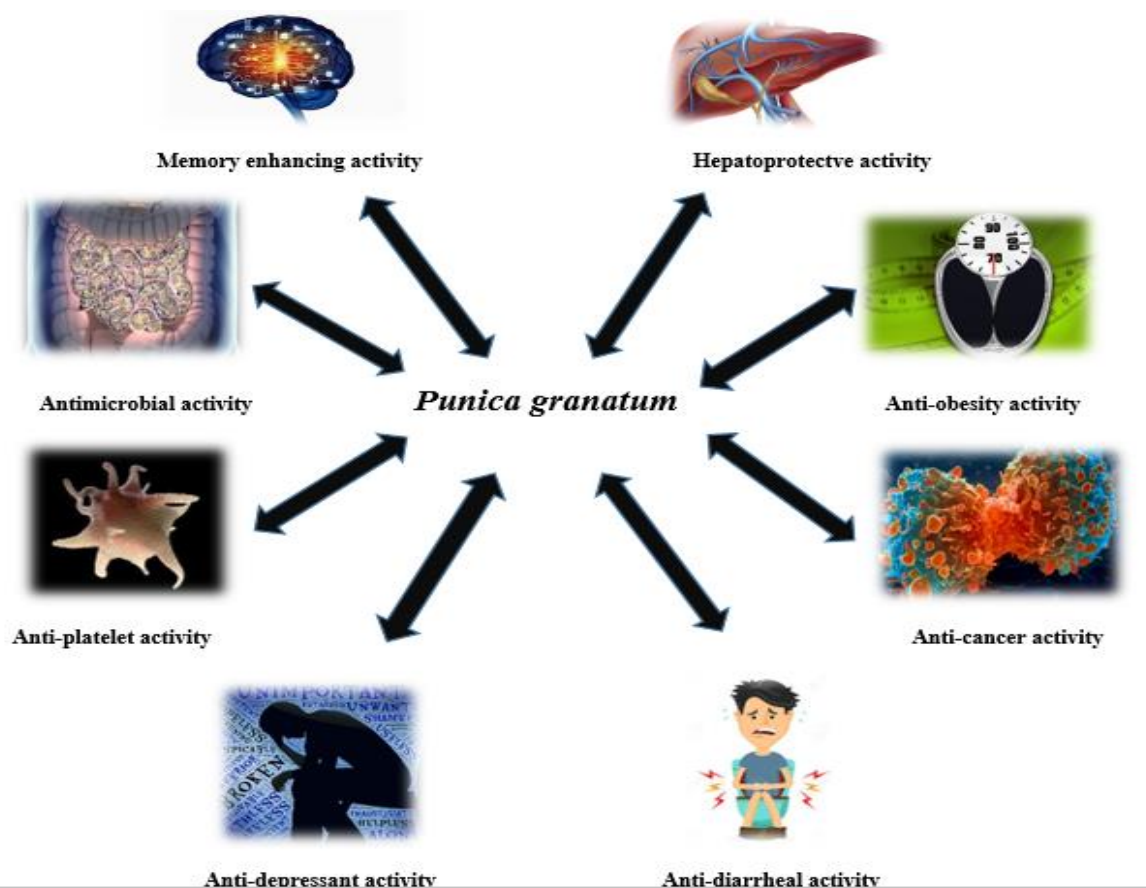


Figure 3. Schematic diagram of biological activities of *P. granatum*.

Pre-Clinical Studies

The edible and nonedible portions of *P. granatum* have been explored for its cardio-protective and hepatoprotective potentials as well as for striated muscle in obesity induced rats [64-67]. A study reported by Nikseresht, Fallahzadeh [68] revealed the promising role of pomegranate seed oil on fertility and semen quality of rats without having deleterious effects as like that of ROS (Reactive Oxygen Species). Moreover, the fruit extract of pomegranate also enhanced the sperm motility, viability, membrane integrity, total count and decreased lipid peroxidation resulting in increased ram semen quality after defrosting [50]. The oral *P. granatum* fruit extract demonstrated the pro-apoptotic and anti-proliferative properties against PC3 and CWR22R1 prostate cancer cell in athymic nude mice [69]. Few pre-clinical and clinical effects have been illustrated in Figure 4.

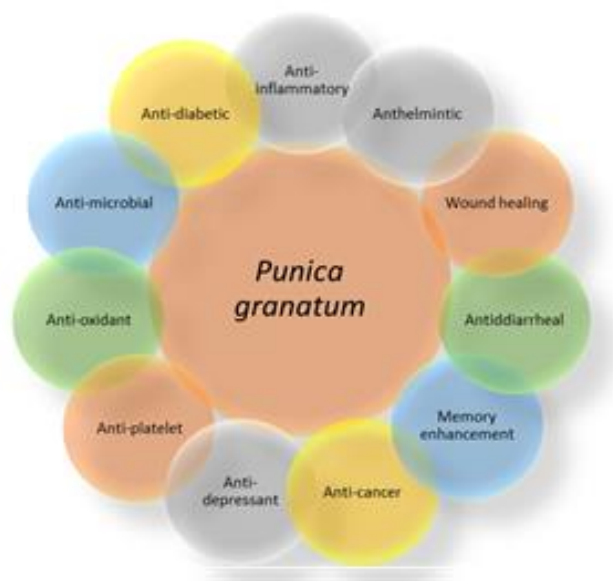


Figure 4. Preclinical and clinical effects of *Punica granatum* fruit.

Clinical Studies

Over the last ten decades, *P. granatum* has gained valuable importance due to its anti-diabetic biomolecules like gallic acid, ellagic acid, ursolic acid, oleanolic acid and punicalagin. Similarly, tannins and anthocyanins are capable to reduce the incidence of type II diabetes effectively [70, 71]. Research by Malik, Afaq [69] showed the preventive effect of pomegranate oral administration against human prostate cancer. Moreover, Malik and Mukhtar [72] described the role of *P. granatum* in tumor growth

inhibition together with the reduction in Prostate-Specific Antigen (PSA) serum levels. Additionally, Kilicgun, Arda [73] reported the usefulness of pomegranate as nutritional fertility enhancer, improve longevity and promote growth in humans. However, the quantity should be adjusted carefully to avoid detrimental effect.

Antimicrobial activity

Punica granatum has a strong antimicrobial property against *Staphylococcus aureus* and *Pseudomonas aeruginosa* [74]. Tannins isolated from pomegranate is effective against herpes virus (HSV-2) as well as shows stronger blocking effect against virus [75]. Moreover, Pomegranate has anti-bacterial effects against *Salmonella typhi*, *S. aureus*, *E. coli*, MRSA (methicillin-resistant *Staphylococcus aureus*) and some streptococci strains [76-79].

In vitro studies showed detrimental effect of *Punica granatum* aqueous extract to parasitic fungi while it also acts as fungi toxic to *Puricularla oryzae* and *Colletotrichum falcatum* in acetone extract. Moreover, the activity of *Listeria monocytogenes* and *Yersinia enterocolitica* is inhibited by methanol extract of *P. granatum* [52]. Whereas, *in vivo* studies on peel extracts showed significant antibacterial activity against *Salmonella typhi* (ATCC 19943) in a mouse model [80].

Memory Boosting Activity

Memory loss is the primary symptom to manifest in majority of individuals suffering from Alzheimer's disease globally. The main constituents including flavonoids and anthocyanins found in pomegranate got memory boosting effects on brain cells [81]. Meanwhile flavonoids have direct role in enhancing the memory and learning capability by means of increased blood flow to brain [56, 82]. However, flavonoids are responsible for controlling the signaling pathways of cyclic AMP, protein kinase C and cAMP response element-binding protein (CREB) [83]. Flavonoids have powerful interaction among course of information and neurons which are involved in the synthesis of neuronal protein resulting in new synapses and increased neurotransmission [84].

Anti-Inflammatory Activity

Punicic acid present in pomegranate prohibits the inflammation by preventing prostaglandin biosynthesis [85]. A study by Panichayupakaranant,

Tewtrakul [12] reported that standardized rind extract of pomegranate showed a powerful inhibitory effect on nitric oxide production. However, punicalagin and punicalin have significant ability to reduce PGE₂ production by inhibiting pro-inflammatory proteins [86]. Pomegranate peel extract particularly punicalagin and punicalin are responsible to reduce pro-inflammatory expressions of cytokines at a concentration of 10 µg/mL on bovine mammary epithelial cells BME-UV1 treated with lipopolysaccharide displaying an anti-inflammatory effect [87].

Romier, Van De Walle [88] reported the effects of polyphenols in modulation of nuclear factor-κB activation signaling pathway in human intestinal Caco-2 cell line. However, the polyphenolic phytochemicals of pomegranate showed significant role in HT-29 colon cancer cells by suppressing anti-inflammatory cell signaling in Tissue necrosis factor TNFα-induced COX-2 protein expression up to 79% at a dose of 50 mg/L [9]. Leaf as well as hydro-alcoholic extract of *P. granatum* showed anti-inflammatory properties in lipopolysaccharide induced peritonitis and in suppressed TNF-α levels described by Marques, Pinheiro [89]. Gracious Ross, Selvasubramanian [90] described the role of punicalagin in regulating the action T and B lymphocytes as well as the action of macrophages.

Anthelmintic Activity

Helminths infections is the most common parasitic infection that infect approximately 1.5 billion people in developing countries worldwide, that is triggered by Soil-Transmitted Helminths (STH). The phytochemicals of pomegranate responsible for anthelmintic activity may include tannins and alkaloids [91]. A study reported the anthelmintic activity of pomegranate against *Allolobophora caliginosa* resulting in death and paralysis of worms at a concentration of 100, 200 and 300 mg/ml in a dose dependent manner [92]. According to Amelia, Jasaputra [54] 75% peel extract of pomegranate showed anthelmintic effect against female *Ascaris suum*.

Anti-Obesity Activity

Obesity is a metabolic disorder which occurs due to discrepancy of energy and could lead to serious cardiovascular diseases and different health problems. Pomegranate and its bioactive constituents

can be consumed worldwide for its anti-obesity effects. Vroegrijk, van Diepen [66] demonstrated the role of pomegranate seed compound punicic acid in high fat diet induced obesity and insulin resistance. Moreover, punicalagin may be used as a beneficial component for the management of obesity related non-alcoholic fatty liver diseases by stimulating mitochondrial function, eradicating inflammation and oxidative stress [67].

Antidepressant Activity

Depression is a mood disorder that causes a persistent feeling of sadness, disturb sleep, loss of appetite and loss of pleasure. According to WHO, approximately 300 million people having depression worldwide. The estrogenic compounds of *P. granatum* are responsible for the antidepressant activity at a dose of 400 mg/kg revealed by forced swimming test [93]. Moreover, estrogens may augment the role of central adrenergic systems by reducing the activity of mono amino oxidase (MAO) and enhancing norepinephrine content [94]. Abdul Rahman, Abdul Kadar [49] found that pomegranate pulp extract at 25 mg/kg produce significant antidepressant effect in tail suspension and forced swimming test by decreasing the immobility time in mice model.

Antidiarrheal Activity

The constituents of *P. granatum* aqueous extract responsible for antidiarrheal activity include ellagic acid, punicalagin and corilagin. A study reported by Zhao, Ma [95] demonstrated the antidiarrheal effect of *P. granatum* bioactive constituent and bioactivity-guided fractions. In this study castor oil was used to alter intestinal membrane permeability to water and electrolytes that results in diarrhea [96]. However, Das, Mandal [97] explored the inhibitory effect pomegranate seed methanol extract in castor-oil induced diarrhea in albino rats. The primary mechanisms for the management of diarrhea display to be anti-enter pooling and antispasmodic.

Antioxidant Activity

Tzulker, Glazer [98] suggested punicalagin as key phytochemical having complete antioxidant capability, whereas anthocyanins contain negligible antioxidant action. By using ferric reducing ability of plasma (FRAP) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay Fazeli, Bahmani [99] demonstrated antioxidant abilities of unprobioticated and probioticated aril's

extracts of sweetened and bitter pomegranate varieties. Aqueous extracts of different pomegranate components were analyzed by the DPPH and 2,2'-azino-bis 3-ethylbenzothiazoline-6-sulphonic acid (ABTS) methods to determine *in vitro* antioxidant activities [100]. Report by Amri, Ghorbel [101] suggested the beneficial effects on cholinesterase action and oxidative stress of brain in addition to lipid profile in obesity-induced rats in different parts of pomegranate resulting in dose-dependent inhibition of cholinesterase activity.

Anti-Platelet Activity

The polyphenols in pomegranate that are responsible for the inhibition of platelet activation pathway include hydrolyzed tannins and anthocyanidins. A study reported the potential of pomegranate juice to inhibit platelet activation at every single step in arachidonic acid and collagen induced platelet stimulation [102]. However, anthocyanidins was also reported to inhibit platelet aggregation and cyclooxygenase activity in dose-dependent fashion [103]. Additionally, quercetin involved in inhibition of platelet function by deactivating phospholipase C pathway [104].

Dengue is one of the most promptly spreading viral infection worldwide. Meanwhile the incidence of dengue has been enlarged up to 30 folds in urban as well as rural areas. Pomegranates could be consumed as a dietary supplement in anticipation and control of dengue helping to maintain the normal platelet count [105].

Gonadotropin Activity

Fischer, Carle [81] identified various phenolic compounds of *P. granatum* such as flavonoids. However, flavonoids may involve to control diseases associated with reproductive organs [106, 107]. Additionally, they have important part in free radical's suppression as well as in antioxidant activity [108, 109]. Therefore, gonadal adaptations due to reactive oxygen species (ROS) synthesis may stimulate cell DNA damage [110, 111]. A study done by Riaz, Khan [112] revealed the effects of pomegranate on plasma gonadotropin and testosterone levels indicating an increase in luteinizing and follicle stimulating hormones significantly.

Anti-Diabetic Activity

Diabetes is considered as a chronic metabolic disorder that results either when less insulin is

produced or when body fails to utilize insulin effectively. WHO estimates diabetes as seventh principal cause of 1.6 million deaths in 2016. Tang, Liu [57] evaluate the significant role of pomegranate flower in NIDDM rats model by improving the insulin sensitivity in a concentration of 50 and 100 mg/kg following the activation of Akt-GSK3 β (glycogen synthase kinase-3 beta) signaling pathway and inhibition of Endoplasmic reticulum (ER) stress. In alternative system of medicines, the flowers of *P. granatum* were considered to have antidiabetic activity. Esmailzadeh, Tahbaz [113] investigated the significant reduction in lipid profile, ratio of HDL/LDL and total cholesterol that indicate the risk of cardiac diseases in hyperlipidemia patients. However, the aqueous extract of pomegranate flower showed a prominent decline in lipid profile, antioxidant enzymes and fasting glucose levels which indicate its use in treatment and prevention of chronic disorders characterized by provoked antioxidant prominence, reduced glucose uptake and heterogeneous lipid profile [114].

Anticancer Activity

Cancer is a collection of diseases comprising of anomalous cell growth having a potential to invade and affect other parts of the body. In 2018, WHO estimates cancer as one of the two leading causes of 9.6 million deaths annually. According to Van Elswijk, Schobel [115] pomegranate different parts exhibited anti-proliferative effects on various tumors. It was reported to act in different types of cancers including A549 lung cancer cells, MB-MDA-231 breast cells, MCF-7, PC-3 prostate cancer cells, mouth and bowel cancer due to its anti-proliferating property *i.e.* programmed cell death, growth inhibition and cell cycle distraction [18, 116, 117]. Report by Kohno, Suzuki [118] suggested that its seed oil effectively reduces the incidence and multiplicity of colonic carcinoma induced by azoxymethane if it is added in the diet.

Fruit extract of *Punica granatum* found to have chemo-preventative effects against lung cancer explored by Khan, Hadi [47]. The progression of cell was introverted and followed by programmed cell death of human prostate [119]. The constituents modulate inflammatory cell signaling by constraining propagation of cancer cell and apoptosis by modification of cellular transcription factors and also

HT-29 human colorectal cancer cell line signaling proteins.

Wound Healing Activity

The major bioactive constituents of pomegranate that are believed to have wound healing activity are gallic acid and catechin. The relation among antibiotics and methanol extract of *P. granatum* was accomplished by Braga against 30 clinical isolates of *Staphylococcus aureus* and MRSA. Murthy, Reddy [53] evaluated the wound healing property against the omission of skin lesion of Wistar rats in methanol extract of dried pomegranate.

Ajaikumar, Asheef [120] accomplished the inhibition of gastric mucosal injury which concluded that 70% of pomegranate methanol extract has potent inhibitory effect in aspirin and ethanol-induced gastric ulcer.

CONCLUSION AND FUTURE EXPLORATION

The evidence accrued in earlier eras suggest that pomegranate possess various medicinal uses including antidiabetic, anticancer, anti-obesity, anthelmintic, antioxidant and anti-inflammatory effects thus serving as a healthy fruit in human diet. The experimental pharmacological activities may be recognized because of high concentration of essential phytochemicals like flavonoids, polyphenols, tannins and anthocyanins which suggests that there are various opportunities for the food and healthcare production to discover the health benefits of pomegranate.

Flavonoids has a potential to eradicate and preclude the lipid per-oxidation as well as ROS formation because of its antioxidant potential. A report evaluates the occurrence of estrogen and testosterone like compounds in pomegranate that are involved to increase FSH plasma levels significantly [119]. However, in early juvenile period estrogen and testosterone like compounds have favorable effects on follicle stimulating and luteinizing hormones [121]. Therefore, pomegranate can be added in infertile patient's diet in order to avoid harmful side effects of drugs as well as to reduce female infertility. Moreover, flavonoids probably stimulate the activation of CREB required for neutrophins-protein production ultimately enhancing the neurotrophic factor levels in the hippocampal brain area [122]. Pomegranate fruits have memory boosting effect might be due to

improved genes expression or neuronal protein synthesis that strengthen the communication among neurons. Furthermore, advance studies are needed on biochemical investigations to reveal the precise role on memory enhancement.

Further studies associated with some important issues regarding identification, metabolism, toxicity, bioavailability and complete description of dose response has not been well documented yet. However, further studies are required to authenticate that pomegranate can be consumed as a nutraceutical compound. This review aims to highlight the active components and pharmacological activities of *P. granatum* in order to draw attention of the researchers all over the world to study and discover its remarkable health promoting potentials.

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