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Pharmacological Characterization and Beneficial Uses of *Punica granatum*

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Abstract: *Punica granatum* L. commonly known as Pomegranate belongs to the Family Punicaceae. Pomegranate has been known to be a reservoir of secondary metabolites which are being exploited as source of bioactive substance for various pharmacological purposes. Many researchers have focused their interest to investigate the bioactive compounds of *Punica granatum* for human health. In order to facilitate the further investigation and exploit the said plant, this study summarized herein the research achievements on some of the phytochemical and pharmacological properties of *Punica granatum*. The different types of phytochemicals have been identified from various parts of the pomegranate tree and from pomegranate juice, leaves, flower, fruits and seeds. The constituents of this plant were thoroughly reviewed discussed based on literatures.

Key words: *Punica granatum*, phytochemicals, bioactive, secondary metabolites, pharmacological, constituents

INTRODUCTION

Alternative approach to drug discovery is through the medicinal plants. The researchers currently focused on herbal formulation to overcome the problems associated with synthetic drugs. Currently used antimicrobial synthetic drugs are effective but they lag behind the desired properties since they frequently produce side effects, have poor patient compliance and are expensive. Thus, herbal formulations are better alternative antimicrobial natural remedies to prevent various microbial diseases. They are safe, simple, effective self administrative source of treatment. Many people rely on traditional medicine, plant derived drugs products for their primary healthcare (Raghuveer *et al*., 2011; Joshi *et al*., 2012a; Jasuja *et al*., 2012). Presently, medicinal plants are the source traditional medicine, herbal medicine and various dietary supplements (Shafaei *et al*., 2011; Kaewseejan *et al*., 2012). World-wide, pharmaceutical scientist pushing strong demand to find out active pharmaceutical ingredients from medicinally important plant (Bairwa *et al*., 2011; Joshi *et al*., 2012b; Karmegam *et al*., 2012). *Punica granatum* is ethnomedicinal important plant and depicted ameliorating medicinal value which used for the treatment of various diseases (Miguel *et al*., 2010). It belongs from Punicaceae family and extract of *P. granatum* has been reported to have various medicinal values i.e., antioxidant, antibacterial, antidiabetic, cardioprotective and anticarcinogenic activity (Morton, 1987; Longtin, 2003; Ajaikumar *et al*., 2005; Adhami and Mukhtar, 2007; Abdel Moneim, 2012; Rahimi *et al*., 2012). Kokate reported that flowers of *P. granatum* were useful in astringent, antimicrobial and antiviral activity and it has also suggested as an alternative source of remedy for injury, bronchitis, diarrhoea, digestive problems, man sex power reconstituent, dermal infected wounds (Kokate *et al*., 2006; Jurenka, 2008). It was found industrially important and used to prepare fresh juice, canned beverage, jelly, jam, paste, flavouring and colouring agents (Fadavi *et al*., 2005). Recently, it has been included for treatment of Acquired Immune Deficiency Syndrome (AIDS) (Lee and Watson, 1998), in addition to use for cosmetic beautification (Kawamada and Shimada, 2002; Moayadi, 2004) and enhancement (Curry, 2004), hormone replacement therapy (Lansky, 2000), resolution of allergic symptoms (Watanabe and Hatakoshi, 2002), cardiovascular protection (Shiraishi *et al*., 2002; Aviram and Dornfeld, 2003), oral hygiene (Kim and Kim, 2002), ophthalmic ointment (Bruijn *et al*., 2003), weight loss soap (Guojian, 1995) as an adjunct therapy to increase bioavailability of radioactive dyes during diagnostic imaging (Il'iasov, 1975; Amorim *et al*., 2003).

CHEMICAL CONSTITUENTS AND COMPONENTS

The several chemical constitutes of *P. granatum* were identified and isolated from different parts of the plant such as juice, pericarp, leaves and seeds i.e., punicalagin, ellagic acid, luteolin, quercetin, kaempferol, ellagitannins, anthocyanins (delphinidin, cyanidin and

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pelargonidin) and EA-glycosides, several fatty acids, sterols, triterpenes, flavonoids tannins. Various factors influence the chemical composition of fruit such as climate, cultural practice, storage conditions, growing area and cultivar (Melgarejo *et al*., 2000; Nanda *et al*., 2001; Barzegar *et al*., 2004; Miguel *et al*., 2004; Fadavi *et al*., 2005). The physical and chemical properties of pomegranate have been evaluated in Italy (Barone *et al*., 2001), Turkey (Ozkan, 2003). On an average basis the pomegranate has following components as shown in Fig. 1 and Table 1.

The different types of phytochemicals that have been identified from various parts of the pomegranate tree and from pomegranate juice, leaves, flower, fruits and seeds are listed in Table 2.

Zongo *et al*. (2009) earlier reported the antimicrobial activity of the total alkaloids from the leaves of *Mitragyna inermis* (Willd.) O. Kuntze (Rubiaceae) and confirmed the use of the plant in traditional medicine against some infectious diseases. The physicochemical analysis of powder (flower material) exposed the moisture content (loss on drying), total ash, acid insoluble ash, water soluble extractives, chloroform soluble extractives petroleum ether soluble extractives are as shown in Fig. 12.

De Pascual-Teresa *et al*. (2000) reported the anthocyanins, a natural pigments, responsible for the red colour in pomegranate may play an important role in the defense mechanisms of plants and Sentandreu *et al*. (2010) also reported the 35- flavonol-anthocyanins from pomegranate juice. De Pascual-Teresa and Sanchez-Ballesta (2008) revealed that the catechin and gallocatechin are the major flavon-3-ol among others in pomegranate fruit and Plumb *et al*. (2002) isolated the prodelphinidins (tannins) derived from the polymerization of gallocatechin in pomegranate peel.

Chemical investigation of juice peels and seed oil of *Punica granatum* by Kim *et al*. (2002) and Lansky and Newman (2007) reported the cyaniding, delphinidin (both are anthocyanins), caffeic acid, chlorogenic acid (both are phenolic acids), gallic acid, ellagic acid (tannic acids), luteolin, quercetin (flavones), kaempferol (a flavonol), naringenin (a flavanone) as well as 17 alpha estradiol, estrone, estriol, testosterone, beta sistosterol, coumestrol, gamma-tocopherol, punicic acid, campesterol and stigmasterol etc., which are chemopreventive. Elfalleh *et al*. (2009) have also been identified the ellagic acid from juice and seed oils of pomegranate which has the activity against cancer of skin, pancreas, breast, prostate, colon, intestine, oesophagus, bladder, oral, leukaemia, liver and neuroblastoma.

Table 1: Pomegranate chemical composition (Bakhru, 1994)

Components	Concentration (mg)
Electrolytes	
sodium	3
Potassium	236
Minerals	
Calcium	10
Copper	18%
Phosphorus	36
Iron	0.30
Magnesium	12
Manganese	0.119
Zinc	0.35
Vitamin	
Vitamin C	10.2
Vitamin B complex	Trace amount
Vitamin K	16.4 μg
Vitamin E	0.60
Energy	83 kcal

Values are per 100 g of edible portion

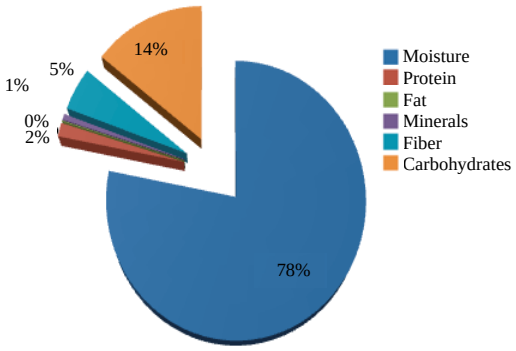

Fig. 1: Food value of *Punica granatum*, percentage of food value are per 100 g edible portions (Dahham *et al*., 2010)

PHARMACOLOGICAL PROPERTIES

Antioxidant activity: Surveswaran *et al*. (2007) studied the effect of pomegranate constituents such as phenolic hydroxyl groups and double bonds including tannins, flavonoids and unsaturated fatty acids and used as an antioxidant agent. In pomegranate phenolics are the dominant antioxidant as a positive linear correlation were found between total antioxidant capacities and phenolic contents. Earlier it has been reported that pomegranate is an important source of anthocyanins, hydrolysable tannins punicalagin and punicalin (Afaq *et al*., 2005), ellagic and gallic acids (Lansky and Newman, 2007) and also contains vitamin C (Turk *et al*., 2008). Leaves and fruit are the main source of antioxidant substance including seed, juice and pericarp, free radicals like Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH) and Nitric Oxide (NO) can be efficiently quenched by juice and aqueous extract of leaves and their effect is greater than that of the fruit extracts. (Halvorsen *et al*., 2002; Xu *et al*., 2009; Kaur *et al*., 2006; Guo *et al*., 2007) even juice can

Table 2: Phytochemicals of pomegranate

Plant part	Compounds
Juice	85.4% Water, 10.6% total sugars (Fig. 2), 1.4% Pectin, 0.2-1.0% Polyphenols and fatty acids, amino acids (Fig. 8) organic acids (Fig. 3), Indoleamines; tryptamine, serotonin, melatonin (Fig. 9a-c), Sterols, triterpenoids, tocopherol; α-tocopherol, anthocyanins (Fig. 7), glucose, hydroxybenzoic acids; gallic acids, ellagic acids, quinic acid (Fig. 4a-c), Hydroxycinnamic acids; caffeic acid, chlorogenic acid, *p*-coumaric acid (Fig. 5a-c), flavonoids and their glycosides; catechin (Fig. 6a), Epicatechin (Fig. 6b), EGCG, Quercetin (Fig. 6c), rutin (Fig. 6d), Ellagitannins; punicalin, punicalagin, corilagin, casuarinin, gallagyldilacton, numerous minerals, particularly iron
Seed oil	Hydroxybenzoic acids; ellagic acid, conjugated fatty acids; 95% punicic acid, Non-conjugated fatty acids; linoleic acid, oleic acid, palmitic acid, stearic acid, sterols, tocopherols; γ-tocopherol, isoflavones, triterpenes, phenyl aliphatic glycosides
Pericarp (peel, rind)	Hydroxybenzoic acids: gallic acid; ellagic acid, hydroxycinnamic acids: caffeic acid; chlorogenic acid; *p*-coumaric acid, cyclitol carboxylic acids: quinic acid, Alkaloids: peleteriene (Fig. 11), ellagitannins: punicalin; punicalagin; corilagin; casuarinin; gallagyldilacton; pedunculagin; tellimagrandin; granatin A; granatin B, Anthocyanins: cyaniding; pelargonidin; delphinidin and other fatty acids, catechin, EGCG; quercetin, rutin, kaempferol (Fig. 10a), naringin (Fig. 10b), kaempferol-3-O-glycoside (Fig. 10c), kaempferol-3-O-rhamnoglucoside (Fig. 10d)
Leaves	Tannins (punicalin and punicafolin); and flavones glycosides, including luteolin and apigenin
Flower	Gallic acid, ursolic acids, triterpenoids, including maslinic and Asiatic acids; other unidentified constituents
Roots and bark	Ellagitannins; including punicalin and punicalagin, numerous piperidine alkaloids

(Melgarejo *et al*., 2000; Nanda *et al*., 2001; Barzegar *et al*., 2004; Miguel *et al*., 2004; Fadavi *et al*., 2005)

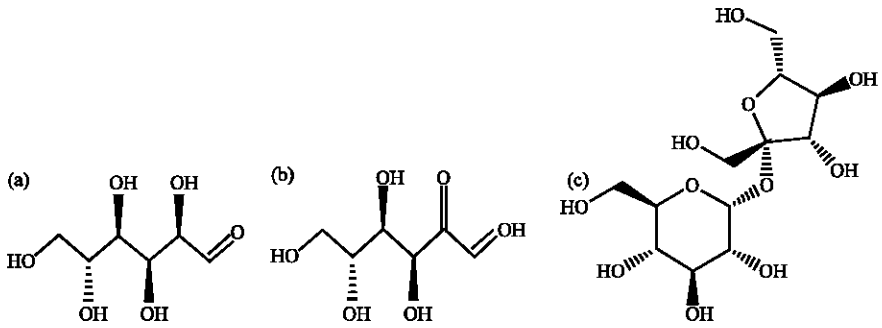

Fig. 2(a-c): Sugars (a) Glucose, (b) Fructose and (c) Sucrose from pomegranate juice (Cui *et al*., 2004; Gabbasova and Abdurazakova, 1969)

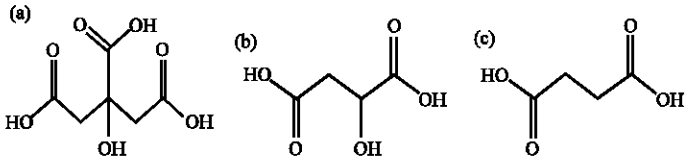

Fig. 3(a-c): Organic acid (a) Citric acid, (b) Malic acid and (c) Succinic acid from pomegranate juice (Poyrazoglu *et al*., 2002)

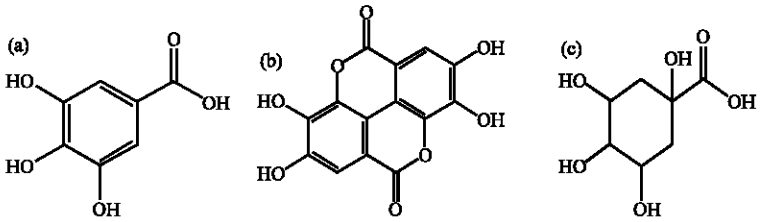

Fig. 4(a-c): Cyclitol carboxylic/hydroxybenzoic acids (a) Gallic acid, (b) Ellagic acid and (c) Quinic acid from pomegranate juice (Amakura *et al*., 2000a, b; Wang *et al*., 2004; Huang *et al*., 2005b)

suppress the production of oxLDL *in vitro* (Fuhram and Aviram, 2001) and *in vivo* in rats effectively decrease the oxLDL level (Xu *et al*., 2005). Murthy *et al*. (2002) showed 54% reduction of lipid peroxidation values compared to controls in rats with CCl_4^- induced liver damage demonstrated pretreatment with a Pomegranate Peel Extract (PPE) enhanced or maintained the free-radical scavenging activity of the hepatic enzymes catalase, super oxide dismutase peroxidase. It has been reported that in pomegranate, two

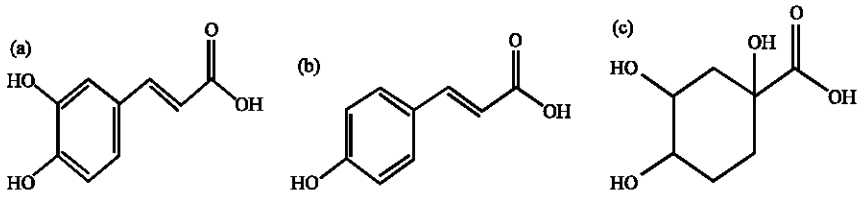

Fig. 5(a-c): Hydroxycinnamic acids (a) Caffeic acid, (b) Chlorogenic acid and (c) p-coumaric acid from pomegranate juice (Artik, 1998; Amakura *et al*., 2000a)

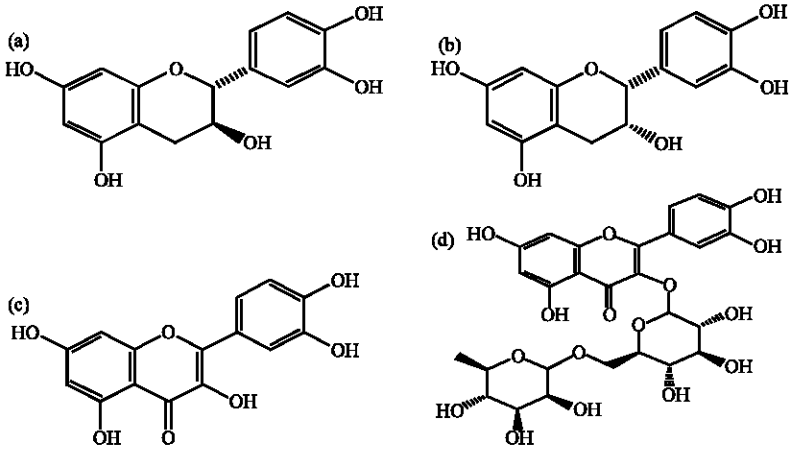

Fig. 6(a-d): Flavan-3-ols/flavonoids (a) Catechin and (c) Quercetin and their glycosides (b) Epicatechin and (d) Rutin from pomegranate juice (Artik, 1998; De Pascual-Teresa *et al*., 2000)

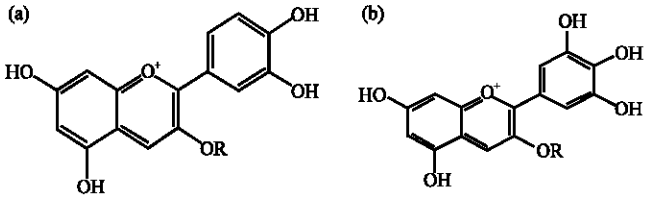

Fig. 7(a-b): Anthocyanins from pomegranate juice and peel (Noda *et al*., 2002). R = H; Cyanidin, R = H; Delphinidin. R = β-D-glucopyranosyl; Cyanidin-3-O-glucoside, R = β-D-glucopyranosyl; Delphinidin-3-O-glucoside

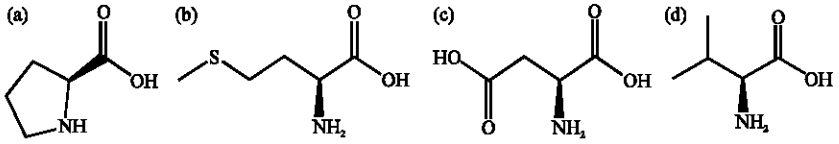

Fig. 8(a-d): Amino acid (a) Proline, (b) Methionine, (c) Aspartic acid and (d) Valine from pomegranate juice (Velioglu *et al*., 1997; Seppi and Franciosi, 1980)

tannins namely ellagic acid and punicalagin have an important role in antioxidant activity and also reported the major flavonoids namely catechin, quercetin, kaempferol and equol, play an important role in antiperoxidative activity, antioxidant activity and photo-protective effects on UVB-induced skin damage which is demonstrated by the increased expression level of procollagen type I and decreased expression level of matrix metalloproteinases-I (MMP-I) (Wang *et al*., 2006; Sestili *et al*., 2007; Suo *et al*., 2009; Park *et al*., 2010). The studies of

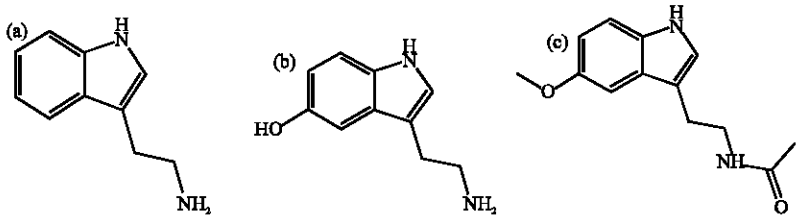

Fig. 9(a-c): Indoleamines (a) Tryptamine, (b) Serotonin and (c) Melatonin from pomegranate juice (Badria, 2002)

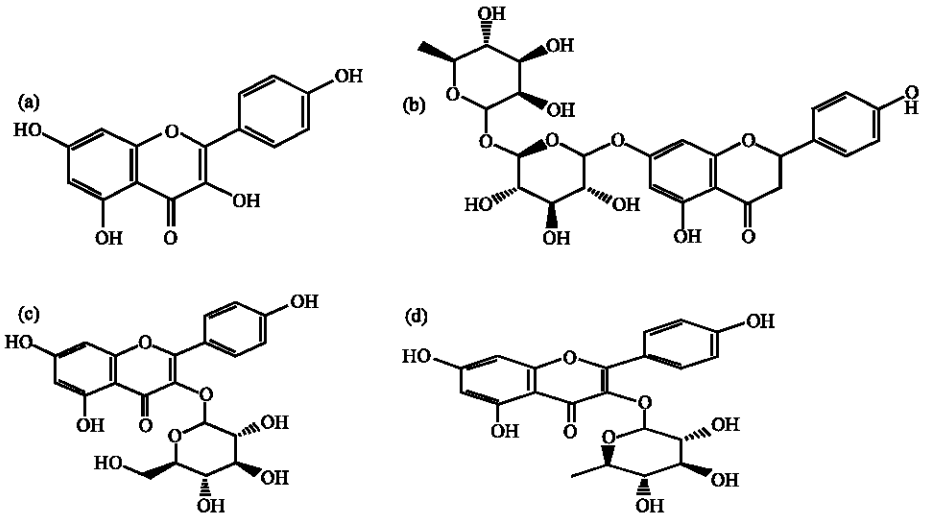

Fig. 10 (a-d): Flavonoids (a) Kaempferol and (b) Naringin and their glycosides (c) Kaempferol-3-O-glycoside and (d) Kaempferol-3-O-rhamnoglucoside from pomegranate peels (Van Elswijk *et al*., 2004; Kim *et al*., 2002)

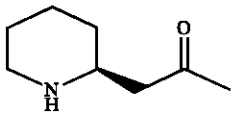

Fig. 11: Alkaloids (pelletierine) from pomegranate peels (Neuhofer *et al*., 1993; Vidal *et al*., 2003)

Sudheesh and Vijayalakshmi (2005) revealed that the concentrations of malondialdehyde, hydroperoxides and conjugated dienes in the liver, heart and kidney were significantly reduced and the activities of the enzymes such as catalase, SOD, glutathione peroxidase, glutathione reductase the concentration of glutathione in the tissue were significantly enhanced after the rats were orally administered with total flavonoids from pomegranate. Other compounds i.e., phenolic hydroxyl groups or unsaturated double bonds such as lignans including coniferyl 9- O - [α- D- apiofuranosyl (1>6)]- O-α-D-glucopyranoside and sinapyl 9-O - [α- D- apiofuranosyl (1>6)]-O-α-D-glucopyranoside and unsaturated fatty acids are the active antioxidant constituents of pomegranate (Elgareo *et al*., 1995; Wang *et al*., 2004; Seeram *et al*., 2005).

Antimicrobial activity: Plant extracts of *Punica granatum* has activity against Methicillin-Sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant (MRSA) *Staphylococcus aureus*, *Escherichia coli* O157:H7, *Salmonella typhi* and some *Streptococci strains* (Machado *et al.,* 2003; Voravuthikunchai *et al*., 2004; Rani and Khullar, 2004; Braga *et al*., 2005; Neurath *et al*., 2005; Vasconcelos *et al*., 2006). Crude extract of seeds of *N. sativa* have a promising effect on multi-drug resistant *Staphylococcus aureus* (ATCC 25923) (Dadgar *et al*., 2006) and also showed the antibacterial activity against *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (ATCC 19615), *E. coli* (ATCC 25922) and *Bacillus cereus* (ATCC 11778) (Zuridah *et al*., 2008).

Menezes *et al*. (2006) studied the hydroalcoholic extract (HAE) of *Punica granatum* were very effective against dental plaque microorganisms in an *in vivo* study,

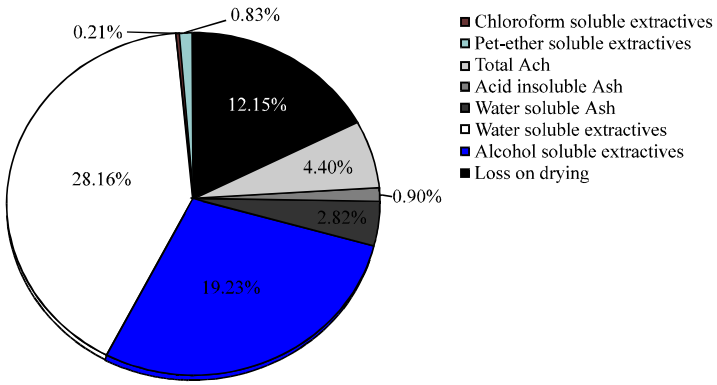

Fig. 12: Physicochemical parameter of Punica granatum (Dahham *et al*., 2010)

decreasing the number of colony forming units per milliliter by 84% versus the control group's 11% decrease (distilled water) and results indicate that the HAE may be a possible alternative for the treatment of dental plaque bacteria. Earlier study suggested potential inhibitory effect of *Citrus lemon* (lemon), *Citrus sinensis* (orange), *Curcuma longa* (turmeric) and *Zingiber officinale* (ginger) essential oils on lipophilic, yeast like fungus *Malassezia furfur* which causes *Pityriasis versicolor*, chronic superficial fungal disease of the skin (Sharma and Sharma, 2010; Sharma *et al*., 2011, 2012). Antimicrobial effect of dye powders obtained from *P. granatum* has also been reported on *S. aureus* ATCC 25923, *Shigella sonnei* RSKK 877, *E. coli* ATCC 35218, *B. megaterium* RSKK 5117, *B. subtilis* RSKK 244, *B. cereus* RSKK 863, *P. aeruginosa* ATCC 29212, *Streptococcus epidermidis* and *P. aeruginosa* 27853. The natural dyes with antimicrobial activities found were assayed in solution and in textile substrate (wool fabric). Maximum inhibition rate obtained against *Bacillus subtilis* of wool samples dyed from *P. granatum* was 80%. Natural dyes possess antimicrobial activity either in solution or in substrate (Han and Yang, 2005; Calis *et al*., 2009).

Pomegranate extracts have been used as antagonist effects against microorganisms which caused urinary tract infections. Methanolic extract have broad-spectrum activity against 159 multi-drugs resistant bacterial strains isolated from urine of patients who had urinary infection (Gopalakrishnan and Benny, 2009; El-Sherbini *et al*., 2010; Endo *et al*., 2010). El-Sherbini *et al*. (2010) attributed the *in vitro* antifungal activity of punicalagins against *Candida albicans* and *Candida parapsilosis* and *in vivo* achievable concentrations of punicalagins showed a powerful synergistic interaction with commonly used as antifungal fluconazole. Pomegranate derived products have effective therapies for treatment of multiple drug resistant urinary tract infections. Punicalagin are more effective compound of pomegranate antimicrobial properties (Endo *et al*., 2010; Dell'Agli *et al*., 2010).

Antiviral activity: Zhang *et al*. (1995, 1997) reported that the aqueous extract of pericarp have high content of tannins significantly inactivated HSV-2 and HBV via inhibiting the DNA polymerase in a dose dependent manner *in vitro*. Neurath *et al*. (2004) studied that *Punica granatum* used as a topical microbicide for HIV prevention and *in vitro* research also reported that an anti-HIV-1 microbicide could potentially be made from *P. granatum*. Haidari *et al*. (2009) worked on polyphenol extract that suppressed the replication of human influenza A/Hong Kong (H3N2) *in vitro* and also suppressed replication of influenza A virus in MDCK cells inhibited agglutination of chicken red blood cells (cRBC) caused by influenza virus. Anti-influenza effect were showed in four major polyphenols of pomegranate i.e. ellagic acid, caffeic acid, luteolin punicalagin and the results shown that punicalagin is the most effective one. Punicalagin had a virucidal effect and blocked replication of the virus RNA, inhibited agglutination of chicken RBC induced by virus.

Anti-hepatoprotective activity: The hepatoprotective effect of pomegranate has been investigated by animal experiments *in vivo* but detailed mechanism and the effective compounds were not identified. Flower extract of pomegranate demonstrated the hepatoprotective effect against ferric nitrilotriacetate (Fe-NTA) induced hepatotoxicity in mice which was considered to be probably resulted from the potent antioxidant activity of polyphenols in flower extract (Kaur *et al*., 2006; Celik *et al*., 2009).

The studies of Khalil (2004) revealed that the aqueous fruit bark extract of pomegranate have

hepatoprotective activity against overdose acetaminophen it was found that the pretreatment of rats with aqueous rind extract of *Punica granatum* 0.43 g kg^{-1} b.wt. for 3 days before intraperitoneally (i.p.) injection of 0.5 g acetaminophen significantly reduced the acute elevation of serum aspartate aminotransferase (AST), serum alanine aminotransferase, lactate dehydrogenase (LDH) and alleviated the degree of liver damage after the i.p. injection of hepatotoxin. The group treated only with 0.5 g acetaminophen displayed significant increase in serum (AST), (ALT), (LDH) and liver displayed congestion of central and hepatic portal veins, vacuolization and ballooning also a lot of pyknotic nuclei were detected with many small necrotic areas of hepatocytes. Inflammatory cells in between hepatocytes and around the portal tract were observed. Some fatty droplets were scattered in the hepatocytes. The aqueous extract of pomegranate peels possess a strong antioxidant capacity could ameliorate the damage occurred in liver by overdose acetaminophen (Khalil, 2004).

Anti-diabetic activity: Katz *et al.* (2007) studied the global epidemic of metabolic syndrome and its associated pathologies obesity, type 2 diabetes cardiovascular disease have anti-diabetic agents with low toxicity suitable for long-term use. The previously unknown polyphenols of Pomegranate Flower Extract (PFE) were discovered by Chinese scientists in 2006 which have combats weight gain, impaired glucose control and systemic inflammation (Wang *et al*., 2006). Jafri *et al.* (2000) demonstrated the ability of flower extract to influence blood sugar in normal and diabetic rats. Huang *et al.* (2005a) studied that 6 weeks of supplementing obese diabetic rats with PFE prevented blood sugar increases following a glucose-laden meal- but had no such effect in normal rats. Anti-diabetic activity of PFE also enhanced gene expression of the vital transcription factor PPAR-gamma, which regulates cellular responses to energy intake and its normalized expression of a glucose-transporting protein in heart muscle, enabling the diabetic animal's hearts to better utilize energy from sugar (Huang *et al*., 2005c). Huang *et al.* (2005a) also reported the viable molecular pathway for improved insulin sensitivity i.e. an important step in preventing diabetic complications. PFE reduce cardiac muscle triglyceride content and total cholesterol levels in the blood. Normalization of these vital lipid parameters occurred through up regulated expression of PPAR-alpha, the gene transcription factor that controls how cells take up and utilize fatty acids. These twins finding have profound implications: drug companies have spent millions in the effort to find a pharmaceutical that could induce these effects. As a dual PPAR-alpha and PPAR-gamma activator, pomegranate flower extract offers potential realization of that effort through a safe, low-cost, natural intervention (Li *et al*., 2008). It is reported that PFE significantly reduced heart muscle fibrosis (thickening and stiffening) (Huang *et al*., 2005b). The extract reduced gene expression of the inflammatory regulatory molecule NF-κB (Huang *et al*., 2005c), which plays an important role in controlling the inflammation and metabolic alterations associated with obesity (Zoico *et al*., 2009). Oral administration of PFE reversed all of these conditions in a laboratory rat model of type 2 diabetes, highlighting its potential utility for aging individuals at risk for diabetes and its cardiovascular complications (Bagri *et al*., 2009). The extract also helps ameliorate fatty liver disease (Xu *et al*., 2009), the most common cause of liver function abnormalities in people with obesity and type 2 diabetes.

P. granatum rind extract also possessed significant blood sugar lowering activity (Nogueira and Pereira, 1984; 1986a; 1986b; Zafar and Singh, 1990). Nogueira and Pereira (1986b) studied the antihyperglycaemic action of the peel extract of *P. granatum*, to the inhibitory intestinal absorption of glucose in rats. It has also been reported that the role of Pomegranate Peels Extract (PPE) in its human therapeutic dose on beta cell numbers blood glucose and plasma insulin levels in normal and alloxan diabetic rats for 4 weeks of treatment. Pomegranate aqueous extract increased insulin levels in normal and diabetic treated rats and decreased blood glucose. Pancreas showed increased number of beta cells in normal and treated diabetic rats. Pomegranate peel aqueous extract can reduce blood sugar through regeneration of β cells (Nogueira and Pereira, 1984).

Anti- inflammation activity: Schubert *et al.* (1999) studied the anti- inflammatory activity of pomegranate seeds and observed that polyphenols and fatty acids were the major anti- inflammatory constituents. Polyphenols and fatty acid from cold pressed seed oil of pomegranate showed 31-44% inhibition of sheep cyclooxygenase and 69-81% inhibition of soybean lipoxygenase, while the extract from fermented juice showed 21-30% inhibition of soybean lipoxygenase. Polyphenols suppress inflammatory cell signaling in colon cancer cells (Adams *et al*., 2006). Pomegranate extract used as anti-inflammatory medicine by effecting the inhibition of inflammatory cytokine-induced production of PGE2 and nitric oxide *in vivo* (Shukla *et al*., 2008). Haqqi (2008) showed that blood samples collected from rabbits fed pomegranate extract inhibited inflammation. The studies of Hontecillas *et al.* (2009) revealed that punicic acid

(PUA) caused a dose-dependent increase peroxisome proliferator-Activated Receptor (PPAR) alpha and gamma reported activity in 3T3-L1 cells and bond although weakly to the Ligand Binding Domain (LBD) of human PPAR gamma. Dietary PUA inhibited the NF-kappa B activation, TNF- alpha expression and unregulated PPAR alpha- and gamma-responsive genes in skeletal muscle and adipose tissue. Loss of PPAR gamma impaired the ability of dietary PUA to improve glucose homeostasis and suppress inflammation.

Anticancer activity: Carcinogenesis is influenced by various factors. The occurrence and development of tumors is affected by Pomegranate such as inflammation development, angiogenesis, apoptosis, proliferation and invasion. it has been reported that the seed oil of pomegranate play important role in repair of aging skin, immune function modulation and inflammation reduction (Aslam *et al*., 2005; Yamasaki *et al*., 2006; Lansky and Newman, 2007; De Nigris *et al*., 2007a). The data on pomegranate seed oil's cancer fighting potential is most compelling in tissues of the male and female reproductive systems. Pomegranate seed oil is a potent inhibitor of aromatase, the enzyme that produces estrogen from testosterone 17-beta-hydroxysteroid dehydrogenase type 1, which is responsible for the conversion of estrone to potent estradiol. This enzymatic blockade contributes to pomegranate seed oil's ability to inhibit growth of estrogen-dependent breast cancer cells in culture. It also reduces the cancer cells' invasiveness. Cancer cells need to grow new blood vessels to support their rapid growth and tissue invasion (angiogenesis). They typically do this by ramping up production of a variety of growth factors, including Vascular Endothelial Growth Factor (VEGF) and inflammatory interleukins. Pomegranate seed oil powerfully inhibits production of VEGF while up regulating production of Migratory Inhibitory Factor (MIF) in breast cancer cells. In a laboratory model of vessel growth, these modulations translated into a significant decrease in new blood vessel formation (Toi *et al*., 2003). Pomegranate seed oil's capacity to block breast cancer development also demonstrated in an organ culture model of mouse breast cancer (Mehta and Lansky, 2004). Treating the glands with the oil prior to exposure to a powerful carcinogen resulted in an astonishing 87% reduction in the number of cancerous lesions compared with controls-substantially greater protection than has been previously reported for derivatives of pomegranate juice. As with flower extracts, pomegranate seed oil contains a number of unique chemical constituents with potent biological effects. Punicic acid is an omega-5 polyunsaturated fatty acid that inhibits both estrogen-dependent and estrogen-independent breast cancer cell proliferation in lab cultures. Punicic acid also induced apoptosis at rates up to 91% higher than those in untreated cell cultures-effects which appear to be related to fundamental regulation of cancer cell signaling pathways (Grossmann *et al*., 2010). Another common malignancy that often depends on sex hormones for its growth is prostate cancer, a leading cause of cancer-related mortality in American men, accounting for more than 29,000 deaths each year (Syed *et al*., 2008). Because of its slow rate of growth and appearance later in life, prostate cancer has been identified as an ideal target for nutritional chemoprevention (Syed *et al*., 2007).

Pomegranate seed oil sharply inhibits proliferation of a number of human prostate cancer lines through changes in the cell growth cycle and also by inducing apoptosis (cell death). At the same time, it has been shown to powerfully suppress cancer cell invasion (Albrecht *et al*., 2004). Pomegranate oil also acts in synergy with other pomegranate components, suppressing prostate cancer proliferation and metastatic potential more effectively than each component individually (Lansky *et al*., 2005).

Anti-atherosclerotic activity: Pomegranate derived products have anti-atherogenic effects that are used in the prevention and attenuation of atherosclerosis (Aviram *et al*., 2004; Rosenblat *et al*., 2006b; De Nigris *et al*., 2007a, b; Aviram *et al*., 2008). Lavi *et al*. (2008) reported that atherosclerosis, cardiovascular disease with a major incidence involves inflammatory and oxidative processes that entail to endothelial dysfunction by affecting Nitric Oxide (NO) bioavailability among others. Oxidative stress and inflammation have been suggested like the main targets of atherosclerosis treatment by dietary phytochemicals (Basu and Penugonda, 2009). The role of pomegranate in atherosclerotic injury, focused on the endothelial function and NO biochemistry as these are implicated in pathology. Some researchers studied on hypercholesterolemic mice, fed with high- fat diet, also exhibited the protective effects on atherosclerosis of a prolonged (6-months) pomegranate derivatives supplementation (De Nigris *et al*., 2007b). Prolonged intake of Pomegranate also exhibited the anti-atherogenic effect; however, short-term consumption may also beneficial. It is revealed that administration of pomegranate juice for a week also enhances the oxidative status and reduces the lipid peroxidation, rather than an acute dosage. However, anti-atherogenic activity of pomegranate depends on different dose levels (Aviram and Dornfeld, 2001; Rosenblat *et al*., 2006a, b). An approach to find out the compounds

responsible for the anti-atherosclerotic activity of different fruit part of pomegranate has been reported. Aviram *et al*. (2008) investigated that pomegranate juice and arials extract are rich source of anthocyanins and hydrolysable tannins, responsible to reduce serum oxidative stress in contrast to pomegranate peel extracts, which display a higher beneficial effect on the extent of Ox-LDL uptake by macrophages and on their oxidative status. Pomegranate juice was more effective in reducing the cholesterol level as compare to peel extracts (De Nigris *et al*., 2007a).

Alzheimer's disease: The neuroprotective properties of pomegranate polyphenols (juice) were evaluated in Alzheimer's transgenic mice. Almost 50% less accumulation of soluble amyloid-beta and less hippocampal amyloid deposition was observed when administered with juice. Animals also exhibited improved learning of water maze tasks and swam faster than control animals (Hartman *et al*., 2006). *P. granatum* may also be effective in the treatment of cognitive disorders such as dementia and Alzheimer's disease. Ethanolic extract of *Punica granatum* seeds was found effective on cognitive performance of aged and scopolamine treated young mice. Chronic administration (21 days) of *Punica granatum* extract and vitamin C significantly ($p< 0.05$) reversed the age induced or scopolamine induced retention deficits in both the paradigms. *P. granatum* extract also significantly reduced lipid peroxidation level and increased antioxidant glutathione level in brain tissues (Kumar *et al*., 2008).

Antiepileptic activity: Antiepileptic effect of hydro alcoholic PPE observed in mice. They were intraperitoneally administrated at dose 400 mg kg^{-1} by 20 min before acetic acid injection and the number of writhing was counted as later group. In formalin test; the formalin was subcutaneously injected in foot of mice. In other group, the extract was intraperitoneally administrated 400 mg kg^{-1} by 20 min before formalin injection. One group of mice received strychnine at dose 3 mg kg^{-1} as negative control. The PPE was administrated 100, 200, 400 and 600 mg kg^{-1} before strychnine administration. The onset, duration and number of convulsion were measured and time of death was determined in 30 min after strychnine administration. It has been reported that PPE was considerably decreased licking and writhing. PPE had significantly anticonvulsive effect (Olapour and Najafzadeh, 2010).

OTHER ACTIVITIES

Other pharmacological activities i.e., immunostimulatory activity and stimulated both the humoral and cell-mediated immune responses found in aqueous suspension of pericarp of *Punica granatum*. It was evidenced by the enhanced inhibition of leucocyte migration and increased antibody titer to typhoid-H antigen (Russ *et al*., 2001). The seed oil also involved to produce immunoglobulin in the spleen cells of mice and may improve the function of β cells *in vivo* (Yamasaki *et al*., 2006). The aqueous extract and the seed oil can promote proliferation of hypodermis and epidermis, whereas the aqueous extract of pericarp can suppress the sperm fertility and prevent the rabbit from pregnancy; the petroleum ether extract of the seeds exhibited potent estrogenic activity which can be antagonize by progesterone (Sun *et al*., 1994; Li *et al*., 2002; Aslam *et al*., 2005).

Pomegranate seeds contain the estrogenic compounds, estradiol and estrone and isoflavone phytoestrogens i.e., daidzein and genistein (Heftmann *et al*., 1996). Mori-Okamoto *et al*. (2004) investigated the effect of seed extract on the estrogen deficiency in ovariectomy animals (OVX). Administration of seed extract for 2 weeks to OVX mice prevented the loss of uterus weight and shorted the immobility time. Bone histomorphometric parameters, i.e,. OV/BV, OS/BS, Ob, S/BS, ES/BS and N. Oc/B. Pm, also improved (Mori-Okamoto *et al*., 2004). Study confers that pomegranate seeds have estrogenic activity due to the amelioration on the depressive state, a clinically significant mental profile of women menopausal syndrome (Gerdes *et al*., 1982) especially due to the uterotrophic action. Only the bark and root were reported to be toxic due to presence of alkaloid content (Tripathi and Singh, 2000). Vidal *et al*. (2003) determined the LD_{50} of the whole fruit extract, in OF-1 mice of both sexes after intraperitoneal administration was 731 mg kg^{-1}. The acute and subchronic toxicity of punicalagin from pomegranate fruit extract, acute oral LD_{50} in Wistar rats and albino mice was greater than 5000 mg kg^{-1} b.wt. and the subchronic No-Observed-Adverse- Effect Level (NOAEL) was determined as 600 mg kg^{-1} b.wt. day^{-1} (Patel *et al*., 2008). Ghasemian *et al*. (2006) worked on the peel extracts of two Iranian pomegranate cultivars exhibited marked antioxidant capacity but at each concentration, this capacity was higher in Aghamohammadali cultivar than that of Malas-Saveh. Peel extracts of both cultivars decreased sodium azide mutagenicity in *Salmonella* Typhimurium strains (TA100 and TA1535) strongly, except for Malas-Saveh cultivar extract at 625 mg kg^{-1} plate concentration that decreased sodium azide mutagenicity moderately. Therefore Rahimi *et al*. (2011) reported that *P. granatum* may reduce gastric diseases by eradication of *Helicobacter pylori*

and also, it may reduce gastric disease symptoms and inhibit the progression of these diseases by its valuable properties.

CONCLUSION

Pomegranate is found to be associated with various pharmacological activities due to presence of wide range of bioactive compounds as described in this review. Likewise evidence indicated that it consist a lot of bioactive compounds i.e., alkaloids, ellagic acid, punicalagin, ellagitannins, anthocyanins, flavonoids, tannins and other phytochemicals which have a lot of biological activities such as antioxidant, antimicrobial, antiviral, anti-diabetic, anti-atherosclerotic, antihepatoprotective, anticancer, antiepileptic, Alzheimer's disease and other different disease. According to this review we can lead thoroughly understand this plant and provide a foundation for safe and efficient use. The most recent research suggested that the various constituents of the fruit tree may be required to obtain pomegranate's full protective benefit, in particular its flowers, juice, leaves, bark and seeds. An explosion of over the last decade has led to numerous *in vitro*, animal clinical trials. Pomegranate flower extract have been shown to suppress signaling of endothelin-1, a blood vessel-narrowing peptide implicated in cardiac fibrosis (abnormal thickening of the heart valves) and to help arrest the onset of metabolic syndrome as well as its associated pathologies of obesity, type 2 diabetes heart disease.

Pomegranate seed oil offers further promise as a powerful anti-cancer agent, with particular potential in combating breast and prostate cancers. Research has mainly been focused on the role of ellagitannins as responsible of potential applications of pomegranate without almost regarding the prospects of anthocyanins, a kind of phenolics that have displayed a wide array of therapeutic benefits when contained in many other fruits. Many plants have preventive or therapeutic potentials. Therefore, further studies are required to medications with natural remedies.

Secondary metabolites of *P. granatum* may be basis for many drugs or food supplements currently used to treat or prevent pathologic conditions. Since the present study had shown that frequent oral administration of high doses of pomegranate to animal models was not toxic, it is expected that pomegranate peel polyphenolic extracts do not show any severe toxicity in humans. However, further investigations are needed to confirm its safety in humans.

In previous studies, pomegranate juice and its ellagitannins inhibited proliferation and induced apoptosis in HT- 29 colon cancer cells. Adams *et al.* (2006) reported that ellagitannins inhibit the COX-2 (cyclooxygenase; COX-1 and COX-2), AKT (Protein Kinase B) NF-κB (Nuclear Factor Kappa-B) into the anticancer mechanism in the HT- 29 human colon cancer cell line and provide a direction for future studies into its role in the treatment and prevention of colon cancer. The pomegranate juice, seed, peel extract can also be considered as a natural reducing and capping agent to produce various biogenic nanoparticles i.e., silver (Ahmad and Sharma, 2012). It also provides a direction for future studies of this plant derived nanoparticles by drug formulation its role in the treatment of various diseases.

RECOMMENDATION

The use of plant drugs for the prevention and treatment of various health ailments has been in practice from time immemorial. *Punica granatum* has been reported to be effective against a variety of disease including diabetes, skin disease and most concerning with cancer. These results suggest that *Punica granatum* extract is a good natural source of bioactive compounds and they may have beneficial health effects for consumption which may use as preliminary information and could be further studies for uses in food industry or health products, as medicinal food, pharmaceutical exploits and researches in biology, biotechnology general medicine. Further work may be isolation and characterize the bioactive compounds from this plant to evaluate their more biological activities.

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