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Research Journal of Agricultural Sciences
An International Journal

P- ISSN: 0976-1675

E- ISSN: 2249-4538

Volume: 12

Issue: 05

Res Jr of Agril Sci (2021) 12: 1760–1766



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Phytochemistry, Pharmacological and Therapeutic Properties of *Punica granatum*

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Received: 01 Jul 2021 | Revised accepted: 07 Sep 2021 | Published online: 05 Oct 2021
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ABSTRACT

Punica granatum (pomegranate) is a high-polyphenol, high-bioavailability fruit that is often regarded as a superfood. The fruits have long been employed in the prevention and treatment of many malignant illnesses, and their involvement in pathophysiological processes has been documented in both scientific and non-science literature. The medicinal potential of pomegranate fruit is extensively mentioned in the ancient literature and also used in different system of medicines. These fruits are known for major bioactive compounds such as quercetin, ellagic acid, punicalagin, pedunculagin, tannic acid, anthocyanins, rutin, catechin and polyphenols. These compounds are well known for their antioxidant, neuroprotective, anti-inflammatory, anti-angiogenic, anticancerous, anti-mutagenic, cytoprotective, cardiovascular protective, anti-diabetic, anti-ulcerogenic, hepatoprotective, antibacterial and antifungal potentials. The present review highlights the beneficial effects of pomegranate on human health and also represents the mechanisms involved in its action. [Peel extracts (rind), seed extract, juice and whole fruit on the selected bacteria and fungi activity]. The review will be extended to anti-microbial, wound healing activities and anti-cancerous activity. The pomegranate genotypes have an important value in health and nutrition of the human. The pomegranate peels could be utilized by the food industry and pharma/nutraceutical's industry (Pomegranate peel extract-based nanoparticles by chemical complication method). Pomegranate contains secondary metabolites such as alkaloids, flavonoids, steroids, phenolic, terpenes and volatile oils. This review will focus the areas for which pomegranate has shown therapeutic properties in different mechanisms. This review article presents the recently published findings on different aspects of this plant, with a focus on its bioactive compound properties. The pomegranate peel is an inexhaustible resource with many potential functions in numerous industries; added exploration of the fruit peel infected, premature and damaged fruit peel due to natural calamities may lead to new and novel ways of creating wealth from waste.

Key words: *Punica granatum*, Polyphenol, Anticancerous, Anthocyanins

Punica granatum L. (Pomegranate) is a deciduous shrub and a member of family Lythraceae native to Iran, commonly known as Anar. Pomegranate has widely been used as a source of traditional medicine [1]. Pomegranate fruit has medicinal properties such as anti-inflammatory and antibacterial activities. The pomegranate seed oil has phytoestrogenic compounds. The pomegranate seed oil has inhibitory effect on skin and breast cancer. The fruit is rich in phenolic compounds with strong antioxidant activity. The fruit and bark of pomegranate is used against intestinal

parasites, dysentery and diarrhea [2]. The pomegranate peel, considered as an agro-industrial waste, is a chief source of valuable secondary plant metabolites and nutrients. The peel has greater biological activity than the pulp. It is used as animal feed, mostly discarded, creating an environmental problem due to the moisture content [3-4]. The strong biological activity is concurrent to its specific chemical composition, especially the secondary metabolites, such as flavonoids and plant phenolics [5]. Nowadays, Pomegranate as a fruit not only attracts a public interest but research focuses on its medicinal properties and food industry. So, a wide range of research studies has already been launched in this field. However, there are not enough studies performed on the medicinal properties of pomegranate.

Pomegranate peel is proving to be more valuable in the form of food additives or supplements. By optimising food waste recovery strategies that could be used in the food and bioprocess industries, it also has the potential to produce innovative products that can meet the needs of the growing

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health market. In the area of nanotechnology biosynthesis of nanoparticles using biological agents has gained attention in the past decade [6].

Pomegranate peel serves as Bio-based protocols for the synthesis of nanoparticles. This protocol is the economical, environment friendly and suitable for large-scale production under non-aseptic environments are in command. Pomegranate peel extracts are suggested to be good reducing agents that are used in the green synthesis of silver nanoparticles [7-9]. Silver nanoparticles are utilised for a wide range of applications, in electrochemistry, catalysis, bioengineering, cosmetics, food packaging [10].

Due to the multi-functionality and nutritional properties of pomegranate fruit peel, several industries are interested in its special benefits and new ways of using the fruit peel. In the food and beverage industry, pomegranate peel has been used for the fortification and formulation of food products such as cereal bars, beverages, ice cream, and yoghurts to enhance their functional properties [11].

Pomegranate fruit peel have a rich source of vitamins and minerals which are utilized as food, feed, and in many dietary ingredients after proper processing. Numerous studies conducted on fruit peel waste have shown that these waste products possess many biological activities, such as antioxidant, antimicrobial, anticancer activities etc. [12-13].

Nowadays Pomegranate, as a fruit not only attracts a public interest but research focuses on its medicinal properties and food industry [14]. So, a wide range of research studies has already been launched in this field. However, there are not enough studies performed on the medicinal properties of pomegranate. This review article presents the recently published findings on different aspects of this plant, with a focus on its bioactive compound properties. The pomegranate peel is an inexhaustible resource with many potential functions in numerous industries; added exploration of the fruit peel infected, premature and damaged fruit peel due to natural calamities may lead to new and novel ways of creating wealth from waste.

Cultivation

The pomegranate cultivation area is estimated to be around 300,000 hectares with a yield of 3 million metric

tons [15]. At 0.81 metric tonnes, India is the most important producer. The southern hemisphere contributes about 10% of the pomegranate fruit (Pomegranate Industry Overview. availableonlinehttp://www.hortgro.co.za/portfolio/pomegranates)

Geographical origin and distribution of pomegranate

Pomegranate is one of the first domesticated fruits that has been cultivated. It is native to Iran and adjacent nations, and it spread from central Asia to the Himalaya, Anatolia's Eyalet, the Middle East, and the Mediterranean. It also thrives in Arizona and California, and has been cultivated in the Mediterranean region, South Asia, and the Middle East countries; Kandahar in Afghanistan is famous for its high-quality pomegranate. Today, pomegranate is cultivated in most regions of the world, including Iran, Spain, Italy, Afghanistan, America, India, China, Russia, Uzbekistan, Morocco, and Greece [16] Iran is one of the world's leading pomegranate growers. The provinces of Markazi, Yazd, Fars, Khorasan, and Kerman have the greatest production rates in Iran [17].

Morphology

The pomegranate is a fruit bearing deciduous shrub belongs to the family Punicaceae [18]. The pomegranate which has abundant foliage, a height around 5 m, the leaves are green, elongated. The flower is red and consists of 5 to 8 bright orange petals [19-20].

Chemical constituents

Pomegranate peel contains minerals like calcium, phosphorus, magnesium, potassium, and sodium as well as sugars (glucose, fructose, sucrose and maltose), protein, crude fibers, fatty acids, organic acids, and alkaloids [21-23]. Pomegranate fruits have various types of constituents in different parts such as seeds, peels and arils. Such ingredients show curative role in the health management through the modulation of various biological activities. Peels of the pomegranate covers around 60% of the fruit and they hold various types of ingredients including flavonoids, ellagitannins and proanthocyanidin compounds and minerals such as calcium, magnesium, phosphorus, potassium and sodium [24].

Pomegranate chemical composition

Proximate compounds	Concentrations	Minerals and vitamins	Concentration in mg
Moisture (%)	78.0	Calcium	10 mg
Protein (g/100g)	1.6	Phosphors	70mg
Fat (g/100g)	0.1	Iron	0.3 mg
Minerals (g/100g)	0.7	Vitamin C	16.0 mg
Fibre (g/100g)	5.1	Vitamin B complex	Trace amounts
Carbohydrates (g/100g)	14.5	-	-

Adopted and modified from (Bakhrū [25])

Secondary metabolites

The secondary metabolites in various parts of the pomegranate fruit and tree include various kinds of sugars, organic acids, polyphenols, flavonoids, anthocyanins, fatty acids, alkaloids and vitamins. Alkaloids found in pomegranate peel include ellagic acid, gallic acid, chlorogenic acid, cinnamic acid, hydroxy protocatechuic acid, hydroxy benzoic acid, caffeic acid, ferulic acid, coumaric acid, p-coumaric acid, o-coumaric acid,

pelletierine, isopelletierine, methylpelletierine, pseudopelletierine, punicalagin, punicalin, phloridzin, quercetin, and catchin [26-28]. According to Ozkan [29], pomegranate's colour is caused by its components, particularly anthocyanin. As the pomegranate ripens, the colour of the fruit changes gradually; however, this shift is modest and intensifies after the middle stage of development. The amount of diglucoside anthocyanins appears to be higher in the early stages of growth than the

monoglucoside forms; however, the pattern reverses at the end of development and ripening [30].

Bioactive compounds

Many studies have shown that different portions of pomegranate plants are high in bioactive microconstituents and can be used to make a variety of goods. Pomegranate peel is frequently discarded by the food sector without being valorized. Pomegranate peel itself represents approximately 50% of fruit weight and is reported to contain stronger antioxidant activity compared to the juice [31-32]. The ellagic acid, punicalagin, and urolithin found in pomegranate have powerful antioxidant activities, which reduce oxidative or inflammatory stress, enhance the protective signaling phenomena, and inhibit lipase, α -glucosidase, and dipeptidyl peptidase-4 in a dose-dependent manner [33].

Ellagitannins

Contents of these compounds in pomegranate fruits include ellagitannins are found 2020–2660 mg/L in wonderful variety [34].

Ellagic acid

Ellagic acids are found 5700 mg/L in Mollar variety [35]. Ellagic acid may be found in pomegranate fruits in a complexed form as ellagitannins. It is mainly found in sarcotestas of pomegranate seeds [36-42].

Punicalagin

Punicalagin in pomegranate fruits is 1500–1900 mg/L in wonderful variety [43].

Antibacterial activity

The antibacterial activity of dried pomegranate peel extracts revealed that, regardless of the drying processes used, the peel extracts were more efficient against the microorganisms tested. It's possible that this is due to a higher retention of antioxidant activity after drying. Similarly, the action against all of the test bacteria (both Gram-positive and Gram-negative) indicates that the extracts include a wide range of metabolic toxins [44].

Anticancer activity

Pomegranate peel has been shown to have anticancer properties in the cases of breast cancer, lung cancer, and prostate cancer. Pomegranate peel extracts have been shown to be beneficial against breast cancer through a variety of mechanisms, including cell migration inhibition, up-regulation of expressions, and down-regulation of levels and fibronectin [45]. Pomegranate extract has been exposed to alleviate the reproduction of prostate cancer cells, which has been attributed to the ant inflammation effects of this plant [46]. Pomegranate fruit extract prohibited from lung and prostate cancer in rat by inhibiting growth or metastasis. It also showed a positive impact on inflamed cells in colon cancer [47-49]. Pomegranate fruit peel and seed oil also shows anticancer activity and act against cancer cells invasion [50].

Antifungal activity

The antifungal activity of Pomegranate peel extracts on *Fusarium oxysporum* mycelia growth was assessed, and the primary antifungal components (punicalagins and ellagic acid) were identified using a simple HPLC-MS-MS analytical approach [51].

Other phenolic compounds (Tannin type) in pomegranate peel

Tannin type	Amount (g/100g)	Variety	References
α -punicalagin	1480	Borde de Albaterra	Rosas-Burgos <i>et al.</i> [52]
β -punicalagin	1070	Borde de Albaterra	Rosas-Burgos <i>et al.</i> [52]
Ellagic Acid Glycosides	7.68	-	Moreira <i>et al.</i> [53]
Granatin B	0.59	-	Fischer, Carle, and Kammerer [51]
Lagerstannin C	0.39	-	Fischer, Carle, and Kammerer [51]
Punicalagin	839	-	Li <i>et al.</i> [54] 2016
Punigluconin	0.38	-	Fischer, Carle, and Kammerer [51]
Pedunculagin I	0.35	-	Fischer, Carle, and Kammerer [51]
Total Athocyanin content	82 mg/L	Izmir 8	Cam, Hisil, and Durmaz [55]
Total phenolic content	244000 mg/L	Gaeta 1	Russo <i>et al.</i> [56] 2018

Table 1 Medicinal uses of *Punica granatum* L.

Plant part	Medicinal uses	References
Peel	Diarrhoea	Lev and Amar [57] 2002
Peel	Treat vaginal white discharges	Ong <i>et al.</i> [58] 1999
Peel	Stomach disorders	Ganguly [59] 2017
Peel	Against diarrhoea, dysentery, and intestinal parasites	Lasure <i>et al.</i> [60] 2012
Root and bark	Vermifuge and anthelmintic	Naqvi <i>et al.</i> [61] 1991
juice	Blood tonic	Lad and Frawley [62] 1986
Leaves and bark	Wound healing, Antiparasitic	Egharevba <i>et al.</i> [63] 2010
Flower	Antidiabetic properties	Jafri <i>et al.</i> [64] 2000

Table 2 Pharmacological studies on *Punica granatum* L.

Plant part	Test method	Pharmacological role	References
Peel extracts	Spectrophotometric method	Antityrosinase properties	Fawole <i>et al.</i> [3]
Peel extracts	Column chromatography combined with in vitro bioassay-guided fractionation	Anti-inflammatory	Lee <i>et al.</i> [34]
Aril and peel extracts	Agar diffusion	Antimicrobial (<i>S. aureus</i> , <i>P. aeruginosa</i> and <i>E. coli</i>)	Opara <i>et al.</i> [4]
Leaf, peel, and seed extracts	Agar diffusion	Antifungal (<i>Penicillium italicum</i> , <i>Rhizopus stolonifera</i> and <i>Botrytis cinerea</i>)	Tehranifar <i>et al.</i> [65]
Peel powder	2,20-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS)	Antioxidant properties	Altunkaya <i>et al.</i> [66]
Peel extracts	In vivo experiment, 56 Wister albino rats were distributed into 8 groups and compared with standard drugs (glibenclamide and atorvastatin). For antioxidant activity: DPPH (2,2-diphenylpicrylhydrazyl) and ABTS (2,20-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid))	Antihyperglycaemic, antihyperlipidaemic, and antioxidant properties	El-Hadary and Ramadan [67]

Table 3 Phytochemical constituents in different parts of the pomegranate plant (Lansky [46], Newman [49], Arun [68])

Plant parts	Constituents
Roots and bark	Ellagitannins, including punicalagin and punicalin, and several piperidine alkaloids
Leaf	Tannins (which include punicalofolin and punicalin), flavone glycosides, luteolin and apigenin, and brevifolin carboxylic acid.
Pericarp (Peel)	Ellagitannins (punicalin and punicalagin), gallic acid and other fatty acids, catechin and epicatechin, quercetin, rutin and other flavonols, flavones, flavonones, procyanthocyanidins, and anthocyanidins
Flower	Gallic acid, triterpenoids, and ursolic acids, including maslinic and asiatic acids.
Seed oil	Punicic acid, hydroxybenzoic acids (gallic and ellagic), other fatty acids, sterols (daucosterol, campesterol, stigmasterol, beta-sitosterol), and -tocopherol.
Juice	Procyanthocyanidins and anthocyanins, ellagitannins (punicalin and punicalagin), glucose, ascorbic acid, Ellagic acid, gallic acid, catechin and epicatechin, quercetin, rutin, amino acids (methionine, proline, and valine), and many minerals especially irons.

Vitamin and mineral contents

Pomegranate fruit peels are high in vitamins and minerals, and after processing, they can be used as food, feed, and a variety of dietary supplements. Numerous research on fruit peel waste have revealed that these waste products have a wide range of biological activity, including antioxidant, antibacterial, and anticancer properties [2-3]. Study of Fawole and Opara [4], showed composition of major and minor minerals in the peels of seven pomegranate cultivars (Namely Arakta, Bhagwa, Ganesh, Herskawitz, Ruby, Molla de Elche, and Wonderful) and highlighted significant differences among these seven varieties the Bhagwa cultivar has the greatest nitrogen, phosphorus, potassium, sulphur, and chlorine contents at 351.50, 33.03, 554, 19.43, and 122.96 mg/kg, respectively. Ruby, Arakta, and Wonderful, on the other hand, had the greatest calcium (60.65 mg/kg), magnesium (26.4 mg/kg), and sodium (117.40 mg/kg) values, respectively. The nutritional content of fresh pomegranate (cv. Bhagwa) peel powders exhibited increased vitamin A at 14.06 g/gm [69]. Copper, iron, magnesium, potassium, and sodium are also present in this powder, with concentrations of 6.2 g/gm, 22.6 g/gm,

1644.47 mg/kg, 16,237.4 mg/kg, and 763.66 mg/kg, respectively.

Application of pomegranate in traditional medicine

Pomegranate root, stem, leaves, fruit peel and flower, have all been utilized in traditional medicine [70]. All of the tannins in the Pomegranate fruit have a comparably significant caustic action. Traditional medicine has employed decoctions of plant flowers to treat uncomplicated diarrhea and vaginal discharge. The extract of pomegranate peel has been used to treat pancreas inflammation [71]. Gallbladder problems can be treated using the juice of pomegranate fruit. Pomegranate fruit decoction is used to cure a variety of ailments, including common diarrhoea, dysentery, and stomach problems [71]. Pomegranate aril's tannin content is commonly used to treat women's vaginal discharge and wound healing [72]. Intestinal parasites are removed using ethanolic preparations of pomegranate root barks (fresh or dried). Because of its antibacterial and anti-inflammatory qualities, it is widely employed in traditional medicine [71-72].

CONCLUSION

Pomegranate fruits have a lot of bioactive compounds in them. Pomegranates have antibacterial, antioxidant, antifungal, and anticarcinogenic properties. The role of the pomegranate peel was the subject of this study. Also, pomegranate peels contain both traditional and modern

medicinal qualities. Pomegranate peels have been dubbed a famous treatment in countries that employ them in traditional medicine. Pomegranate phytochemistry revealed a high variety of polyphenolic chemicals in large quantities. The peel, juice, seed, leaf, bark, flower and root of the pomegranate all have pharmacological properties.

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