Pomegranate, fruit of the desert, a functional food, and a healthy diet

Mohamad H. SHAHRAJABIAN\textsuperscript{1a*}, Wenli SUN\textsuperscript{1b}, Qi CHENG\textsuperscript{1,2}

\textsuperscript{1}Chinese Academy of Agricultural Sciences, Biotechnology Research Institute, Beijing 100081, China; hesamshahrajabian@gmail.com (*corresponding author); sunwenli@caas.cn
\textsuperscript{2}Hebei Agricultural University, College of Life Sciences, Baoding, Hebei, 071000, China; Global Alliance of HeBAU-CLS&HeQiS for BioAl-Manufacturing, Baoding, Hebei 071000, China; chengqi@caas.cn
\textsuperscript{*a,b} These authors equally contributed to this paper

Abstract

Traditional medicinal plants contain various ranges of chemical contents and they have become popular because of effectiveness, frequently inadequate provision of modern medicine, preferences and cultural beliefs. Pomegranate belongs to the family of Punicaceae, and its various pharmacological activities are due to presence of wide range of bioactive compounds. The current searching was done by the keywords in main indexing systems including PubMed/MEDLINE, Scopus, and Institute for Scientific Web of Science as well as the search engine of Google Scholar. The keywords were traditional medicine, health benefits, pharmaceutical science, pomegranate, punicalagin, punicalin, and ellagitannins. Major polyphenols in peel and juice of pomegranate are flavonoids such as flavonols (catechin, epicatechin, galloycatechin), condensed tannins, phenolic acids such as gallic, ellagic and caffeic, hyrolysable tannins such as ellagitannins and gallotannins. The main organic acids in pomegranate juice are malic and citric, and in seed is fatty acids (punicic). The major alkaloids and lignans in peel are punigratane and isolariciresinol, respectively. Pomegranate fruit has been proven to act against various diseases like cancer, cardiovascular disorders, diabetes, AIDS, Alzheimer's disease, male infertility, inflammation, coronary heart disease, and aging. The review summarizes the beneficial impacts of pomegranate which is recommended for consumption. Pomegranate is a high potential natural functional food due to its high pharmacological activities as an ancient efficacious natural drug.

Keywords: ellagitannins; health benefits; pomegranate; punicalagin; traditional medicine

Introduction

Pomegranate occurrence and classification

Population rise, inadequate supply of drugs, prohibitive cost of treatments, side effects of several synthetic drugs and development of resistance to currently used drugs for infectious diseases have led to increased emphasis on the use of plant materials as a source of medicines (Shahrajabian \textit{et al}. 2021; Sun \textit{et al}. 2021a,b,c). Herbal medicines proved to be the major remedy in traditional system of medicine (Shahrajabian \textit{et al}. 2020a,b,c,d,e). Pomegranate (\textit{Punica granatum} L.) which is a perennial fruit tree from the Punicaceae native in Iran, has been considered a functional fruit in many countries especially Iran, India, Turkey and China (Sharma \textit{et al}. 2011; Soloklui \textit{et al}. 2012). Its name come from the Latin name of the fruit \textit{Malum granatum}, which means granular apple; and the most important producers are Iran, India, Turkey, China, the USA and
etc (El Barnossi et al., 2021). Pomegranate has been known for hundreds of years as a healing food (Mohapatra, 2014; Tanveer et al., 2015). It has shown positive health properties due to the presence of bioactive constituents such as polyphenols, tannins and anthocyanins (Pirzadeh et al., 2020). As a functional food and nutraceutical source, pomegranate fruit quality depends on climate and growing conditions (Mirzapour and Khoshgoftarmanesh, 2013; Rahimi et al., 2017); moreover, it is also considered as an ancient medicine (Yisimayili et al., 2019). On the basis of the Bible and the Koran, pomegranate has been a symbol of fertility (Mars, 2000; Ismail et al., 2014). In Iran, it is one of the most important Iranian horticultural products, which is usually cultivated in arid and semi-arid regions (Tatari et al., 2020). The pomegranate seeds are rich in crude protein, crude lipids, dietary fiber and minerals such as K, P, Mg and Ca (Dadashi et al., 2013). In Iran, Alak was the most promising cultivar due to highest fruit size, fruit weight, and juice and least skin percentage, Sour-Sweet, Rabab, and Black Skin cultivars showed the highest content of total anthocyanins, total phenolics, and ascorbic acid, and total soluble solid, which are suitable for fresh consumption and human health benefits (Asadi-Gharneh et al., 2017). The peal and arils of the fruits of Black Skin are being used in Persian traditional medicine (Asadi-Gharneh et al., 2017). The pomegranate has narrow and lance-shaped leaves which are glossy and leathery. The attractive scarlet, white or variegated flowers are over an inch across and have 5 to 8 crumpled petals and a red, fleshy, tubular calyx which persists on the fruit. The flowers may be solitary or grouped in twos and threes at the ends of the branches. The pomegranate is self-pollinated as well as cross-pollinated by insects. Cross-pollination increases the fruit set and wind pollination is insignificant. The wide fruit is crowned at the base by the prominent calyx, the tough, leathery skin or rind is typically yellow overlaid with light or deep pink or rich red. Its classifications are on the basis of agronomical characteristics, especially color and shape (Ozkan, 2005; Orhan et al., 2014). The cracking of mature fruit is an important physiological disorder which causes great economic loss to pomegranate. The pomegranate seed is the whole grain and constitutes the edible part of the fruit (Melgarejo et al., 2020). The peel is the main by-product after juice processing (Mphahlele et al., 2019). It has been reported that higher fruit temperature, firmness, and peel thickness decreased bruise damage to the pomegranate fruit, and both storage time and increased radius of curvature increased the bruise volume and bruise area, respectively (Shafie et al., 2015). Chinese cultivars have some unusual features such as spur-type growth habit, double flowers and white flowers (Verma et al., 2010). Seedless fruits contain soft-seeded compared to old varieties (Stover and Mercure, 2007). The aim of this article is survey and introduce the most important health benefits of pomegranate with considering its chemical constituents.

**Pomegranate nutritional composition and chemical constituents**

The most important known compounds of pomegranate are amino acids such as lysine, methionine, cysteine, isoleucine, leucine, phenylalanine, tyrosine, histidine, aspartic, glutamic, serine, glycine, arginine, alanine, and proline; minerals such as calcium (Ca), magnesium (Mg), potassium (K), sodium (Na), phosphorus (P), iron (Fe), zinc (Zn), manganese (Mn), copper (Cu), and selenium (Se); Vitamins such as thiamine (B1), riboflavin (B2), L-Ascorbic acid (C), α-Tochoferol (E), and retinol (A); Fats such as myristic, palmitic, stearic, arachidic, behenic, stearoleic, gadoleic, erucic, ecosapentaenoic, docosatetraenoic and etc (Hasnaoui et al., 2011; Ahmad et al., 2018; Ma et al., 2019). Pomegranate’s nutrient values for 100 g have been shown in Table 1. Nutrient content of pomegranate peel (per 100 g) is presented in Table 2.
Table 1. Pomegranate’s nutrient values for 100 g (Ahmad et al., 2018)

| Composition          | Content  |
|----------------------|----------|
| Water                | 77.93g   |
| Energy               | 83 kcal  |
| Protein              | 1.67g    |
| Total lipid (Fat)    | 1.17g    |
| Ash                  | 0.53g    |
| Carbohydrates        | 18.70g   |
| Fiber                | 4.0g     |
| Sugars               | 13.67g   |
| Calcium              | 10mg     |
| Iron                 | 0.3mg    |
| Magnesium            | 12mg     |
| Phosphorus           | 36mg     |
| Potassium            | 236mg    |
| Sodium               | 3mg      |
| Ascorbic acid        | 10.2mg   |
| Choline              | 7.6mg    |

Table 2. Nutrient content of pomegranate peel (per 100 g) (Ahmad et al., 2018)

| Composition         | Content  |
|---------------------|----------|
| Total solid         | 94.50    |
| Moisture            | 5.40     |
| Total sugars        | 17.70    |
| Reducing sugars     | 4.34     |
| Protein             | 4.90     |
| Crude fiber         | 16.30    |
| Fat content         | 1.26     |
| Ash                 | 3.40     |

Proximate composition of pomegranate seeds is percentage moisture (8.6%), total lipids (27.2%), crude protein (13.2%), crude fiber (35.3%), pectin (6%), total sugars (4.2%), and ash (2%); trace minerals present in pomegranate seeds are iron (1.3 ppm), sodium (6 ppm), magnesium (12.4 ppm), potassium (45.2 ppm), zinc (1 ppm), and copper (1.2 ppm) (Khan et al., 2017). Nutritional values of pomegranate seeds are shown in Table 3. Fatty acids found in pomegranate seeds are presented in Table 4. The name, peel color, aril color, taste and origin of 31 pomegranate cultivars in Iran are mentioned in Table 5.

Table 3. Nutritional values of pomegranate seeds (Khan et al., 2017)

| Compounds          | Nutritional value          |
|--------------------|----------------------------|
| Energy             | 72 calories                |
| Carbohydrates      | 16.3 grams                |
| Protein            | 1.5 grams                 |
| Fat                | 1 gram                    |
| Fiber              | 3.5 grams                 |
| Sugar              | 11.9 grams                |
| Vitamin K          | 14.3 micrograms (17.9% DV) |
| Vitamin C          | 8.9 milligrams (14.8% DV)  |
| Folate             | 33 micrograms (8.3% DV)    |
| Potassium          | 205 milligrams (5.9% DV)   |
| Vitamin B6         | 0.07 milligrams (3.5% DV)  |
| Phosphorus         | 31 milligrams (3.1% DV)    |

Percent DV indicates daily values.
Table 4. Fatty acids found in pomegranate seeds (Khan et al., 2017)

| Fatty acids    | Values (%) |
|----------------|------------|
| Caproic acid   | 2.16       |
| Punicic acid   | 65.3       |
| Capric acid    | 0.95       |
| Lauric acid    | 6.62       |
| Myristic acid  | 7.56       |
| Myristoleic acid| 0.41     |
| Palmitic acid  | 4.8        |
| Palmitoleic acid| 0.47     |
| Stearic acid   | 2.3        |
| Linoleic acid  | 6.6        |
| Oleic acid     | 5.13       |

Table 5. The name, peel color, aril color, taste and origin of 31 pomegranate cultivars in Iran (Nemati et al., 2012)

| Cultivars                     | Peel color | Aril color | Taste       | Origin           |
|-------------------------------|------------|------------|-------------|------------------|
| 'Shirine Dane Sefide Ferdos'  | Red        | Red        | Sweet       | Khorasgan        |
| 'Torsheshahvare Kashmar'      | Red        | Red        | Sour        | Khorasgan        |
| 'Shishe Kab'                  | Red        | Red        | Sweet-sour  | Khorasgan        |
| 'Mazarie Bajestan'            | Pink       | Yellow     | Sweet-sour  | Khorasgan        |
| 'Dom Anbaroti'                | White      | Yellow     | Sour        | Khorasgan        |
| 'Shirin Dane Ghermez Ferdos'  | Pink       | Red        | Sweet       | Khorasgan        |
| 'Khazar Bajestani'            | Red        | Red        | Sweet-sour  | Khorasgan        |
| 'Leili Post Nazok'            | Red        | Red        | Sweet-sour  | Khorasgan        |
| 'Leili Post Kolofit'          | Pink       | Yellow     | Sweet-sour  | Khorasgan        |
| 'Torshe Shalhware Ferdos'      | Red        | Red        | Sour        | Khorasgan        |
| 'Bazmanic Post Nazok'          | Pink       | Pink       | Sweet-sour  | Sistan o Balochestan |
| 'Savehei Post Sefid'           | White      | Pink       | Sweet-sour  | Sistan o Balochestan |
| 'Savehei Post Ghermez'         | Pink       | Yellow     | Sweet-sour  | Sistan o Balochestan |
| 'Malase Porbare Saravan'       | Pink       | Pink       | Sweet-sour  | Sistan o Balochestan |
| 'Malase Mamolie Sarjo'         | Red        | Red        | Sweet-sour  | Sistan o Balochestan |
| 'Shekanare Post Kolofit'       | White      | Pink       | Sweet       | Mazandaran       |
| 'Vahshie Janghalie Ghaemshah'  | Red        | Yellow     | Sweet-sour  | Mazandaran       |
| 'Mahalie Parande Gorgan'       | White      | Red        | Sour        | Mazandaran       |
| 'Post Sefide Dezfol'           | Red        | Red        | Sour        | Khozestan        |
| 'Malase Dane Siahe Ramhormoz'  | White      | Red        | Sweet-sour  | Khozestan        |
| 'Malase Post Sorkh'            | Red        | Red        | Sweet-sour  | Khozestan        |
Several bioactive compounds were extracted by the pomegranate peels which can be employed for the preparation of nutraceuticals (Turrini et al., 2019). Around 153 different phytochemicals have been found in pomegranate which have ability to fight against various diseases (Karimi et al., 2017). Its fruit peel contains phenolic compounds including ellagic acid, ellagitannins, lignins, catechin, rutin, punicalagin and epicatechin (Fischer et al., 2011; Glazer et al., 2012; Rosas-Burgos et al., 2017), and the peel consists of cellulose, ligning, pectin and proteins (Hasnaoui et al., 2014; Abid et al., 2017). Rowayshed et al. (2013) also reported catechins, phenol gallic acid, caffeic acid, ellagic acid, p-coumaric acid and resocenol compounds in pomegranate peel powder. Peels and membranes of pomegranate fruits can be recommended as a source of highly and lowly methyl-esterified pectic polysaccharides (Shakhmatov et al., 2019). The most abundant compounds in pomegranate in Mexico were hexanol, (Z)-3-hexen-1-ol, hexanal, 4-terpineol, α-terpineol, and 2-ethyl-1-hexanol, and in the peel, high concentration of color, phenols, flavonoids, and antioxidants were observed (Escarcega et al., 2020). Pomegranate exerts antiproliferative, anti-invasive and antimetastatic effects, induces apoptosis through modulation of Bcl-2 proteins, increases p21 and p27, and downregulates cyclin-ckd network (Faria and Calhau, 2011). Pomegranate seed oil is a rich source of rare conjugated fatty acids (puniceic acid) (Paul et al., 2020). Ellagic acid (EA) is one of the most important biological molecules found in pomegranate which may induce vasorelaxation, oxygen free radical scavenging, hypolipidemic, anti-inflammatory and anti-carcinogenic activities (Usta et al., 2013). Pomegranates have the potential to cause toxicity to ruminants, because large amounts of toxic gallic acid can potentially be produced through rumen fermentation of punicalagin (Read et al., 2019). Concentrated pomegranate peel extract supplementation increases milk antioxidant capacity which have higher benefits in individuals with lower natural productivity capacity (Argov-Argaman et al., 2020). Pomegranate juice powder can replace some or all sucrose in fermentation matrix for the production of functional yogurt (Pan et al., 2019). There are 11 volatile organic compounds namely 1-hexanol, (Z)-3-hexen-1-ol, 1-octanol, α-terpineol, β-myrcene, limonene, [E]-α-bergamotene, β-caryophyllene, hexanal, [E]-2-hexenel, and guaiacol are common to pomegranate juices and seeds; hexalin, phenylacetaldehyde, 3-methyl butanal, and methyl-(1-methylethenyl) benzene are found just in seeds (Guler and Gul, 2017). Pomegranate juices has similar or higher sweetness than apple, orange and sour cherry juice (Topalovic et al., 2020). The fruit quality of pomegranate is a balance between taste attributes and nutraceutical compounds (Tozzi et al., 2020). It contains significant amounts of phenolic ingredients, and the antioxidant and anti-inflammatory impacts of pomegranate poly phenols have been confirmed previously (Yan et al., 2017; Pontonio et al., 2019; Morvaridzadeh et al., 2020). Pomegranate peel polysaccharides (PPP) is a good source for dietary supplement application, which has good antioxidant activity in vivo (Wu et al., 2019). A positive correlation between antioxidant activity and total phenolic content was reported (Derakhshan et al., 2018). The reason of the bright color of pomegranate flowers is a type of the flavonoids, which is anthocyanins (Zhang et al., 2011; Ben-Simhoun et al., 2015). The pomegranate peel polysaccharides are composed of rhamnose, glucuronic acid, galacturonic acid, glucose and xylose in the molar percentage of 0.71%, 27.07%, 22.05%, 22.12%, and 28.05%, respectively (Wu et al., 2019). Habibnia et al. (2012) found that the predominant fatty acids in Iranian pomegranate was punicic acid, and beta-sitosterol and γ-tocopherol were the main sterol and

| Pomegranate Name | Color  | Color  | Sweetness  | Origin  |
|------------------|--------|--------|------------|--------|
| 'Shirine Post Ghermez' | Red    | Red    | Sweet      | Azarbaejan |
| 'Shirine Post Sefid' | Pink   | Pink   | Sweet      | Azarbaejan |
| 'Malase Post Nazok' | White  | Yellow | Sweet-sour | Azarbaejan |
| 'Zagh Yazdi' | Red    | Red    | Sour       | Yazd   |
| 'Malase Yazdi' | Red    | Red    | Sweet-sour | Yazd   |
| 'Gorje Shahvar' | Pink   | Pink   | Sweet      | Yazd   |
| 'Agha Mohammadali' | Red    | Red    | Sweet      | Markazi |
| 'Alake Shirine Saveh' | Red    | Red    | Sweet      | Markazi |
| 'Malase Saveh' | Red    | Red    | Sweet-sour | Markazi |
tochopherol present in the extracted oil, respectively. The pomegranate peel, seed and whole fruit powder consists of moisture content, ash, protein, crude fiber, fat and minerals such as sodium, calcium, magnesium, potassium, phosphorus and iron (Sharma et al., 2018). Pomegranate seed oil (PSO) nanoemulsion is widely used as a promising delivery system for α-tocopherol (Sahafi et al., 2021). Pomegranate ellagitannins may inhibit α-flucosidase activity in vitro possibly affecting in vivo starch digestion (Bellesia et al., 2015). Its juice could be beneficial as a dietary supplement in patients receiving chemotherapy medications (Bakir et al., 2015). The polyphenols are useful indicators to differentiate the geographical localities of pomegranate peel which can be used to predict their antioxidant activities (Kam et al., 2013). Pomegranate flower consist of triterpenoids, asiatic acid and ursolic acid; pomegranate juice consists of catechin, ascorbic acid, iron, glucose and amino acids; pomegranate leaves consist of flavones, tannins, luteolin and glycosides; pomegranate seed oil consists of sterols, ellagic acid, 95% punicic acid and fatty acids; pomegranate root and bark consist of piperidine alkaloids, ellagitannins and punicin; and pomegranate rind consists of flavonoids, quercetin rutin and fatty acids (Huang et al., 2005; Lan et al., 2009). Principle constituents of pomegranate root and bark are ellagitannins, piperidine alkaloids, pyrrolidine alkaloid and pelletierine alkaloids (Neuhofer et al., 1993; Gil et al., 2000). The most important constituents of pomegranate leaves are carbohydrates, reducing sugars, sterols, saponins, flavanoids, tannins, piperidine alkaloids, flavones, glycoside and ellagitannins (Nawwar et al., 1994; Chaitra et al., 2012). Lignins, sterols and terpenoids are the most important active phytochemicals in seed, bark and leaves (Lansky and Newman, 2007), alkaloids in bark and leaves, and fatty acids and triglycerides in seed oil (Lansky and Newman, 2007). Simple gallyol derivatives and organic acids have been reported in leaves and juice, respectively (Ender et al., 2002). Flavonols is one of the main phytochemicals in rind, fruit (Mirdehghan and Rahemi, 2007), and bark and leaves (Lansky and Newman, 2007; Jaiswal et al., 2010). Anthocyanins and anthocyanidins, catechin and procyanidins have been found in juice and rind (Jasiwal et al., 2010), estrogens in seeds and peel extracts (Kho et al., 2010), and essential oils in seeds (Abbasi et al., 2008). Name of different compounds along with their parts are shown in Table 6. Nozohour et al. (2018) reported that the main phytochemicals identified in the ethanolic extracts of the pomegranate peel and seed are furfural, heptacosane, 5-hydroxymethylfurfural, ellagic acid, ellagic acid, 3,3′-di-O-methyl, ellagic acid, 3,3′,4′-tri-O-methyl, punicin, pyrogallol, gallic acid, catechin, epicatechin, gallocatechin, gallocatechin-(4,8)-catechin, ascorbic acid, linoleic acid, stigmasterol, and gamma-sitosterol (Tanaka et al., 1986; Schubert et al., 1999; Amakura et al., 2000; Hornung et al., 2002; Wang et al., 2004; Nozohour et al., 2018).

Table 6. Name of different compounds along with their parts (Ahmad et al., 2018)

| Pomegranate part | Chemical compounds |
|------------------|--------------------|
| Peels            | Gallic acid, Ellagic acid, Punicalin, Punicalagin, Caffeic acid, Ellagitannins, Pelletierine alkaloids, Luteolin, Kaempferol, Quercetin |
| Seeds            | 3,3′-Di-O-methyllic acid, 3,3′,4′-Tri-O-methyllic acid, Punicic acid, Pleic acid, Palmitic acid, Stearic acid, Linoleic acid, Sterols, Tocopherols, Sex steroids |
| Juice            | Simple sugars, Aliphatic organic acids, Gallic acid, Ellagic acid, Quinic acid, Flavonols, Amino acids, Minerals, EGCG, Ascorbic acid |
| Leaves           | Carbohydrates, Reducing sugars, Sterols, Saponins, Flavanoids, Tannins, Piperidine alkaloids, Flavone, Glycoside, Ellagitannins |
| Root and Bark    | Ellagitannins, Piperidine alkaloids, Pyrrolidine acid, Pelletierine alkaloids |
| Flower           | Gallic acids, Ursolic acid, Triterpenoids, Fatty acids |
Potential Pharmaceutical and Health Benefits of Pomegranate in Traditional Medicine and Modern Medicine Industry

In traditional medicine, it may helpful for treating diseases such as ordinary diarrhea, dysentery, and stomach disorders (Lansky et al., 2000), and tannin content of pomegranate seed is usually used to treat women vaginal discharge and wound healing (Amin, 1991). The effect of pomegranate on different types of cancer such as bladder cancer (Lee et al., 2013), breast cancer (Adams et al., 2010; Sturgeon and Ronnenberg, 2010), colon cancer (Kohno et al., 2004; Waly et al., 2014), leukemia (Joseph et al., 2012), liver cancer (El-Ashmawy et al., 2016; Song et al., 2016), lung cancer (Khan et al., 2007), prostate cancer (Lucci et al., 2015; Deng et al., 2017), skin cancer (Afaq et al., 2010; George et al., 2011) have been reported. It has reported that pomegranate juice has the highest antioxidant activity among all various food types (Guo et al., 2003). Pomegranate juice powder (PJP) rich in phenolic compounds was used as some or all sucrose in the fermentation matrix for the preparation of set yogurts (Pan et al., 2019). It has been reported in many researches that polyphenols present in pomegranate imparts significant anti-inflammatory and anti-oxidant properties for prevention of various diseases (Guo et al., 2003; Lee et al., 2010). Sharma et al. (2017) reported that pomegranate has stronger anti-oxidant activity compared to β-carotene, ascorbic acid and vitamin E than green tea, and also can affect pathways involved in cancer development like cellular transformation and angiogenesis (Khan et al., 2008). The dietary supplementation with 200 and 300 mg/kg pomegranate peel extract (PPE) may increase the antioxidant potential and quality indices of broilers breast meat, and the antioxidant potential of PPE was equal to that of α-Toc in refrigerated meat (Saleh et al., 2017). The potentiated virucidal activity of pomegranate rind extract (PRE) by co-administered zinc (II) has potential as a multi-action novel topical therapeutics against Herpes simplex virus (HSV) infections, like as cold sores (Houston et al., 2017). The usage of pomegranate extracts orally at the dose of 1500 mg/kg showed the potential of increasing sexual behavior in rats (Katana et al., 2019). The pomegranate peel is a promising feedstock for second generation ethanol production (Demiray et al., 2018). On the basis of one study, 2 g/kg supplementation of pomegranate peel powder meal may improve the water binding capacity of broiler breast meat because of reduced cooking loss of the meat (Akuru et al., 2020). Pomegranate peel and seed methanolic extracts have notable total flavonoid and phenolic contents and also antioxidant activity, which can protect the liver against histo-pathological and some enzymatic changes induced by the Methotrexate (MTX) in rats (Doostan et al., 2019). Pomegranate peel extract was capable to boost the functional characteristics of chitosan/gelatin-based materials enhancing the desired properties for their potential application as food coatings (Bertolo et al., 2020). Pomegranate molasses has anti-inflammatory (Lee et al., 2010), antidiabetic properties (Xu et al., 2009), and important role to reduce the risk of cardiovascular diseases (El Darra et al., 2017). Ridzwan et al. (2020) reported the potency of pomegranate extract as a non-opioid substitution therapy for both in-vitro and in-vivo studies; in-vitro studies showed using of pomegranate extract treatment may be effective in decreasing the α-opioid receptor (MORs) and cyclic adenosine monophosphate (cAMP) protein levels in U-87 cells at a concentration of 0.125 mg/mL. Pomegranate peel extract consumption in diabetes mellitus type 2 subject may have favourable impacts on some metabolic parameters, blood pressure, lipid profile and plasma lipid fatty acids composition (Grabex et al., 2020). Pomegranate peel extract can be used as alternative therapy for blastocystosis and for improving novel anti-Blastocystis drugs (Abdel-Hafeez et al., 2016). Pomegranate juice shows microbicidal properties for both oral hygiene and chemo-preventive in immune deficiency and cardiovascular diseases (Faria and Calhau, 2011), with tremendous anti-atherogenic and anti-anti-atherosclerotic characteristics for decreasing high blood pressure and density lipoprotein oxidation (Turk et al., 2008).

Rashidi et al. (2013) reported that concentrated pomegranate juice consumption was not effective on blood glucose and lipid profiles concentrations in type 2 diabetic patients. Pomegranate seed oil demonstrated and important therapeutic effect in the treatment of ovarian ischemia and reperfusion injury (Yayla et al., 2018). Pomegranate juice can be recommended as a suitable transport medium for avulsed teeth, and 1% of its juice was as effective as Hank’s balanced salt (HBS) for maintaining PDL cell viability (Tavassoli-Hojjati et al., 2018). T he effect of pomegranate on different types of canc er...
Pomegranate seed extract exhibited therapeutic potential for avoidance memories, because it is a potent phytoestrogenic and antioxidant which may have compensating effects for peripheral estrogen deficit (Sarkaki et al., 2015). Black pomegranate peel extract could effectively suppress angiogenesis potentially through a vascular endothelial growth factor (VEGF) dependent mechanism (Dana et al., 2015). Natural pomegranate juice is also a potent inflammatory, and anti-thrombocytopenia treatment among elderly population (Achraf et al., 2018). Saleh et al. (2018) reported that the antioxidant potential of pomegranate pomace extract supplementation was equal to that of α-tocopherol acetate in refrigerated meat. Martinez et al. (2019) concluded that natural extracts from pomegranate, rosemary, and hydroxytyrosol delayed the lipid oxidation, and addition of it to fish products contributed to extend the shelf life to fish. The whole fruit extract of pomegranate has cardioprotective effect against Dox-induced cardiotoxicity in rats (Hassanpour-Fard et al., 2011). Pomegranate peel extract was found to have strong anti-inflammatory activity by the reduction in the levels of Interlukin-6 (IL-6) and tumor Necrosis Factor-α (TNF-alfa), and rich in phenolic and flavonoids which may enhance its reducing activity and free radical scavenging ability (Qabaha et al., 2019).

Pomegranate juice has the potential as a nutraceutical to improve health span and lifespan in human beings (Balasubramani et al., 2014). The pomegranate vinegar may prevent a high-fat diet (HFD)-induced obesity and obesity-related cardiac complications because of anti-inflammatory and anti-adiposity properties of vinegar (Bounihi et al., 2017). Under accelerated oxidation conditions, pomegranate peel metahanolic extract have the potential capability to improve the shelf life of edible oils in comparison with the most powerful synthetic antioxidant [tert-butyl hydroquinone (TBHQ)-200 ppm] (El-Hadary and Taha, 2020). The pomegranate peel extract can be used in the treatment of oral candidiasis with no negative effects following administration in the rats (Bassiri-Jshromi et al., 2018). Pomegranate seed oil (PSO) clearly attenuate hexachlorobutadiene (HCBD)-induced nephrotoxicity (Bouroshaki et al., 2010). A decrease in hematotoxic and genotoxic effects induced by pomegranate peel is due to its powerful antioxidant capacity (Elwej et al., 2016). The fruits of some pomegranate genotypes could be used to obtain extracts very rich in punicalagins and that these substances could be used as an alternative to synthetic products to control plant disease and improve the quality of the plant products, avoiding the impact of synthetic chemicals on the environment (Rongai et al., 2019). The pomegranate peel extract showed anti-herpes simplex virus-1 (HSV) activity, probably by inhibiting the adsorption stage with SI value of 7.7 (Moradi et al., 2015). Pomegranate peel pectin can act as an effective emulsifier, and can be used as a novel polysaccharide emulsifier in the food industry (Yang et al., 2018). The antimetastatic effect of pomegranate may be attributed to molecular changes of the extracellular matrix (Ahmadiankia, 2019).

The most notable pharmaceutical benefits of pomegranate have been shown in Table 7.

| Health benefits | Mechanisms and impacts | Reference |
|-----------------|------------------------|-----------|
| Acute Pancreatitis | The higher doses of three fractions (250 and 500 mg/kg for pomegranate freeze-dried power and pomegranate seeds extract and doses of 100, 200 μL/kg for pomegranate seed oil fraction) significantly reduced amylase and lipase activity in serum, pancreatic myeloperoxidase activity, edema, leukocyte infiltration and vacuolization in comparison to the control group. | Minaiyan et al. (2014) |
| Alzheimer | Pomegranate extract is more efficacious as a protectant than a therapeutic measure in reducing histopathological hallmarks in Alzheimer’s disease. | Almuhayawi et al. (2020) |
| Anti-depressant effects | The aqueous extract of pomegranate (AE-PG) administered by intraperitoneal route induced anti-depressant like effects, and the mechanism of action involved the activation of the Estrogen receptor β (ERβ) and the | Valdes-Sustaita et al. (2021) |
| Anti-diabetes effects | a. Pomegranate seed oil (PSO) has a protective effect against diabetes complications in rats, and also significantly reversed streptozotocin (STZ)-induced depletion in thiol content and histological abnormality. | Mollazadeh et al. (2016) |
| | b. No significant impacts of pomegranate supplementation on metabolic parameters in patients with type 2 diabetes mellitus (T2DM) was found. | Jandari et al. (2020) |
| | c. Pomegranate juice consumption as an antioxidant may have a contribution in changing fasting blood sugar, lipid profiles, lipoprotein oxidation and human serum paraoxonase (PON1) activity. | Parsaeyan et al. (2012) |
| | d. Consumption of 2000 mg pomegranate seed oil (PSO) per day for 8 weeks had no impact on fasting blood sugar (FBS), insulin resistance and lipid profile in diabetic patients. | Faghihimani et al. (2016) |
| Anti-diarrheal activity | a. Its extract showed a concentration-dependent inhibition of the spontaneous movement of the isolated rat ileum and attenuated acetylcholine-induced contractions. | Qnais et al. (2007) |
| | b. Its extract also caused a dose-dependent decrease of gastrointestinal transit and significantly protected rats against castor oil-induced diarrhea enteropooling. | Qnais et al. (2007) |
| Anti-cancer activity | a. Pomegranate extracts inhibit the growth of breast, prostate, colon and lung cancer cells in culture. Polyphenols from pomegranate has been used for prevention of prostate cancer. | Adhami and Mukhtar (2006) Adhami et al. (2009) Nallanthigal et al. (2016) Boggula and Peddapalli (2017) |
| | b. The extracts derived from pomegranates had significant concentration-dependent anti-proliferative and pro-apoptotic effects against MCF-7 (ER+) and MD-MBA-231 or MD-MBA-435 (ER-) breast cancer cell lines. | Mehta and Lansky (2004) |
| | c. Pomegranate extract suppresses the melanocyte and melanin synthesis through inhibiting tyrosinase activity which is important in treatment of skin cancer. | Yoshimura et al. (2005) |
| | d. The photo chemo preventive effects of pomegranate against UVA and UVB Irradiations in normal human epidermal keratinocytes (NHKEK) as a test system has been proved. | Syed et al. (2006) |
| | e. Pomegranate fruit extracts (PFE) dose-dependently inhibited NF-κB-dependent reporter gene expression associated with proliferation invasion, and motility in aggressive breast cancer phenotypes while decreasing RhoC and RhoA protein expression. | Khan et al. (2009) |
| | f. Pomegranate juice gains lots of attractions due to its remedial and preventative roles against prostate cancer because of its ability in inhibiting cell growth and inducing apoptosis. | Koyama et al. (2010) |
| | g. Pomegranate extract decreased the expressions of genes of the enzyme involved in the synthesizing androgen and at the same time downregulate the hypoxia-inducible factor 1-α (HIF-1α) to constrain angiogenesis in prostate cancer. | Sartippour et al. (2008) |
| h. | The inhibitory effects of pomegranate juice on progression of prostate cancer as well as its role on increasing adhesion and decreasing migration of the live cells has been confirmed. |
| i. | Pomegranate extract suppresses cancer stem cells characteristics in part due to inhibition of epithelial-to-mesenchymal which can be exploited in the prevention of breast cancer. |
| j. | Ellagic acid induced a greater effect than luteolin, suggesting that ellagic acid might be a promising candidate for further preclinical testing for treatment of human ovarian cancer. |
| k. | Black peel pomegranate is a worthy bio-agent in silver nanoparticle biosynthesis and treatment of cancer. |
| l. | The MTT assay showed 94.53% inhibition on the oral cancer cell lines and clonogenic assay showed decrease in the colonies after treating with the peel extract. |
| m. | Pomegranate juice possesses a promising inhibitory effect on bladder cancer (BC) development, probably due to its anti-oxidant and anti-inflammatory properties. It can correct the expression of pro-inflammatory cytokines (interleukin 6 and hypoxia-inducible factor 1), it also press angiogenesis by down-regulation of hypoxia-inducible factor and supports apoptosis through reduction of the tumor suppressor gene p53. |
| n. | Dwarf pomegranate extracts showed potent growth inhibitory activities in human prostate cancer cells (DU145), which appear to be mediated by a pro-apoptotic mechanism. |
| o. | Nano-pomegranates have great potential in anti-breast cancer treatment, because MCF-7 cells have shown remarkable efficiencies of enhancing cellular uptake, inhibition and necrosis and apoptosis at in vivo rat experiments. |
| p. | The pomegranate fruit fleshy pericarp acts as a natural agent to synthesize silver nanoparticles (AgNPs) which can be considered as an anticancer agent. |
| q. | Pomegranate extract and tangeretin may be effective in preventing breast cancer development. |

**Anti-inflammatory and analgesic effect**

| a. | The methanol extract Amrouz (MoEA) and methanol extract Sefri (MoES) have both analgesic and anti-inflammatory properties. |
| b. | Pomegranate juice may have an anti-inflammatory effect in patients with type 2 diabetes (T2D), because it may reduce interleukin 6 and hs-CRP concentrations in plasma. |
| c. | The phosphorylation of ERK1/2, p38, JNK and translocation of the NF-B p65 subunit into nuclei were inhibited by the pomegranate flower ethanol (PFE) treatment, and PFE produced potential anti-inflammatory effect. |
| d. | Pomegranate peel extracts is a promising food supplement for dairy cattle, especially around calving, when the animals are more subject to oxidative stress and inflammatory diseases. Pomegranate supplementation significantly |
| Reduced hs-CRP, IL-6, and TNF-α. Anti-inflammatory effects of pomegranate poly phenols have been confirmed. | Karwasta et al. (2019) |
|---|---|
| e. Pomegranate (200 mg/kg) attenuate pain and inflammation by down-regulating the activation of TNF-R1, TNF-α, IL-1β, IL-6, NF-κB, oxidative stress markers and tissue histology. | |
| f. Oral pre-treatment with its dried extract produced statistically significant and dose dependent inhibition of edema induced when compared to the control groups. | Bagri et al. (2010) |
| g. Standardized pomegranate rind extract and the equivalent ellagic acid (EA) dose-dependently reduced the croton oil-induced mouse ear edema. | Mo et al. (2013) |
| **Antioxidant activity** | |
| a. All parts of pomegranate had antioxidant activity with high total phenolic, flavonoid and flavonol contents. | Fazeli et al. (2011) Surek and Nilufer-Erdil (2014) Elwej et al. (2016) Lantzouraki et al. (2016) Derakhshan et al. (2018) Drinic et al. (2020) |
| b. Pomegranate leaf, peel and seed exhibited very strong antioxidant activity. | Kotamballi et al. (2002) Singh et al. (2002) |
| c. Pomegranate peel polysaccharides has good antioxidant activity in vivo, and it is a good natural source for dietary supplement application. The pomegranate juice contains potent antioxidant nutrients capable of reducing the cyrototoxicity of hypercholesterolemia and atorvastatin which enhance the structure and function of the cerebellar cortex. The pomegranate peel as a by-product has the potential to develop bio-functional edible films intended for packaging food products. | Wu et al. (2019) El-Sayyad et al. (2020) Moghadam et al. (2020) |
| d. The antioxidant capacity of pomegranate peel extract is 10 times higher than the pulp extract. | Shams Ardekani et al. (2011) |
| e. Pomegranate peel because of its high antioxidant activity can be added to yoghurt for the development of freeze-dried yoghurt with functional ingredients on an industrial scale. | Kennas et al. (2020) |
| **Anti-microbial activity** | |
| a. Fresh pomegranate juice has antimicrobial activity, which might be attributed to its high polyphenol content and antioxidant capacity. | Sadeghian et al. (2011) Betanzos-Cabrera et al. (2015) |
| b. The isolated compounds are economically viable of safe antimicrobial agents that possess an inhibitory action to pathogenic *H. pylori*. | Gould et al. (2009) Khalid et al. (2018) Andrade et al. (2019) Nazeam et al. (2020) |
| Pomegranate by-products have powerful antioxidant and antimicrobial activities. | |
| c. According to X-ray diffraction, pomegranate peel retained its semi-crystalline structure in the film, which can shown its importance as an edible film and food grade packaging material. | Ali et al. (2019) |
| **Anti-bacterial activity** | |
| a. The hydro-alcoholic extract (HAE) from pomegranate presents antibacterial activity against selected microorganisms, and maybe a possible alternative for the treatment of dental plaque bacteria. | Menezes et al. (2006) Jagdale et al. (2019) Shahid et al. (2019) Monir et al. (2020) |
| Pomegranate peel extracts enhances immunity | |
and increased the protection against pathogenic bacteria.

| Characteristics                              | Description                                                                                           | Reference                     |
|----------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------|
| b. Total phenolic and flavonoid content of   | The total phenolic and flavonoid content of pomegranate has positively associated with the antibacterial  | Mahboubi et al. (2015)        |
| pomegranate                                   | activities of the fractions with chloroform extract exhibiting lowest antibacterial activity against  |                               |
|                                              | *Escherichia coli* (MIC 25 mg/ml), and the methanol fraction exhibiting the highest antibacterial effect  |                               |
|                                              | against *Staphylococcus aureus* (MIC 0.19 mg/ml).                                                    |                               |
| c. Pomegranate peel extracts                 | The pomegranate peel extracts showed antibacterial activities against *Pseudomonas aeruginosa* and   | Nezhamour et al. (2018)       |
|                                              | *Staphylococcus aureus*.                                                                             |                               |
| d. Antibacterial effects of pomegranate       | Because of its antibacterial effects, pomegranate peel is a potential source of natural preservatives  | Yemis et al. (2019)           |
|                                              | for the control of *Cronobacter sakazakii* in food.                                                   |                               |
| Anti-aging activity                           | Pomegranate anthocyanins could be used as a safe, stable, homogeneous, nonirritant and effective      | Abdellatif et al. (2020)      |
|                                              | topical anti-aging drug formulation for aged people.                                                 |                               |
| Anti-apoptotic activity                       | The methanolic extract of pomegranate peel has beneficial influences and could be able to inhibit    | Abdel Moneim et al. (2013)    |
|                                              | Al-induced oxidative stress and histopathological alterations in liver and kidney of female rats.     |                               |
| Anti-bacterial effects                        | All pomegranate extracts contain high levels of phenolics and exhibited antibacterial activity against  | Nuamsetti et al. (2012)       |
|                                              | *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhimurium*.        |                               |
|                                              | Pomegranate peel extract contains bioactive compounds which mitigate the deleterious impacts of an    | Smith et al. (2020)           |
|                                              | in vivo infection with the model enteropathogenic bacteria *Citrobacter rodentium* (Cr.).               |                               |
| Anti-angiogenic effects                       | Pomegranate peel extract (PPE) showed anti-angiogenic effects and it could be mediated in part        | Dana et al. (2016)            |
|                                              | through peroxisome proliferator-activated receptors (PPARs) dependent pathway.                       |                               |
| Anti-hepatotoxic effects                      | The hepatoprotective potential of the acetone extract of *Punica granatum* fruits on tissue defense   | Yogeeta et al. (2007)         |
|                                              | systems during isoniazid- and rifampicin induced hepatotoxicity in rats was found.                    |                               |
| Nausea and vomiting                           | Pomegranate seems to be more effective than vitamin B6 in the treatment of Nausea and vomiting        | Abdolhosseini et al. (2017)   |
|                                              | pregnancy (NVP).                                                                                     |                               |
| Natural preservative and anti-atherogenic     | Polyphenolic fraction of pomegranate juice can act as antiatherogenic supplementation and natural     | Faisi et al. (2018)           |
| supplementation                                 | preservative for meat and fatty foods through direct inhibition of LDL oxidation.                     |                               |
|                                              | The pomegranate peel phenolics may improve stored meat products quality, such as instrumental color   | Derakhshan et al. (2018)      |
|                                              | retaining, limitation of                                                                         | He et al. (2019)              |
|                                              |                                                                                                       | Smaoui et al. (2019)          |
Shahrajabian MS et al. (2021). Not Sci Biol 13(3):11085

| Nephroprotective effects | a. The prophylactic consumption of pomegranate juice for 14 days could show nephroprotective effects by reducing oxidative stress and potassium depletion. | Alimoradian et al. (2017) |
| b. Pomegranate juice may lead to the stabilization of kidney function despite using captopril and gentamicin. | Alimoradian et al. (2017) |

| Skin health | a. The pomegranate extract and its phenolics may ameliorate the adverse effects against \( \text{H}_2\text{O}_2 \)-induced oxidative stress and cytotoxicity in keratinocytes supports their utilization as natural cosmeceuticals for skin health. | Liu et al. (2019) |
| b. Pomegranate peel extract can prolong the shelf-life of bighead carp fillets for about 2 days, and it can be considered as a promising preservative in aquatic products. | Zhuang et al. (2019) |
| c. Pomegranate extract showed effectual at protecting human skin fibroblasts from cell death following UV exposure. | Pacheco-Palencia et al. (2008) |
| d. Pretreatment of epiderm with pomegranate-derived products resulted in inhibiting of UVB-induced; collagenase gelatinase, stromelysin, marilysin, elastase and tropoelastin. | Afaq et al. (2009) |

| Anti-liperoxidant activity | Owing to the high anti-liperoxidant property of pomegranate, acetone extract may have possible application in the food industry. | Zhang et al. (2007) |

| Anti-obesity effects | a. A significant decrease in feed consumption and body weight of female rats after exposure them to a diet containing 20% of pomegranate extract (6%) for 37 days. | Cerda et al. (2003) |
| b. The pomegranate lead extract in a mouse model of high-fat diet-induced obesity, and the effects appear to be partly mediated by inhibiting pancreatic lipase activity and suppressing energy intake. | Lei et al. (2007) |

| Anti-viral effects | The crude pomegranate peel extract and its n-butanol and ethyl acetate fractions had the highest inhibitory effect against influenza A virus with IC\(_{50}\) value of 6.45, 6.07 and 5.6 \( \mu \text{g/ml} \) in Madin-Darby Canine Kidney (MDCK) cells, respectively. | Moradi et al. (2019) |

| Anti-ulcer effects | The pomegranate peel extract, especially sour summer has curative potential as an antulcer, possibly via its high antioxidant activity. | Moghaddam et al. (2013) |

| Oral health management | a. Pomegranate juice is efficacious against dental plaque microorganisms. | Kote et al. (2011) |
| b. Hydroalcoholic extract was effectual against dental plaque microorganisms. | Menezes et al. (2006) |

| Sexual behavior | a. Administration of the pomegranate extract orally at the dose of 1500 mg/kg produced significant augment of sexual activity in male rats. | Lydia et al. (2019) |
| b. Pomegranate juice consumption led to an increase in epididymal sperm concentration. | Turk et al. (2008) |
sperm motility, spermatogenic cell density, and the diameter of seminiferous tubules and germinal cell layer thickness; it also decreased the abnormal sperm rate when compared to the control group.

c. Ellagic acid has a protective effect against testicular and spermatozoa toxicity induced by cyclosporine A. Turk et al. (2010)

Vertigo

Pomegranate concentrated juice as a stomach tonic led to the improvement of the digestive symptoms and vertigo. Monfared et al. (2019)

Wound healing

a. The extract of the top layer of the peel significantly improved the wound healing process, but the pulp showed no promising impacts.

b. The ethanol extract of pomegranate exocarp has the higher amounts of tannins and flavonoids, compounds that are known to be beneficial for wound healing. Ghaleh Mohammadi and Mirghazanfari (2019)

c. 10% standardized pomegranate extract accelerates the healing of deep second-degree burn wound, and pomegranate standardized with 40% ellagic acid is a promising for the healing of burn wound skin. Lukiswanto et al. (2019)

The most important biological effects of methanol extract of pomegranate fruits are antiestrogenic in breast, no induction of proliferation in endometrial, ovarian, and cervical cancer cells, suppressed TNFα-mediated endothelial cell apoptosis, estrogen inducible gene expression was not altered, reduced LDL cholesterol levels cardioprotective effect, no DNA adduct formation or oxidative DNA damage and has osteoprotective effects (Sreekumar et al., 2014). Fruit peel administration showed a noteworthy amelioration of abnormalities related Cd-nephrotoxicity (El-Habibi, 2013), and flower extract has protective role and ameliorate nephrotoxicity induced by gentamicin (El-Daly, 2016). The methanolic extract of peels was a potent inhibitor for Listeria monocytogenes, S. aureus, Escherichia coli, and Yersinia enterocolitica (El-Zoreky, 2009; Devatkal et al., 2013). Extracts from fruit skin showed good antibacterial activity against S. aureus and P. aeruginosa (Sadeghian et al., 2011); and tannin from the pericarp is a very effective constituent against genital herpes virus (HSV-2) (Zhang et al., 1995). Acidity of pomegranate juice and concentrated liquid extract (POMxl) solutions contributed to rapid anti-influenza activity (Sundararajan et al., 2010), and treated mice with pomegranate peel significantly showed reduction in parasitemia as compared to untreated control (Mubaraki et al., 2016). Water extracts from arils has shown antibacterial effects against Bacillus megaterium, P. aeruginosa, S. aureus, Corynebacterium xerosis, E. coli, Enterococcus faecalis and Micrococcus luteus (Duman et al., 2009), and the aqueous and methanol extracts from whole fruit showed antibacterial effects on S. typh, Salmonella typhimurium, and Salmonella paratyphi (Pasha et al., 2009). Nascimento et al. (2000) showed antibacterial effects of ethanol extracts of the whole fruit on P. aeruginosa, and B. subtilis; and Salgado et al. (2009) indicated the antibacterial effects of raw extract of pomegranate whole fruit on P. aeruginosa, E. coli, Enterococcus faecalis, Enterobacter aerogenes, S. aureus and Micrococcus luteus. The most important health benefits of pomegranate are shown in Figure 1.
Pomegranate is native to Persia and Mediterranean zone which has been widely used in many countries and cultures, especially in west and center of Asia. Nutrient content of pomegranate peel is total solid, moisture, total sugars, reducing sugars, protein, crude fiber, fat content and ash. Fatty acids found in pomegranate seeds are caproic acid, punicic acid, capric acid, lauric acid, myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, stearic acid, linoleic acid and oleic acid. Chemical compounds in pomegranate peels are gallic acid, ellagic acid, punicalin, punicalagin, caffeic acid, ellagitannins, pelletierine, alkaloids, luteolin, kaempferol and quercetin. Chemical constituents in pomegranate seeds are 3,3-Di-\(O\)-methylellagic acid, 3,3,4-Tri-\(O\)-methylellagic acid, punicic acid, pleic acid, palmitic acid, stearic acid, linoleic acid, sterols, tocopherols and sex steroids. Chemical compounds in pomegranate juice are simple sugars, aliphatic organic acids, gallic acid, ellagic acid, quinic acid, flavonols, amino acids, minerals, EGCG, and ascorbic acid. Pomegranate leaf contains carbohydrates, reducing sugars, sterols, saponins, flavanoids, tannins, piperidine alkaloids, flavone, glycoside, and ellagitannins. The main chemical compounds in root and bark are ellagitannins, piperidine alkaloids, pyrrolidine alkaloid, and pelletierine alkaloids. Flower chemical constituents are gallic acids, ursolic acid, triterpenoids, and fatty acids. The most important potential benefits of pomegranate are antioxidant, cancer prevention, Alzheimer's disease protection, reduce inflammation in the gut and improve digestion, a powerful anti-inflammatory fruit, positive contributes to osteoarthritis and cartilage damage, heart-healthy juice, may lower systolic blood pressure, antiviral effects, improve learning and memory, a good source for potential fertility aid, a traditional remedy for diabetes, rich in different vitamins such as vitamin C, E, K., and a good source of folate and potassium.

**Conclusions**

Figure 1. The most important health benefits of pomegranate
Authors’ Contributions

All authors contributed equally to literature research, writing manuscript, etc. All authors read and approved the final manuscript.

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Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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