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Review

Pomegranate as a promising opportunity in medicine and nanotechnology

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ABSTRACT

Pomegranate tree is one of the oldest fruit trees known to humans (4000 and 3000 BCE). Pomegranate blooms as a symbol of life, permanence, wellbeing, femaleness, fertility, knowledge, immortality, and holiness. In efforts to figure out the best source of phenolic compounds in human diet, pomegranate receives a great amount of popularity owing to the biological effects that exerts through free radical scavenging capabilities by its phenolic compounds. Pomegranate has risen to fame for its medical applications since ancient times. Antioxidant, immunity-boosting, and anti-carcinogenic properties are the major virtues of the pomegranate as a fruit that can be applied as an herbal cure. Unique antimicrobial, antihelminthic, and antioxidant effects seen in pomegranate extracts encourage scientists to employ them as cancer preventative agents. Present review is aimed to study the different parts of the pomegranate along with their characteristics and components, chemical compositions, antibacterial effects and the mechanisms of its bactericidal behavior, medicinal applications and its anticancer properties. Then, nanotechnology applications of pomegranate including its use in biosynthesizing different nanoparticles (NPs) and developing drug delivery systems like nanoemulsion, nanoparticles, nanoliposomes, phytosomes, nanovesicles and niosomes will be discussed in detail.

1. Introduction

Human has been familiar with pomegranate since ancient times (4000 and 3000 BCE). Pomegranate blooms as a symbol of life, permanence, wellbeing, femaleness, fertility, knowledge, immortality, and holiness (Mahdihassan, 1984). Pomegranate belongs to the *Punicaceae* family and can grow up to 6–10 m and live for a long time (Morton, 1987) and to the best of our knowledge it is originally native to Iran (Kulkarni & Aradhya, 2005). Pomegranate is now harvested in many counties like India, Pakistan, Israel, Afghanistan, Egypt, China, Japan, the USA, Russia, Australia, South Africa, and Saudi Arabia, and also in the subtropical areas of South America (Holland, Hatib, & Bar-Ya'akov, 2009). Annual worldwide production of this remedial fruit is around 2,000,000 Metric Tons; 50% of which is produced in India. Iran is the second producer of pomegranate with an estimated 55,000 ha in production (Lye, 2008). Iran has been the capital of pomegranate cultivation, with a total production of 910,000 tons in 2013 (Iran Statistical Yearbook, 2013), consisting of more than 800 genotypes which are collected and retained in the Yazd and Saveh germplasm facilities (Behzadi Shahrebabaki, 1998). Pomegranate ranked 18th according to the annual global fruit consumption statistics (Brodie, 2009), and its health-promoting properties promotes its popularity, particularly in the developed countries (Lansky & Newman, 2007). It can survive through dry and harsh conditions. Fruit harvesting time is when a waxy shining layer is formed and the fruit is fully ripe (Biale, 1981). During maturation, physiological, biochemical, and structural changes develop the size, color and taste of the fruit that eventually make the fruit palatable (Al-Maiman & Ahmad, 2002). Internal factors like color, total soluble solids and acidity play important roles in determining the extent of the ripeness (Kader, 2006; Holland et al., 2009). Pomegranate is used in different forms like fresh juice, fresh fruit, concentrated juice, arils, and products such as teas, pharmaceutical and medicinal products, dyes and decoration (Lye, 2008). Pomegranate is used in producing jellies, wine, jam, paste and coloring beverages, pomegranate salad dressing and seed oils in industry (Holland et al., 2009). Present

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review is aimed to study the different parts of the pomegranate along with their characteristics and components, chemical compositions, antibacterial effect and the mechanism of its bactericidal behavior, medicinal applications and its anticancer properties. Then, nanotechnology applications of pomegranate including its use in biosynthesizing different nanoparticles (NPs) and developing drug delivery systems like nanoemulsions, NPs, nanoliposomes, phytosomes, nanovesicles and niosomes will be discussed in detail.

1.1. Different parts of the pomegranate

Pomegranate is composed of three parts: 1) Seeds constitute about 30% of the fruit weight which is mainly made of sugars, vitamins, polysaccharides, polyphenols, minerals (Melgarejo and Artes, 2000) and a small amount of oil that contains polyunsaturated (n-3) fatty acids (Singh, Murthy, & Jayaprakasha, 2002). Seeds are covered by a thin white membrane and its high tannic acid content makes it bitter. Seeds open new avenues in beauty and productiveness businesses (Aslama, Lansky, & Varani, 2006). 2) About 30% of the fruit's weight is the juice, which is a good source of potassium, phosphorous, calcium, iron, manganese, zinc and copper. Pomegranate juice (PJ) is produced through squeezing the whole fruit; thus major of the water soluble ingredients such as ellagitannins and punicalagins are found in juice rather than pulp. PJ is rich in anthocyanins, 3-glucosides and 3, 5-diglucosides of delphinidin, cyanidin, pelargonidin, citric and ascorbic acids (El-Nemr, Ismail, & Ragab, 1990). About 90% of the antioxidant activity of pomegranate is assigned to ellagitannin. Punicalagin is the most dominant ellagitannins in PJ (Gil, Tomas-Barberan, Hess-Pierce, Holcroft, & Kader, 2000; Tzulker et al., 2007). Punicalagin concentration may vary (from 0.017 to 1.5 g/L of PJ) depending on the fruit cultivar, maturity index, seasonal changes, processing and storage conditions (Gil et al., 2000; Seeram, Lee, & Heber, 2004a). PJ possesses the highest amounts of antioxidants (Aviram, 2002) that should be about 3 times higher than antioxidant levels in red wine, and green tea (Gil et al., 2000; Schubert, Lansky, & Neeman, 1999). PJ is a popular beverage especially in Iran, which is used in health promoting studies (Aviram, 2002) and is well regarded as a perfect candidate for healthy products and nutraceuticals manufacturers (Singh et al., 2002). 3) Peels comprise 26–30% of the total fruit weight and encompass the inner membranes (Lansky & Newman, 2007). Astringency is attributed to the peel (pericarp) (Aslama et al., 2006). Despite the high amount of polyphenol compounds and beneficial biological activities of pomegranate peel (PP) (Al-Said, Opara, & Al-Yahyai, 2009) unfortunately it is frequently treated as waste and disposed (Li et al., 2006). Phenolic compounds like anthocyanins, ellagic acid glycosides, free ellagic acid, ellagitannins, punicalagin, punicalin and gallotannins are profoundly found in PP (Cristofori et al., 2011; Saad et al., 2012; Seeram, Schulman, & Heber, 2006). Pomegranate peel extract (PPE) is profuse of phenolics, flavonoids and tannins, thus has found an important place in food industry to provide the co-products of PJ-related preparations (Viuda-Martos, Perez-Alvarez, Sendra, & Fernandez-Lopez, 2013). As an example, adding about 0.5% of dried PPE to tomato and orange juice could elevate their antioxidant levels (Salgado et al., 2012). Ibrahim has suggested food preservative role for PPE (Ibrahim, 2010).

Pomegranate parts fit for human consumption are aril, which is about 52% of the total weight of fruit and is mainly composed of 78% juice and 22% seeds. Analysis of the data acquired by researchers showed that each 100 g of aril contains 72 kcal of energy, 1.0 g protein, 16.6 g carbohydrate, 1 mg Na, 379 mg K, 13 mg Ca, 12 mg Mg, 0.7 mg Fe, 0.17 mg Cu, 0.3 mg niacin, and 7 mg acid ascorbic (Grove & Grove, 2008). Other parts of the pomegranate such as bark (Tanaka, Nonaka, & Nishioka, 1986b), leaf (Nawwar, Hussein, & Merfort, 1994b; Tanaka, Nonaka, & Nishioka, 1985), and husk contain ellagitannins and gallotannins. Furthermore, apigenin and luteolin glycosides could be detected in pomegranate leaves (Nawwar et al., 1994a) while, hydrolysable tannins like punicalagins and punicalin are found in pomegranate husk (Tanaka et al., 1986a).

1.2. Chemical compositions of a pomegranate

Adverse health effects that synthetic compounds leave in human body, encourage the consumers to use the natural ingredients from the fruit origin (Negi, Jayaprakasha, & Jena, 2003; Poyrazoglu, Gokmen, & Artak, 2002; Singh et al., 2002). Pomegranate is gaining growing attention owing to its phenolics, anthocyanins, and vitamin C contents, which provide its nutritional and therapeutic effects (Peärez-Vicente et al., 2002). Pomegranate is an extremely nutritious fruit, mainly composed of acids, sugars, vitamins, polysaccharides, polyphenols and minerals (Al-Maiman & Ahmad, 2002). Proteins, sugars and minerals are the main constituents of the pomegranate (Elfalleh et al., 2012). About 85.4% of the fresh juice is water, other than that, total soluble solids (TSS), total sugars, reducing sugars, anthocyanins, phenolics, ascorbic acid, proteins (El-Nemr et al., 1990), and antioxidants (Gil et al., 2000; Kulkarni, Aradhya, & Divakar, 2004) exist. Pomegranate owes its health promoting properties to the beneficial compounds like tannins, flavonoids, alkaloids, organic acids, triterpenes and steroids, found in all over the plant. Zarei and colleagues studied six cultivars of Iranian pomegranate and showed that the variety could influence all the chemical factors of pomegranate. Total soluble solids ranged from 15.77 to 19.56, pH was between 3.06 and 3.74, titrable acidity was from 0.51 to 1.35 (g/100 g), total sugar content was between 16.88 and 22.76 (g/100 g), anthocyanins ranged between 7.93 and 27.73 (g/100 g). Ascorbic acid and total phenolics were measured to be 8.68 to 15.07 (g/100 g) and 526.40 to 797.49 (mg tannic/100 g) while, total tannins expanded between 18.77 and 38.21 (mg tannic/100 g). Antioxidant activity was 46.51–52.71% and extremely dependent on the total phenolics ($r = 0.912$) (Zarei, Azizi, & Bashiri-Sadr, 2010). A brief description about the main constituents of pomegranate could be seen below.

1.2.1. Sugars

Cui and coworkers reported glucose and fructose as the main sugars in pomegranate (Cui, Sasada, Sato, & Nii, 2004). Tezcan and colleagues reported glucose and fructose content of the PJ as 0.36 and 3.6 mg/ml, respectively (Tezcan, Gultekin-Ozguven, Diken, Ozcelik, & Bedia Erim, 2009).

1.2.2. Acids

Citric acid, malic acid, tartaric acid, fumaric acid, succinic acid and ascorbic acid, are the aliphatic organic acids of pomegranate (Poyrazoglu et al., 2002) from which malic and citric acid had the highest levels in the commercial PJs detected by capillary electrophoretic separation method (Tezcan et al., 2009).

1.2.3. Minerals

Minerals like Fe, Ca, Ce, Cl, Co, Cr, Cs, Cu, K, Mg, Mn, Mo, Na, Rb, Sc, Se, Sn, Sr, and Zn exist in the PJ and seeds of a pomegranate (Waheed, Siddique, Rahman, Zaidi, & Ahmad, 2004). Ripening stage of a pomegranate is an important factor to determine the minerals contents of a fruit. The highest detected minerals were K, Ca and Na followed by Mg, P, Zn, Fe, and Co (Al-Maiman & Ahmad, 2002). During maturation the concentrations of the most of the minerals decrease in the following order in aril and peel: $K > N > Ca > P > Mg > Na$ (Mirdehghan & Rahemi, 2007).