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Pomegranate and its Many Functional Components as Related to Human Health: A Review

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Abstract: Pomegranate (*Punica granatum* L.) is an ancient fruit that is widely consumed as fresh fruit and juice. The use of pomegranate fruit dates from ancient times and reports of its therapeutic qualities have echoed throughout the ages. Both *in vitro* and *in vivo* studies have demonstrated how this fruit acts as antioxidant, antidiabetic, and hypolipidemic and shows antibacterial, antiinflammatory, antiviral, and anticarcinogenic activities. The fruit also improves cardiovascular and oral health. These beneficial physiological effects may also have preventive applications in a variety of pathologies. The health benefits of pomegranate have been attributed to its wide range of phytochemicals, which are predominantly polyphenols, including primarily hydrolyzable ellagitannins, anthocyanins, and other polyphenols. The aim of this review was to present an overview of the functional, medical, and physiological properties of this fruit.

Introduction

The pomegranate (*Punica granatum* L.) is an ancient fruit; it has been widely consumed in various cultures for thousands of years. The use of pomegranate fruit dates back to Biblical times and reports of its therapeutic qualities have echoed throughout the millennia (Longtin 2003). The Babylonians regarded pomegranate seeds as an agent of resurrection; the Persians believed the seeds conferred invincibility on the battle fields, while for the ancient Chinese the seeds symbolized longevity and immortality (Aviram and others 2000).

The pomegranate belongs to the family Punicaceae. It is native from the area of Iran to the Himalayas in northern India, and has been cultivated and naturalized over the entire Mediterranean region since ancient times (Meerts and others 2009). Actually, the pomegranate is widely cultivated throughout Iran, India, Mediterranean countries, the drier parts of Southeast Asia, Malaysia, the East Indies, and tropical Africa and, to some extent, in the United States (drier parts of California and Arizona), China, Japan, and Russia (Fadavi and others 2006).

The edible parts of pomegranate fruits are consumed fresh or used for the preparation of fresh juice, canned beverages, jelly, jam, and paste and also for flavoring and coloring beverage products (Fadavi and others 2005; Mousavinejad and others 2009). In addition, it is widely used in therapeutic formulas, cosmetics, and food seasonings. Since ancient times, the pomegranate has been regarded as a "healing food" with numerous beneficial effects in several diseases (Vidal and others 2003). Indeed, the pomegranate was commonly used in folk medicine, for eliminating parasites, as an antihelmintic and vermifuge, and to treat and cure aphtae, ulcers, diarrhea, acidosis, dysentery, hemorrhage, microbial infections, and respiratory pathologies. It was also used as an antipyretic (Larrosa and others 2010; Lee and others 2010).

Recent years have seen increased interest on the part of consumers, researchers, and the food industry into how food products can help maintain health; and the role that diet plays in the prevention and treatment of many illnesses has become widely accepted (Viuda-Martos and others 2010a). At the present time, considerable importance is given to functional foods, which, in principle, apart from their basic nutritional functions, provide physiological benefits and play an important role in disease prevention or slow the progress of chronic diseases (Viuda-Martos and others 2010b). There has been a virtual explosion of interest in the pomegranate as a medicinal and nutritional product because of its multifunctionality and its great benefit in the human diet as it contains several groups of substances that are useful in disease risk reduction. As a result, the field of pomegranate research has experienced tremendous growth (Martínez and others 2006; Jaiswal and others 2010). The aim of this review was to present an overview of the functional, medical, and physiological properties of the pomegranate.

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Chemical Composition of Pomegranates

The pomegranate fruit (Figure 1) has valuable compounds in different parts of the fruit. These can be divided into several anatomical origins: peel, seeds, and arils. Another important

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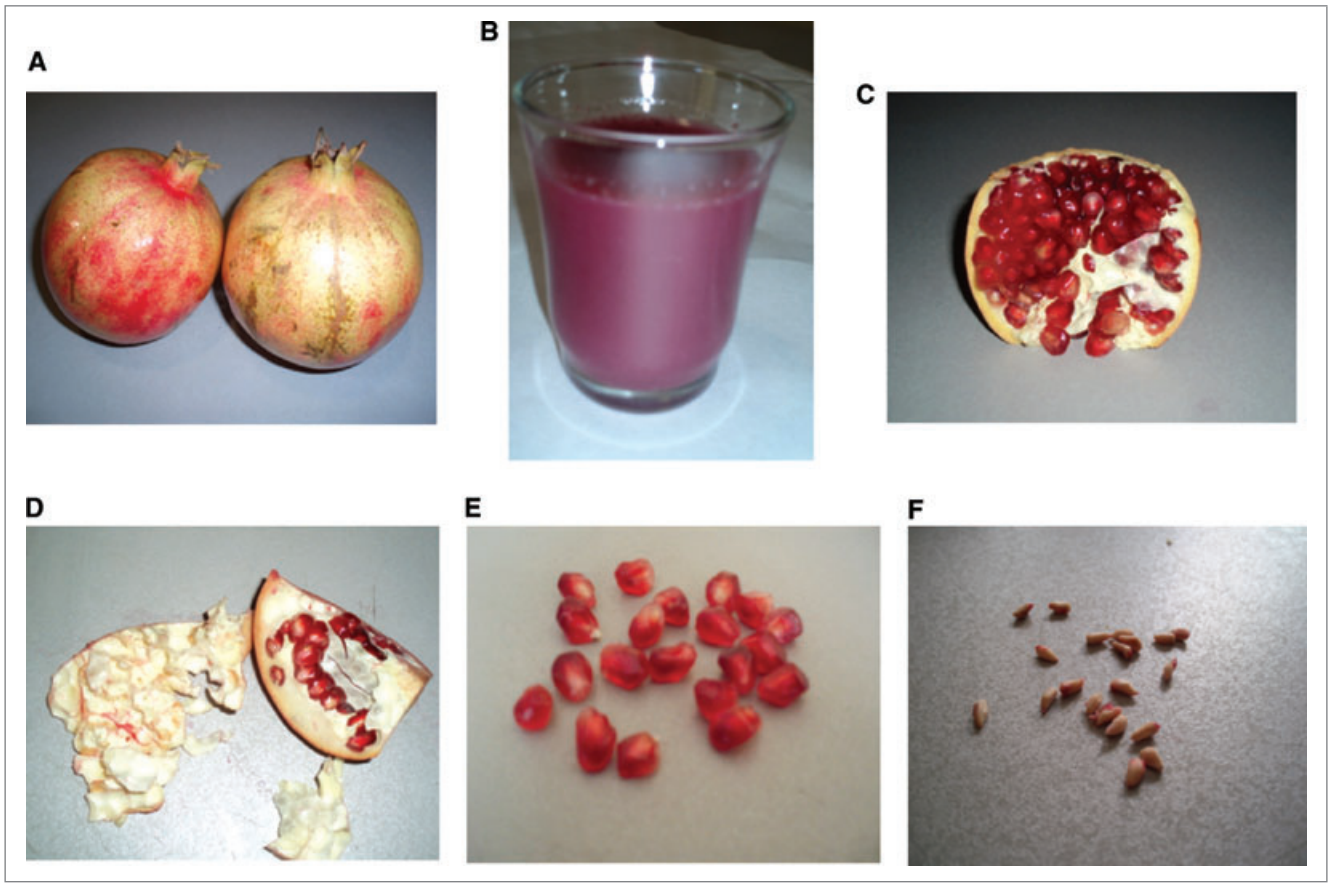

Figure 1–Different parts of the pomegranate fruit (A). B: pomegranate juice; C: section of pomegranate; D: pomegranate peel; E: pomegranate arils; F: pomegranate seeds.

product obtained from pomegranate fruit is the juice that can be obtained from arils or from whole fruit.

The chemical composition of the fruits (Table 1) differs depending on the cultivar, growing region, climate, maturity, cultivation practice, and storage conditions (Poyrazoglu and others 2002; Barzegar and others 2004; Fadavi and others 2005). Significant variations in organic acids, phenolic compounds, sugars, water-soluble vitamins, and minerals of pomegranates have been reported over the years by various researchers (Aviram and others 2000; Mirdehghan and Rahemi 2007; Çam and others 2009; Davidson and others 2009; Tezcan and others 2009). About 50% of the total fruit weight corresponds to the peel, which is an important source of bioactive compounds such as phenolics, flavonoids, ellagitannins (ETs), and proanthocyanidin compounds (Li and others 2006), minerals, mainly potassium, nitrogen, calcium, phosphorus, magnesium, and sodium (Mirdehghan and Rahemi 2007), and complex polysaccharides (Jahfar and others 2003). The edible part of the pomegranate fruit (50%) consists of 40% arils and 10% seeds. Arils contain 85% water, 10% total sugars, mainly fructose and glucose, and 1.5% pectin, organic acid such as ascorbic acid, citric acid, and malic acid, and bioactive compounds such as phenolics and flavonoids, principally anthocyanins (Aviram and others 2000; Tezcan and others 2009). The seeds are a rich source of total lipids; pomegranate seed oil comprises 12% to 20% of total seed weight. The oil is characterized by a high content of polyunsaturated (n-3) fatty acids such as linolenic, linoleic, and other lipids such as punicic acid, oleic acid, stearic acid, and palmitic acid (Ozgul-Yucel 2005; Fadavi and others 2006). The seeds also contain protein, crude fibers, vitamins, minerals, pectin, sugars, polyphenols, isoflavones (mainly genistein), the phytoestrogen coumestrol, and the sex steroid, estrone (El-Nemr and others 2006; Syed and others 2007).

Nowadays, it is widely accepted that the beneficial health effects of fruits and vegetables in the prevention of disease are due to the bioactive compounds they contain (Galaverna and others 2008). The presence of significant amounts of bioactive compounds, such as phenolic acids, flavonoids, and tannins in pomegranate fruits assures them considerable nutritional value (Aviram and others 2000).

Phenolic compounds

One of the main compounds responsible for most of the functional properties of many foods, among them pomegranate fruit, are phenolic compounds in any of their forms (Viuda-Martos and others 2010a). Natural polyphenols can range from simple molecules (phenolic acids, phenylpropanoids, flavonoids) to highly polymerized compounds (lignins, melanins, tannins), with flavonoids representing the most common and widely distributed subgroup (Soobrattee and others 2005). Chemically, phenolic acids can be defined as substances that possess an aromatic ring bound to

Table 1–Principal constituents of different parts of pomegranate tree and fruit.

Plant component	Constituents	Reference
Pomegranate juice	Anthocyanins, glucose, organic acid, ascorbic acid, EA, ETs, gallic acid, caffeic acid, catechin, quercetin, rutin, minerals	Poyrazoglu and others (2002); Ignarro and others (2006); Lansky and Newman (2007); Heber and others (2007); Mousavinejad and others (2009); Jaiswal and others (2010)
Pomegranate seed oil	Conjugated linolenic acid, linoleic acid, oleic acid, stearic acid, punicic acid, eleostearic acid, catalpic acid	Ozgul-Yucel (2005); Fadavi and others (2006); El-Nemr and others (2006); Sassano and others (2009)
Pomegranate peel	Luteolin, quercetin, kaempferol, gallagic, EA glycosides, EA, punicalagin, punicalin, pedunculagin	Van Elswijk and others (2004); Amakura and others (2000); Seeram and others (2005b)
Pomegranate leaves	EA; fatty acids	Ercisli and others (2007) Lan and others (2009)
Pomegranate flower	Polyphenols, punicalagin punicalin, EA	Kaur and others (2006) Aviram and others (2008)
Pomegranate roots and bark	Alkaloids, ETs	Neuhofer and others (1993) Gil and others (2000)

one or more hydrogenated substituents, including their functional derivatives (Marín and others 2001).

Flavonoids are low-molecular-weight compounds consisting of 15 carbon atoms, arranged in a C_6-C_3-C_6 configuration. Essentially, the structure consists of 2 aromatic rings joined by a 3-carbon bridge, usually in the form of a heterocyclic ring (Balasundram and others 2006).

Anthocyanins are the largest and most important group of flavonoids present in pomegranate arils, which are used to obtain the juice. These pigments give the fruit and juice its red color (Afaq and others 2005). There is a great variety of anthocyanins present in pomegranate juice (Figure 2a), principally cyanidin-3-*O*-glucoside, cyanidin-3,5-di-*O*-glucoside, delphinidin-3-*O*-glucoside, delphinidin-3,5-di-*O*-glucoside, pelargonidin-3-*O*-glucoside, and pelargonidin-3,5-di-*O*-glucoside (Lansky and Newman 2007; Jaiswal and others 2010). The main differences between them are the number of hydroxylated groups, the nature and the number of bonded sugars to their structure, the aliphatic or aromatic carboxylates bonded to the sugar in the molecule, and the position of these bonds (Kong and others 2003). The phenolic acids present in pomegranate juice (Figure 2b) can be divided into 2 groups: (1) hydroxybenzoic acids, mainly gallic acid and ellagic acid (EA) (Amakura and others 2000); and (2) hydroxycinnamic acids, principally caffeic acid, chlorogenic acid, and *p*-coumaric acid (Poyrazoglu and others 2002).

Tannins

Tannins are high-molecular-weight plant polyphenols divided into 3 chemically and biologically distinct groups: condensed tannins or proanthocyanidins (as found in tea, grapes, cranberries, and so on) and hydrolyzable tannins or ETs (as in raspberries, strawberries, and so on) as well as gallotannins (GTs) (Seeram and others 2005a). Pomegranate peel is rich in hydrolyzable tannins (Figure 3), mainly punicalin, pedunculagin, and punicalagin (Seeram and others 2005b). They differ from proanthocyanidins in their chemical structures. ETs are esters of hexahydroxydiphenic acid and a polyol, usually glucose or quinic acid (Clifford and Scalbert 2000). In addition to ETs, pomegranate peel contains hydroxybenzoic acids such as gallagic, EA, and EA glycosides (Amakura and others 2000); anthocyanidins are principally cyanidin, pelargonidin, and delphinidin (Noda and others 2002) and flavonoids such as kaempferol, luteolin, and quercetin (Van Elswijk and others 2004).

Bioavailability of Pomegranate Bioactive Compounds

Although the evidence in favor of pomegranate use is very promising, extensive studies are required to fully understand its possible contribution to human health before recommending its regular consumption (Syed and others 2007). Little is known about the absorption, bioavailability, biodistribution, and metabolism of the principal bioactive compounds present in pomegranates and in other fruits, such as phenolic acids, flavonoids, and tannins, although they probably share common pathways (Petti and Scully 2009). Aglycones, that is, the nonconjugated forms, are generally absorbed intact from the digestive tract, while esters, glycosides, or polymers must be hydrolyzed before being absorbed (Petti and Scully 2009). An *in vitro* digestion study of pomegranate juice showed that pomegranate phenolic compounds are available during the digestion in a quite high amount (29%). Nevertheless, due to pH, anthocyanins are largely transformed into non-red forms and/or degraded (97%), and similar results are obtained for vitamin C (Pérez-Vicente and others 2002).

Oral and intestinal microorganisms also are responsible for polyphenol and tannin degradation into aglycones and, occasionally, the production of various simple aromatic acids (Petti and Scully 2009). Thus, Cerdá and others (2004) conducted a study, in which 6 healthy subjects consumed 1 L of pomegranate juice daily for 5 d, showed that ETs from pomegranate juice were metabolized by the colonic microflora into bioavailable urolithins (hydroxy-6H-dibenzopyran-6-one derivatives). In another case study, Seeram and others (2004) conducted an *in vivo* study whereby a human subject consumed pomegranate juice (180 mL) containing EA (25 mg) and hydrolyzable ETs (318 mg, as punicalagins). They concluded that EA was detected in human plasma at a maximum concentration (31.9 ng/mL) after 1 h postingestion but was rapidly eliminated by 4 h. In a studied carried out by Seeram and others (2006), 18 healthy subjects were given 180 mL of PJ concentrate, that contained the following polyphenols: anthocyanins, 387 mg/L; punicalagins, 1561 mg/L; EAs, 121 mg/L; and other hydrolyzable tannins, 417 mg/L. These researchers reported that EA metabolites, including dimethylellagic acid glucuronide (DMEAG) and hydroxy-6H-benzopyran-6-one derivatives (urolithins) were present in the plasma and urine in conjugated and free forms. DMEAG was found in the urine from the subjects on the day of ingestion, demonstrating its potential as a biomarker of pomegranate intake. Seeram and others (2008a) established the bioavailability of polyphenols from pomegranate juice and liquid and powder pomegranate extracts. Thus, 16 healthy volunteers sequentially consumed, with a 1-wk washout period between treatments, pomegranate juice (240 mL, Wonderful fruit variety), a pomegranate polyphenol liquid extract (240 mL), and a pomegranate polyphenol powder extract (1 g). The 3 interventions provided 857, 776, and 755 mg of polyphenols as gallic acid equivalents, respectively. Plasma bioavailability, judged

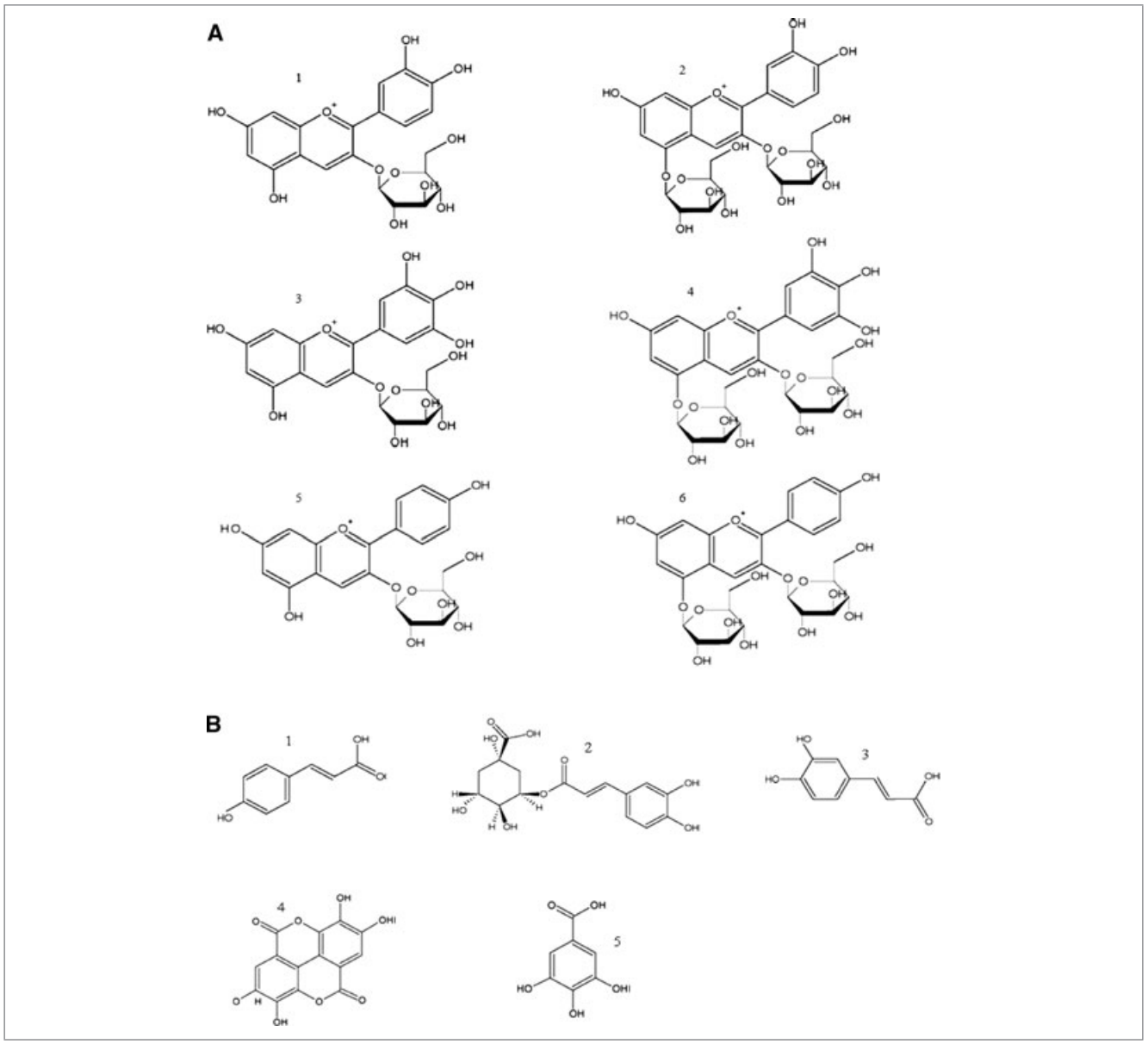

Figure 2–(2A) Principal anthocyanins present in pomegranate juice. 1: cyanidin-3-*O*-glucoside; 2: cyanidin-3,5-di-*O*-glucoside; 3: delphinidin-3-*O*-glucoside; 4: delphinidin-3,5-di-*O*-glucoside; 5: pelargonidin-3-*O*-glucoside; 6: pelargonidin-3,5-di-*O*-glucoside. (2B) Principal phenolic acids present in pomegranate juice: 1: *p*-coumaric acid; 2: chlorogenic acid; 3: caffeic acid; 4: EA; 5: gallic acid.

by EA levels over a 6-h period, did not show statistical differences in the area under the curve for the 3 interventions: 0.14 ± 0.05, 0.11 ± 0.03, and 0.11 ± 0.04 μmol·h/L for pomegranate juice, polyphenol liquid extract, and polyphenol powder extract, respectively. The time of maximum concentration was delayed in the case of polyphenol powder extract (2.58 ± 0.42 h) compared with pomegranate juice (0.65 ± 0.23 h) and polyphenol liquid extract (0.94 ± 0.06 h) (Seeram and others 2008a).

Mertens-Talcott and others (2006) demonstrated the absorbability of EA from a pomegranate extract high in ellagitannin content and its *ex vivo* antioxidant effects. For this they conducted a study with 11 healthy subjects. Each subjects received 2 capsules contained 400 mg of pomegranate extract. The 800 mg of extract used in this study contained 330.4 mg of the major ETs punicalagins and 21.6 mg of ellatic acid. Results indicate that EA from the extract is bioavailable, with an observed C_{max} of 33 ng/mL at t_{max} of 1 h. Thus, on the basis of limited human studies, it appears that the estimation of the bioavailability of pomegranate polyphenols is affected by several factors, including individual variability, differential processing of pomegranate juice, and the analytical techniques used, which need to be sensitive enough to detect low postprandial concentrations of these metabolites (Basu and Penugonda 2009).

Pomegranate as Functional Food

There is no one definition of the term functional food, which is used in many contexts, including references to technological advances, food marketing, and food regulatory norms (Palou and

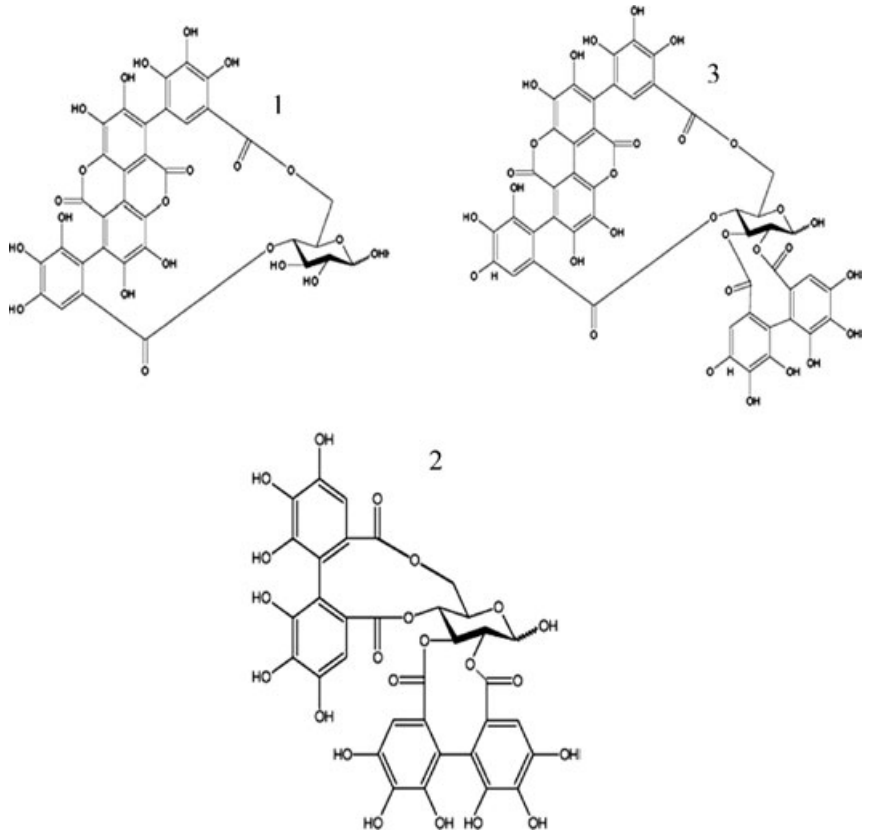

Figure 3–Principal ETs present in pomegranate peel. 1: punicalin; 2: pedunculagin; 3: punicalagin.

others 2003). This term has already been defined several times (Roberfroid 2002) and there is still no unitary accepted definition for this group of foods (Alzamora and others 2005). In most countries, there is no legal definition of the term and drawing a border line between conventional and functional foods is challenging even for nutrition and food experts (Niva 2007).

Several working definitions used by professional groups and marketers have been proposed by various organizations in several countries.

In the United States, functional foods are not officially recognized as a regulatory category by the FDA. However, several organizations have proposed definitions for this rapidly growing food category, most notably the Intl. Food Information Council (IFIC) and the Institute of Food Technologists. The IFIC considers as functional foods those that include any food or food component that may have health benefits beyond basic nutrition (IFIC 2009). Similarly, a recent report of the Institute of Food Technologists (IFT 2009) defined functional foods as "foods and food components that provide a health benefit beyond basic nutrition (for the intended population). These substances provide essential nutrients often beyond quantities necessary for normal maintenance, growth, and development, and/or other biologically active components that impart health benefits or desirable physiological effects."

The European Commission (EC) Concerted Action on Functional Food Science in Europe regards a food as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease. In this context, functional foods are not pills or capsules, but must remain foods and they must demonstrate their effects in amounts that can normally be expected to be consumed in the diet (E.C. 1999).

The concept of functional food is complex and may refer to many possible aspects, including food obtained by any process, whose particular characteristic is that one or more of its components, whether or not that component is itself a nutrient, affects the target function of the organism in a specific and positive way, promoting a physiological or psychological effect beyond the merely nutritional (Viuda-Martos and others 2010a).

The positive effect of a functional food may include the maintenance of health or well-being, or a reduction in the risk of suffering a given illness (Pérez-Álvarez and others 2003). Functional food may be obtained by modifying one or more of the ingredients, or by eliminating the same (Pérez-Álvarez and others 2003). To develop these types of products, one must evaluate consumer perceptions, the most important quality aspects being that they taste good, appear wholesome, and have nutritional value (García-Segovia and others 2007). Also, Pérez-Alvarez (2008) describes that any functional food must be safe, wholesome, and tasty.

Pomegranate fruit conforms to this definition in several ways, although the establishment of any function would involve identifying the bioactive components to help specify their possible beneficial effects on health.

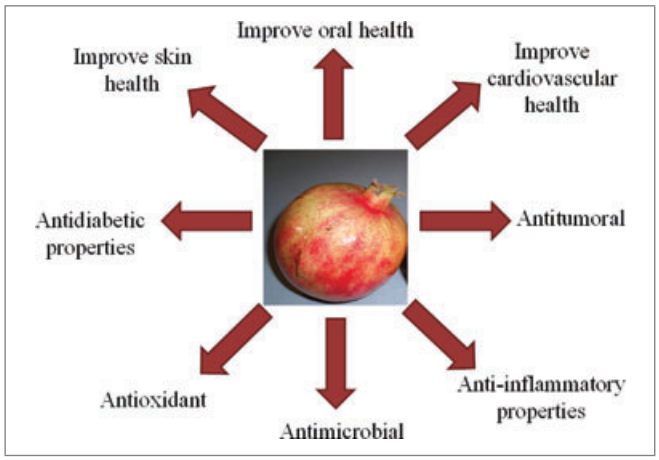

Figure 4–Principal functional and medicinal effects of pomegranate.

Functional Properties

At present, there is a great interest in the scientific community in the functional properties of pomegranate. Science Direct (2010) database now cites 770 scientific papers relating the functional properties (antioxidant, antimicrobial, or to fight vascular diseases, diabetes, and cancer) of pomegranate and its derivates such as juice, seed oil, peel, and so on. However, these effects need to have stronger scientific support.

The pomegranate fruit could be considered a functional food because it has valuable compounds in different parts of the fruit that display functional and medicinal effects (Figure 4). These can act as antioxidant (Çam and others 2009), as antitumoral (Hamad and Al-Momene 2009) or antihepatotoxic (Celik and others 2009) agents, and improve cardiovascular health (Davidson and others 2009). They have been seen to have antimicrobial (Duman and others 2009), antiinflammatory (Lee and others 2010), antiviral (Haidari and others 2009), antidiabetic (Xu and others 2009) properties, and they can improve oral (Di Silvestro and others 2009) and skin (Aslam and others 2006) health. They help prevent Alzheimer's disease (Singh and others 2008) and improve sperm quality (Türk and others 2008) and erectile dysfunction in male patients (Forest and others 2007). However, few well-controlled clinical trials have been completed and these effects have not been solidly established. We agree with Lansky and Newman (2007) who indicated that much deeper investigation into this rapidly growing field is required to assess the overall value and safety of pomegranate as an intact fruit or of various extracts derived from pomegranate components.

Cardiovascular Health

One of the major risk factors for the development of coronary heart disease is dyslipidemia, which is mainly characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C) and/or reduced high-density lipoprotein cholesterol (HDL-C) (Esmaillzadeh and Azadbakht 2008). Oxidation of low-density lipoprotein (LDL) is thought to contribute to atherosclerosis and cardiovascular disease (Heinecke 2006). Oxidation of LDL lipids is thought to render the lipoprotein atherogenic, because oxidized LDL is more readily taken up by macrophages via scavenger receptors (Heinecke 1998).

Epidemiological studies have shown that high concentrations of serum total cholesterol and LDL-C are independent risk factors for cardiovascular disease (Russo and others 2008) and could produce atherosclerosis. Atherosclerosis, a major degenerative disease of arteries involves a series of inflammatory and oxidative modifications within the arterial wall (Fan and Watanabe 2003). Oxidative excess in the vasculature reduces levels of the vasodilator nitric oxide, causes tissue injury, promotes protein oxidation and DNA damage, and induces proinflammatory responses (Xu and Touyz 2006). Oxidative stress induces inflammation by acting on the pathways that generate inflammatory mediators like adhesion molecules and pro-inflammatory cytokines (Valko and others 2007).

In vitro, animal, and human trials (Table 2) have examined the effects of various pomegranate constituents on the prevention and attenuation of atherosclerosis and LDL oxidation (Aviram and others 2000; Fuhrman and others 2005; Ignarro and others 2006; Sezer and others 2007; Basu and Penugonda 2009; Davidson and others 2009; Fuhrman and others 2010).

Aviram and others (2000) analyzed the effect of pomegranate juice consumption by healthy males on lipoprotein oxidation and found that it decreased LDL susceptibility to aggregation and retention and increased the activity of serum paraoxonase (an HDL-associated esterase that can protect against lipid peroxidation) by 20%. Sezer and others (2007) compared the total phenol content and the antioxidant activity to make a comparison between pomegranate and red wines. The phenol levels of pomegranate and red wines (4850 and 815 mg/L gallic acid equivalents, respectively) were in accordance with their total antioxidant activity (39.5% and 33.7%, respectively). Both wines decreased LDL-diene levels following a 30-min incubation period compared with controls (145 μmol/mg of LDL protein). However, pure pomegranate wine demonstrated a greater antioxidant effect on diene level (110 μmol/mg of LDL protein) than pure red wine (124 μmol/mg of LDL protein). Esmaillzadeh and others (2006) investigated the effect of concentrated pomegranate juice consumption (40 g) on lipid profiles of type II diabetic patients with hyperlipidemia (total cholesterol or triglycerides $\geq$ 200 mg/dL). At the end of assay (8 wk) there were no significant changes in serum triacylglycerol and HDL-c concentrations. However, reductions were obtained in total cholesterol (5.43%), LDL cholesterol (9.24%), total/HDL cholesterol ratio (7.27%), and LDL/HDL ratio (11.76%). Fuhrman and others (2005) reported that pomegranate juice exerts a direct effect on macrophage cholesterol metabolism by reducing cellular uptake of oxidized LDL and inhibiting cellular cholesterol biosynthesis. Both of these processes eventually lead to a reduction in macrophage cholesterol accumulation and foam cell formation and attenuation of atherosclerosis development. De Nigris and others (2006) suggest that pomegranate juice can exert beneficial effects on the evolution of clinical vascular complications, coronary heart disease, and atherogenesis in humans by enhancing the endothelial nitric-oxide synthase (NOSIII) bioactivity because the pomegranate juice reverts the potent down-regulation of the expression of NOSIII induced by oxidized low-density liporotein (oxLDL) in human coronary endothelial cells. Ignarro and others (2006) investigated the effects of pomegranate juice for its capacity to protect nitric oxide against oxidative destruction and enhance the biological actions of nitric oxide. The results demonstrate that pomegranate juice was found to be a potent inhibitor of superoxide anion-mediated disappearance of nitric oxide. Pomegranate juice was much more potent than Concord grape juice, blueberry juice, red wine, ascorbic acid, and DL-α-tocopherol. As little as 3 μL of a 6-fold dilution of pomegranate juice, in

Table 2–Overview of *in vivo* clinical trials.

In vivo studies	Clinical status	Part of the plant	Dose	Time (d)	Effect	Reference
Albino Wistar rats	Diabetic	Aqueous flower extracts	250 mg/kg/d	21	Reduction: total cholesterol, triglycerides, LDL-cholesterol, VLDL-cholesterol. Increase: HDL-cholesterol	Bagri and others (2009)
Albino Wistar rats	Diabetic	Methanolic peel extract	20 mg/kg/d	28	Increase the activities of antioxidant enzymes catalase, superoxide dismutase, glutathione peroxidase, glutathione-S-transferase, and glutathione reductase, in liver and kidney	Althunibat and others (2010)
Albino Wistar rats	Healthy	Methanolic peel extract	50 mg/kg/d	28	Protective effect of antioxidant enzymes catalase, peroxidase, superoxide dismutase	Murthy and others (2002)
Mice	Healthy	Pomegranate juice	—	28	Protective effect of antioxidant enzymes catalase, glutathione-S-transferase, glutathione reductase, superoxide dismutase, glutation synthetase	Faria and others (2007)
Albino Wistar rats	Healthy	EA	60 mg/kg/d	45	Decreased: Total cholesterol, free fatty acids, triglycerides and phospholipids	Devipriya and others (2008)
Albino Sprague–Dawley rats	Hyperlipidemic	Peel extract	5%, 10%, 15%	28	Reduction: Total cholesterol, LDL-cholesterol, triglycerides. VLDL-cholesterol	Hossin (2009)
Zucker rats	Diabetic	Flower extract	500 mg/kg/d	Long term	Reduced cardiac triglycerides content, decreased plasma levels of triglycerides and total cholesterol Reduced plasma fatty acid	Huang and others (2009)
Humans	Type II diabetic patients with hyperlipidemia	Concentrated pomegranate juice	40 g/d	56	Reduction: Total cholesterol, (LDL)-cholesterol, LDL cholesterol/HDL-cholesterol and total cholesterol/HDL-cholesterol	Esmaillzadeh and others (2004)
Humans	Type II diabetic patients	Pomegranate juice	50 mL/d	90	Decreased lipid peroxidation levels and cellular uptake of oxidized LDL	Rosenblat and others (2006c)
Humans	Healthy	Pomegranate pulp juice	250 mL/d	28	Increased plasma antioxidant capacity and decreased plasma carbonyl content	Guo and others (2008)
Humans	Healthy	Pomegranate fresh fruit	100 g	10	Increased plasma antioxidant capacity	Hajimahmoodi and others (2009)

a reaction volume of 5000 μL, produced a marked antioxidant effect, whereas 300 μL of undiluted blueberry juice or nearly 1000 μL of undiluted Concord grape juice were required to produce similar effects. Rosenblat and others (2006a) investigated the anti-atherosclerotic effects of a pomegranate co-product extract after the juice was removed. Mice with significant atherosclerosis were given pomegranate co-product extract (containing 51.5 μg gallic acid equiv/kg/d) with an 8-fold higher polyphenol concentration than pomegranate juice for 3 mo. This resulted in a significant reduction in oxidative status as evidenced by a 27% decrease in total macrophage peroxide levels, a 42% decrease in cellular lipid peroxide levels, and a 19% decrease in peritoneal macrophage uptake of oxidized LDL.

Aviram and others (2000) described how pomegranate juice inhibited atherogenic modifications of LDL, including its retention, oxidation, and aggregation. The antiatherogenicity capability of pomegranate juice is related to 3 components of atherosclerosis: plasma lipoproteins, arterial macrophages, and blood platelets. The potent antioxidative capacity of pomegranate juice against lipid peroxidation may be the central link for the antiatherogenic effects of pomegranate juice on lipoproteins, macrophages, and platelets. Basu and Penugonda (2009) suggested that the principal mechanisms of action of pomegranate juice is antiatherogenic and may include the following: increased serum antioxidant capacity, decreased plasma lipids and lipid peroxidation, decreased oxidized-LDL uptake by macrophages, decreased intima media thickness, decreased atherosclerotic lesion areas, enhanced biological actions of nitric oxide, decreased inflammation, decreased angiotensin-converting enzyme activity, and decreased systolic blood pressure, thereby causing an overall favorable effect on the progression of atherosclerosis and the subsequent potential development of coronary heart disease. Indeed, Aviram and Dornfeld (2001) reported that consumption of pomegranate juice, which is rich in tannins; possess antiatherosclerotic properties that could be related to its potent antioxidative characteristics.

Aviram and others (2004) conducted a study where 10 patients were supplemented with pomegranate juice for 1 y and 5 of them continued for up to 3 y. In the control group that did not consume pomegranate juice, common carotid intima-media thickness (IMT) increased by 9% during 1 y, whereas, pomegranate juice consumption resulted in a significant IMT reduction, by up to 30%, after 1 y. Furthermore, serum levels of antibodies against oxidized LDL were decreased by 19%, and in parallel serum total antioxidant status (TAS) was increased by 130% after 1 y of pomegranate juice consumption. Indeed, systolic blood pressure was reduced (21%) after 1 y of pomegranate juice consumption. Sumner and others (2005) carried out a study whether daily consumption of pomegranate juice for 3 mo would affect myocardial perfusion in patients who had coronary heart disease and myocardial ischemia. The experimental and control groups showed similar levels of stress-induced ischemia. After 3 mo, the extent of stress-induced ischemia decreased in the pomegranate group but increased in the control group. This benefit was observed without changes in cardiac medications, blood sugar, hemoglobin A1c, weight, or blood pressure in either group.

High blood pressure or hypertension is one of the most prevalent cardiovascular risk factors and the single greatest contributor to cardiovascular disease worldwide (López and others 2006). Aviram and others (2004) reported that, after 1 y of pomegranate juice consumption, systolic blood pressure was reduced by 21%, an effect the researchers believed to be related to the particularly potent antioxidant properties of pomegranate polyphenols. In a similar study, Aviram and Dornfeld (2001) examined the effect of pomegranate juice consumption (50 mL, 1.5 mmol of total polyphenols per day, for 2 wk) in hypertensive patients on their blood pressure and on serum angiotensin converting enzyme (ACE) activity. These researchers reported a 36% decrement in serum ACE activity and a 5% reduction in systolic blood pressure were noted.

Antiinflammatory Activity

Inflammation, the first physiological defense system in the human body, can protect against injuries caused by physical wounds, poisons, and so on. This defense system, also called short-term inflammation, can destroy infectious microorganisms, eliminate irritants, and maintain normal physiological functions; however, long-term over-inflammation might cause such dysfunctions of the regular physiology as asthma and rheumatic arthritis (Lee and others 2010). The inflammatory process is triggered by several chemical and/or biological aspects that include pro-inflammatory enzymes and cytokines, low-molecular-weight compounds such as eicosanoids, or the enzymatic degradation of tissues (Dao and others 2004). Several studies (Cho and others 2004) have related cyclooxigenase-2 (COX-2) to the inflammatory process. This enzyme is an isoform of cyclooxigenase (COX), which is responsible for catalyzing arachidonic acid to prostaglandin. The other isoform is cyclooxigenase-1 (COX-1), which regulates homeostasis processes (Dao and others 2004). Many studies have pointed to the antiinflammatory properties of pomegranate fruit (Lansky and Newman 2007; Shukla and others 2008; Larrosa and others 2010; Lee and others 2010).

Boussetta and others (2009) reported that punicic acid, a conjugated fatty acid present in pomegranate seed oil has an *in vivo* antiinflammatory effect by limiting neutrophil activation and lipid peroxidation consequences. Lee and others (2010) analyzed 4 hydrolyzable tannins, punicalagin, punicalin, strictinin A, and granatin B, isolated from pomegranate by bioassay-guided fractionation. Each of them displayed a dose-dependent and significant inhibitory effect on nitric oxide production in *in vitro* studies. Furthermore, granatin B inhibited PGE2 production and COX-2 expression in *in vitro* studies to a greater extent than the others. The components of pomegranate juice thus might appear to synergistically suppress inflammatory cytokine expression. More recently, a whole pomegranate methanol extract was also shown to inhibit, in a dose-dependent manner, the production and expression of TNFα in microglial cells, in which inflammation had been induced by lipopolysaccharide (Jung and others 2006). Ahmed and others (2005) suggested that pomegranate fruit extract had an antiinflammatory effect in different disease models and protected chondrocytes against IL-1-induced expression of matrix metalloproteinases by inhibiting the activation of kinases and NF-κβ in human chondrocytes *in vitro*. De Nigris and others (2007) reported that supplementation of an atherogenic diet fed to obese rats with pomegranate juice or pomegranate fruit extract led to a significant decrease in the expression of vascular inflammation markers, thrombospondin (TSP), and cytokine-transforming growth factor-β1 (TGF- β1). Arterial endothelial-nitric oxide synthase (eNOS) expression was significantly increased in animals fed a diet supplemented with pomegranate juice or pomegranate fruit extract, in comparison to controls. Romier-Crouzet and others (2009) reported that pomegranate extract could be particularly promising for dietary prevention of inflammation: it inhibited cytokine IL-8, prostaglandin PGE2, and nitric oxide secretion,

due to the action of the EA present in pomegranate. Larrosa and others (2010) showed that pomegranate extract supplementations led to a decrease in prostaglandin E_2 (PGE2) levels in the colon mucosa by down-regulating the over-expressed COX-2 and prostaglandin E synthase (PTGES) levels due to the action of EA.

Antitumoral Properties

Many of the nonnutritive components of fruits and vegetables are known to possess potential activity as chemoprotective agents against cancer. Among the action mechanisms proposed for these compounds are (Tanaka and Sugie 2008): (1) inhibition of the phase I enzymes or blockage of carcinogen formation; (2) induction of phase II (detoxification) enzymes; (3) the scavenging of DNA-reactive agents; (4) modulation of homeostatic hormones; (5) suppression of hyper-cell proliferation induced by carcinogens; (6) induction of apoptosis; (7) depression of tumor angiogenesis; and (8) inhibition of phenotypic expressions of preneoplastic and neoplastic cells.

Several studies have since been conducted to evaluate the efficacy of pomegranate fruit and derivates endowed with a very high antioxidant activity as an antiproliferative, antiinvasive, and pro-apoptotic agent in various cancer cell lines and animal models (Afaq and others 2005; Lansky and others 2005a, 2005b; Lansky and Newman 2007; Syed and others 2007; Hong and others 2008; Hamad and Al-Momene 2009).

Lansky and others (2005a) demonstrated what appears to be synergy in the interactions of the extracts from the 3 pomegranate compartments (peels, juice, and seeds) in inhibiting prostate cancer cell proliferation, invasion and phospholipase A-2 expression. In this way, Hong and others (2008) demonstrated that pomegranate juice and pomegranate extracts were more potent inhibitors of cell growth than isolated individual polyphenols in cell lines, suggesting synergistic and/or additive effects of several phytochemicals present including proanthocyanidins, anthocyanins, and flavonoid glycosides.

Topical pretreatment with acetone extract of whole pomegranate fruits (2 mg/mouse) prior to 12-*O*-tetradecanoylphorbol 13-acetate applications in treated mice decreased the tumor incidence from 100% to 30% and increased the latency of tumor development from week 9 to 14 (Afaq and others 2005). Albrecht and others (2004) studied the effects of pomegranate cold-pressed oil or supercritical extracted seed oil, fermented juice polyphenols, and pericarp polyphenols on human prostate cancer cell xenograft growth *in vivo*, and/or proliferation, cell cycle distribution, apoptosis, gene expression, and invasion across Matrigel™, *in vitro*. Oil, fermented juice polyphenols, and pericarp polyphenols each acutely inhibited *in vitro* proliferation of LNCaP, PC-3, and DU 145 human cancer cell lines, demonstrates significant antitumor activity of pomegranate-derived materials against human prostate cancer. Kohno and others (2004) indicated that the administration of pomegranate seed oil in the diet significantly inhibited the incidence and the multiplicity of colonic adenocarcinomas in rats. The inhibition of colonic tumors by pomegranate seed oil was associated with an increased content of conjugated linolenic acids in the lipid fraction of the colonic mucosa and liver. Also, the administration of pomegranate seed oil in the diet heightened the expression of peroxisome proliferators-activated receptor (PPAR) γ protein in the nontumor mucosa. Toi and others (2003) studied a possible effect on angiogenic regulation by measuring vascular endothelial growth factor (VEGF), interleukin-4 (IL-4), and migration inhibitory factor (MIF) in the conditioned media of estrogen sensitive (MCF-7) or estrogen resistant (MDA-MB-231) human breast cancer cells, or immortalized normal human breast epithelial cells (MCF-10A), grown in the presence or absence of pomegranate seed oil or fermented juice polyphenols. VEGF was strongly downregulated in MCF-10A and MCF-7, and MIF upregulated in MDA-MB-231, overall showing significant potential for downregulation of angiogenesis by pomegranate fractions.

Kim and others (2002) analyzed, *in vitro*, for possible chemopreventive or adjuvant therapeutic potential in human breast cancer some pomegranate products such as fermented juice, aqueous pericarp extract, and cold-pressed or supercritical CO2-extracted seed oil. The ability to effect a blockade of endogenous active estrogen biosynthesis was shown by polyphenols from fermented juice, pericarp, and oil, which inhibited aromatase activity by 60% to 80%. Fermented juice and pericarp polyphenols, and whole seed oil, inhibited 17-beta-hydroxysteroid dehydrogenase Type 1 from 34% to 79%, at concentrations ranging from 100 to 1000 μg/mL according to seed oil >> fermented juice polyphenols > pericarp polyphenols.

There is evidence that pomegranate juice significantly suppresses TNFα-induced COX-2 protein expression, NF-κB binding, and AKT activation in these cells, significant interactions with other bioactive polyphenols present in juice such as anthocyanins and flavonols may be responsible for this enhanced antiproliferative activity (Adams and others 2006). Seeram and others (2005b) reported that pomegranate juice showed greatest antiproliferative activity against all cell lines by inhibiting proliferation from 30% to 100%. At 100 μg/mL, pomegranate juice, EA, punicalagin, and total pomegranate tannins induced apoptosis in HT-29 colon cells. However, in the HCT116 colon cells, EA, punicalagin, and total pomegranate tannins, but not pomegranate juice, induced apoptosis (Seeram and others 2005b). Lansky and others (2005b) reported that EA, caffeic acid, luteolin, and punicic acid, all important pomegranate components, significantly inhibited the *in vitro* invasion of human PC-3 prostate cancer cells when used individually.

Fjaeraa and Nanberg (2009) showed that EA induced cell detachment, decreased cell viability, and induced apoptosis, as measured by DNA strand breaks and alterations in the cell cycle. Anthocyanins decreased the proliferation of colon cancer HT-29 cells in a concentration-dependent manner, whereas rutin, epicatechin, chlorogenic acid, or p-hydroxybenzoic acid did not show any significant growth inhibitory effect (Wu and others 2007). González-Sarrías and others (2009) suggest that EA and its colonic metabolites, urolithin-A and -B, at concentrations achievable in the lumen from the diet, might contribute to colon cancer prevention by modulating the expression of multiple genes in epithelial cells lining the colon. Some of these genes are involved in key cellular processes associated with cancer development and are currently being investigated as potential chemopreventive targets. Anthocyanins induced apoptosis in colon cancer cells, since DNA fragmentation and an inbalance between Bax and Bcl-2 mRNA expressions were observed (Wu and others 2007). Gallic acid inhibited both COX-1 and -2, accompanied by a dose-dependent induced apoptosis (Madlener and others 2007). Punicalagin impeded the activation of TNF-α-induced COX-2 protein expression or chemokines and prostaglandin-E2 production, respectively, in colon cancer cells (Adams and others 2006). Hong and others (2008) reported that pomegranate juice and pomegranate extract and their polyphenols showed a capacity to arrest proliferation and stimulate

apoptosis in human androgen-dependent and androgen-independent prostate cancer cells. The inhibition of gene expression involved in androgen-synthesizing enzymes may contribute to the growth-inhibitory effects of pomegranate polyphenols and may provide a molecular target for the inhibition of the emergence of androgen-independent prostate cancer (Hong and others 2008). Pantuck and others (2006) investigated whether pomegranate juice consumption had any effect on growth rates or apoptosis of LNCaP prostate cancer cells in culture. Serum collected 9 mo after the beginning of the study and incubated with LNCaP showed a 12% decrease in cell growth in patients compared to the baseline. An average 17.5% increase in apoptosis in patients was also noted. This study indicates pomegranate juice or pomegranate juice constituents may be a promising therapy for prostate cancer. Koyama and others (2010) indicated that treatment of LAPC4 prostate cancer cells with 10 μg/mL pomegranate extracts prepared from skin and arils minus seeds and standardized to an ellagitannin content of 37% punicalagins, resulted in the inhibition of cell proliferation and induction of apoptosis. Schubert and others (2002) have shown that pomegranate wine may serve as a potent inhibitor of NF-κB in vascular endothelial cells. It has been shown that pomegranate seed oil and polyphenols in the fermented juice retard oxidation and prostaglandin synthesis, inhibit breast cancer cell proliferation and invasion, and promote breast cancer cell apoptosis. In a study employing human prostate cancer cells, Malik and others (2005) evaluated the antiproliferative and proapoptotic properties of pomegranate fruit extract. Pomegranate fruit extract (10 to 100 μg/mL; 48 h) treatment of highly aggressive human prostate cancer PC3 cells resulted in a dose-dependent inhibition of cell growth, cell viability and induction of apoptosis.

Antidiabetic Properties

Diabetes is the most common metabolic disease in the world and is still increasing. The Intl. Diabetes Federation mentioned that 194 million people had diabetes in 2003, which will increase to 333 million by 2025 (Sicree and others 2003). According to the World Health Org., it is the 3rd-most prevalent disease after cardiovascular and oncological disorders. One of the ways to control diabetes mellitus is through the diet and it is here that pomegranate fruits and derivates can play a part. Indeed, numerous studies have described their antidiabetic activity (Huang and others 2005; Li and others 2005; Katz and others 2007; Parmar and Kar 2007; Li and others 2008; Bagri and others 2009).

For example, Katz and others (2007) reported on the hypoglycemic activity of flowers, seeds, and juice of pomegranate. The mechanisms for such effects are largely unknown, though recent research suggests pomegranate flowers and juice may prevent diabetic sequelae via peroxisome proliferator-activated receptor-γ binding and nitric oxide production. Pomegranate compounds associated with antidiabetic effects include oleanolic, ursolic, and gallic acids. Li and others (2005) suggest that pomegranate flower extract improves postprandial hyperglycemia in type 2 diabetes and obesity, at least in part, by inhibiting intestinal α-glucosidase activity.

However, Huang and others (2005) demonstrated a potential mechanism for the antidiabetic action of pomegranate flower extract which involved the activation of PPAR-γ. Gallic acid, a component widely distributed in antidiabetic and antiinflammatory herbal medicines, has been shown to be the component most responsible for this activity *in vitro*; in addition, caffeic acid (another component) increases glucose uptake by rat adipocytes and mouse myoblasts (Hsu and others 2000). Jafri and others (2000) reported that oral administration of an aqueous-ethanolic (50%, v/v) extract of pomegranate flowers had a significant blood glucose lowering effect in normal, glucose-fed hyperglycemic and alloxan-induced diabetic rats. This effect of the extract was maximum at 400 mg/kg.

Parmar and Kar (2007) reported that the administration of 200 mg/kg of pomegranate peel extract normalized all the adverse changes induced by alloxan, a widely used compound for inducing diabetes mellitus since it increases the serum levels of glucose and α-amylase activity and the rate of water consumption and lipid peroxidation in hepatic, cardiac, and renal tissues, while decreasing serum insulin levels (Szkudelski 2001), underlining the antidiabetic and antiperoxidative potential of pomegranate peel extracts. Das and others (2001) investigated the hypoglycemic activity of pomegranate seed extract in rats made diabetic by streptozotocin. The seed extract (300 and 600 mg/kg, orally) caused a significant reduction of blood glucose levels in induced diabetic rats of 47% and 52%, respectively, after 12 h.

The main compounds that present antidiabetic properties are polyphenols, which may affect glycemia through different mechanisms, including the inhibition of glucose absorption in the gut or of its uptake by peripheral tissues (Scalbert and others 2005). The hypoglycemic effects of diacetylated anthocyanins in a 10 mg/kg diet dosage were observed when maltose was the glucose source, but not with sucrose or glucose itself (Matsui and others 2002).

This suggests that such effects are due to the inhibition of α-glucosidase in the gut mucosa. Several *in vitro* studies in cultured cells have shown that polyphenols may increase glucose uptake by peripheral tissues, which would diminish glycemia (Scalbert and others 2005). The mechanisms include inhibition of gluconeogenesis (Waltner-Law and others 2002), adrenergic stimulation of glucose uptake (Cheng and Liu 2000), and stimulation of insulin release by pancreatic β-cells (Ohno and others 1993).

Improving Skin Health

Damage to the skin occurs as a consequence of the natural aging process and damage is exacerbated in chronically sun exposed skin (photoaging) (Lavker 1995). Prolonged exposure to ultraviolet (UV) radiation has been identified as a cause of serious adverse effects to human skin, including oxidative stress, premature skin aging, sunburn, immunosuppression, and skin cancer (Widmer and others 2006). Aslam and others (2006) reported that pomegranate seed oil, but not aqueous extracts of fermented juice, peel, or seed cake was shown to stimulate keratinocyte proliferation in monolayer culture. In contrast, pomegranate peel extract (and to a lesser extent, both the fermented juice and seed cake extracts) stimulated type I procollagen synthesis and inhibited matrix metalloproteinase-1 (MMP-1; interstitial collagenase) production by dermal fibroblasts, but had no growth-supporting effect on keratinocytes. These results suggest pomegranate aqueous extracts (especially of pomegranate peel) promoting regeneration of dermis, and pomegranate seed oil promoting regeneration of epidermis.

Pacheco-Palencia and others (2008) described the protective and chemopreventive properties of standardized PEs in human skin fibroblasts against UVA- and UVB-induced damage. The protective effects of pomegranate polyphenolics against UVA- and UVB-induced cell death of human skin fibroblasts may be attributed to reduced generation of intracellular ROS and increased intracellular antioxidant capacity. Afaq and others (2009) suggest that pomegranate-derived products may be useful against UVB-induced damage to human skin due to these products inhibited

UVB-induced MMP-2 and MMP-9 activities and also caused a decrease in UVB-induced protein expression of c-Fos and phosphorylation of c-Jun. Yoshimura and others (2005) found that orally administered pomegranate extract containing 90% EA inhibited UV-irradiated pigmentation on brownish guinea pig skin and suggested that pomegranate extract had a whitening effect on the skin after oral administration. This effect was probably due to inhibition of the proliferation of melanocytes and melanin synthesis by tyrosinase in the melanocytes. Syed and others (2006) suggested that pomegranate extract can protect against UVA-mediated cellular damage that occurs primarily through the release of reactive oxygen species and is responsible for immunosuppression, photodermatoses, photoaging, and photocarcinogenesis due to its extract is an effective agent for ameliorating UVA-mediated damages by modulating cellular pathways and merits further evaluation as a photochemopreventive agent.

Improving Oral Health

Pomegranate contains agents, especially polyphenolic flavonoids, which exert actions that could be considered conducive to good oral health, particularly in relation to gingivitis development (Di Silvestro and others 2009).

Vasconcelos and others (2003) reported that a gel containing pomegranate extract applied 3 times per day for 15 d was effective for patients afflicted by candidiasis associated with denture stomatitis. Mouth-rinsing with pomegranate extracts lowered saliva activities of aspartate aminotransferase, an indicator of cell injury that shows high values with periodontal disease (Nomura and others 2006). Indeed, Menezes and others (2006) studied the effect of the hydroalcoholic extract from pomegranate fruits on dental plaque microorganisms. These authors reported that the hydroalcoholic extract was very effective against dental plaque microorganisms, decreasing the CFU/mL by 84% (CFU × 10[5]) and it may be a possible alternative for the treatment of dental plaque bacteria. Additionally, rinsing the mouth for 1 min with a mouthwash containing pomegranate extract effectively reduced the amount of microorganisms cultured from dental plaque (Di Silvestro and others 2009).

Pomegranate-rinsing also lowered saliva activities of α-glucosidase, a sucrose-degrading enzyme, and increased activities of ceruloplasmin, an antioxidant enzyme (Bielli and Calabrese 2002). A gel containing extracts of *Centella asiatica* and *Punica granatum* was effective as adjunctive periodontal therapy (Sastravaha and others 2005). According to Kandra and others (2004), tannins inhibit human salivary α-amylase, which catalyzes the hydrolysis of starch to oligosaccharides and binds to viridians streptococci and enamel, thus providing an acidogenic food source for cariogenic microorganisms on the tooth surface (Scannapieco and others 1993).

Eating pomegranate as a food could place antibacterial and antioxidant agents into the mouth and gum areas. On the other hand, better oral exposure to these agents could come from more direct chronic exposure with active agents, such as through a toothpaste or mouthwash (Di Silvestro and others 2009). Badria and Zidan (2004) reported that pomegranate flavonoids have shown modest antibacterial action *in vitro* for strains relevant to gingivitis, although pomegranate flower extract can inhibit *in vitro* by both competitive and noncompetitive mechanisms, a bacterial sucrose-digesting enzyme responsible for initiating oral problems, including gingivitis (Li and others 2005).

The earlier hypothesis of the direct antioxidant activity of polyphenols is potentially valid in explaining their preventive effect against diseases of the oral cavity, where polyphenols come into direct contact with tissues before being absorbed and metabolized (Halliwell and others 2000) and are activated into aglycones by human and bacterial enzymes (Walle and others 2005). Indeed, the oral mucosa, where polyphenols reach the highest concentration with respect to all other tissues, is constantly exposed to oxidative stress from the environment and the diet (Johnson 2004).

Antimicrobial Properties

The use of chemical or synthetic agents with antimicrobial activity (as inhibitors, growth reducers, or even inactivators) is one of the oldest techniques for controlling microorganism growth. The application of preservatives to foods is fundamental if their safety is to be maintained (Viuda-Martos and others 2008). Natural antimicrobials, whether of microbial, animal, or plant origin, which show bacteriostatic/fungistatic or bactericidal/fungicidal activity lengthen the useful life of foods and prevent, among other things, health-related problems, off-odors, unpleasant tastes, textural problems, or changes in color, which are basically caused by the enzymatic or metabolic systems of the principal microorganisms that lead to the alteration of foods (Feng and Zheng 2007).

The antimicrobial activity of some of the common pomegranate cultivars has been widely studied (Table 3); several *in vitro* assays demonstrate its bactericidal activity against several highly pathogenic and sometimes antibiotic-resistant organisms (Reddy and others 2007; McCarrell and others 2008; Al-Zoreky 2009; Choi and others 2009; Gould and others 2009).

Braga and others (2005a) showed that pomegranate extracts inhibit or delay *Staphylococcus aureus* growth and subsequent enterotoxin production at 0.01%, 0.05%, and 1% v/v concentrations. At a low extract concentration (0.01% v/v), bacterial growth was delayed, and at a higher concentration (1% v/v), such growth was eliminated. At a concentration of 0.05% (v/v) of extract, *Staphylococcus* enterotoxin production was inhibited. Prashanth and others (2001) also reported methanolic extracts of *Punica granatum* fruit rind to be active against *S. aureus*, *Proteus vulgaris*, *E. coli*, *Klebsiella pneumoniae*, *Bacillus subtilis*, and *Salmonella typhi*. Voravuthikunchai and others (2005) reported that chloroform, ethanol and water extract of pomegranate showed high activity against strains of *E. coli* O157:H7, especially in terms of verocytotoxin inhibition. The mechanisms involved in this process are still unclear, although active compounds may interfere with transcriptional and/or translational steps (Sakagami and others 2001). Reddy and others (2007) showed that pomegranate water and ethanolic and butanolic extracts revealed antimicrobial activity when assayed against *E. coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Cryptococcus neoformans*, methicillin-resistant *S. aureus.* Al-Zoreky (2009) reported that the 80% methanolic extract of pomegranate peels was a potent inhibitor for *Listeria monocytogenes*, *S. aureus*, *E. coli*, and *Yersinia enterocolitica*. Mathabe and others (2005) showed that methanol, ethanol, acetone, and water extracts obtained from pomegranate were active and effective against the tested microorganisms (*S. aureus*, *E. coli*, *S. typhi*, *Vibrio cholera*, *S. dysenteriae*, *S. sonnei*, *S. flexneri*, and *S. boydii*). Choi and others (2009) investigated the *in vitro* and *in vivo* antimicrobial activity of pomegranate peel ethanol extract against 16 strains of *Salmonella*. The minimal inhibitory concentrations were in the range of 62.5 to 1000 μg mL^{-1}. Ahmad and Beg (2001) reported that alcohol extracts of pomegranate fruits showed antibacterial activity when tested against *S. aureus*, *E. coli*, and *Shigella dysenteriae*. The interaction between pomegranate methanolic extract and 5 antibiotics, such as chloramphenicol, gentamicin, ampicillin, tetracycline, and oxacillin

Table 3–Antibacterial properties of pomegranate fruit.

Part of the plant	Extract	Bacterial strains	Reference
Arils	Water extracts	*Bacillus megaterium* *P. aeruginosa* *S. aureus,* *Corynebacterium xerosis* *E. coli* *Enterococcus faecalis* *Micrococcus luteus*	Duman and others (2009)
Whole fruit	Aqueous and methanol extracts	*S. typh* *Salmonella typhimurium* *Salmonella paratyphi*	Pasha and others (2009)
Peels	Water, methanol, petroleum ether, and chloroform extracts	*E. coli* *S. aureus* *B. subtilis* *L. monocytogenes* *Y. enterocolitica* *K. pneumoniae* *P. aeruginosa*	Prashanth and others (2001)
Whole fruit	Water and ethanol extracts	Different strains of *E. coli*	Voravuthikunchai and others (2004)
Peels	hexane, butanol and ethyl acetate	Methicillin-resistant *S. aureus*	Machado and others (2002)
Peels	Water extracts	Methicillin-sensitive and methicillin-resistant *S. aureus*	Gould and others (2009)
Peels	Water extracts	*S. aureus* *B. subtilis* *E. coli* *P. aeruginosa* *Proteus mirabilis*	McCarrell and others (2008)
Whole fruit	Ethanol extracts	*P. aeruginosa* *B. subtilis*	Nascimento and others (2000)
Whole fruit	Raw extracts	*P. aeruginosa* *E. coli* *Enteroccoccus faecalis* *Enterobacter aerogenes* *S. aureus* *Micrococcus luteus*	Salgado and others (2009)
Peels	Water extracts	*S. typhi*	Pérez and Anesini (1994)
Whole fruit	Water and ethanolic extract	*Aeromonas sobria* *Klebsiella pneumonia* *Enterobacter sp.* *Chryseobacterium sp.*	Muangsan and Senamontee (2008)
Peels	Aqeous extract	*P. aeruginosa*	Kelly and others (2009)
Peels and arils	Aqeous extract	*S. aureus* *P. aeruginosa*	Opara and others (2009)
By-products	Aqeous extract	*Pathogenic Clostridium* *S. aureus*	Bialonska and others (2009)
Juice	Aqeous extract	*Aeromonas hydrophila*	Belal and others (2009)
Whole fruit	Ethyl acetate extract	Methicillin-resistant *S. aureus*	Parashar and others (2009)

against 30 clinical isolates of methicillin-resistant and methicillin-sensitive *S. aureus* demonstrated that pomegranate extract enhanced the activity of all antibiotics tested, with a synergistic activity being detected between pomegranate extract and the antibiotics tested (Braga and others 2005b). Melendez and Capriles (2006) have also reported that extracts from *Punica granatum* fruits possess strong *in vitro* antibacterial activity against many bacterial strains tested including *E. coli*, *S. aureus*, *Enterobacter* spp., *Bacillus* spp., and *Micrococcus* spp.

Generally, antimicrobials have different concentration inhibition or inactivation thresholds. These thresholds depend on the specific targets of the antimicrobial substance, including cell wall, cell membrane, metabolic enzymes, protein synthesis, and genetic systems (Raybaudi-Massilia and others 2009). The exact mechanism(s) or target(s) for food antimicrobials are often not known or well defined. It is difficult to identify a specific action site where many interacting reactions take place simultaneously. For example, membrane-disrupting compounds could cause leakage of cellular content, interference with active transport of metabolic enzymes, or dissipation of cellular energy in ATP form (Davidson 2001).

In general, the extent of the inhibitory effects of the pomegranate extracts could be attributed to the phenolic, anthocyanin, and tannin contents of fruits. Thus, structural components of ETs (EA and gallic acid) were tested for antimicrobial activity against *Salmonella enterica*; EA did not inhibit the growth, but gallic acid caused strong inhibition (Puupponen-Pimia and others 2005). In another study, different patterns of inhibition by ellagitannin were noticed for *S. aureus* and *S. enterica*. The growth of *S. aureus* was clearly inhibited, and inhibition was maintained throughout the incubation period, with no viable bacterial cells detected after 24 h. Conversely, *S. enterica* was slightly inhibited at the beginning of the incubation period, and inhibition weakened over time (bacteriostatic, with no complete growth inhibition) (Puupponen-Pimia and others 2001).

The amphipathicity of these compounds can explain their interactions with bio-membranes and thus the antimicrobial activity (Veldhuizen and others 2006). In fact, the hydrophilic part of the molecule interacts with the polar part of the membrane, while the hydrophobic benzene ring and the aliphatic side chains are buried in the hydrophobic inner part of the bacterial membrane (Cristani and others 2007). Furthermore, the involvement of the hydroxyl group in the formation of hydrogen bonds and the acidity of these phenolic compounds may have other possible explanations (Cristani and others 2007). For Naz and others

Table 4–Overview of antioxidant pomegranate studies.

Part of the plant	Assays	Effect	Reference
Leaf extract	DPPH	Pomegranate leaves strongest antioxidant 93.5% enhancement	Lu and others (2003)
Peels	Phosphomolybdenum complex	Ethyl acetate, acetone, methanol exhibited marked antioxidant capacity, but the water extract was the lowest	Negi and others (2003)
Pith and carpellary membrane	DPPH free radical and superoxide radicals	Strong lipid peroxidation inhibitory activity in a liposome model system	Kulkarni and others (2003)
Arils, juice, peels, and EA extracts	DPPH	Good antioxidant acitivity. Strongest from EA extracts of arils	Ricci and others (2006)
Peel, pulp, and seeds	FRAP	High antioxidant activity and might be rich sources of natural antioxidants	Guo and others (2003)
Peel	TEAC	Prodelphinidin potent antioxidants in aqueous phase Gallocatechin-(4,8)-catechin more effective than prodelphinidin in lipid phase	Plumb and others (2002)
Juices	DPPH	Antioxidant activity varied among the cultivars and was directly related to the total phenolics in each type of juice	Mousavinejad and others (2009)
Peel	DPPH and ABTS radicals	Strong antioxidant activity	Rout and Banerjee (2007)
Peel	DPPH and ABTS radicals	High free radical-scavenging power	Okonogi and others (2007)
Arils	FRAP and TEAC	Variability among cultivars was great	Ozgen and others (2008)
Peel, pulp, and seeds	FRAP	Peel of the fruit had greater antioxidant activity than pulp and seed	Hajimahmoodi and others (2008)
Flowers and juice	DPPH and FRAP	Both samples showed high antioxidant activity, due to the anthocyanins and organic acids present in the samples	Miguel and others (2009)
Seeds	FRAP	The extracts obtained using various solvents exhibited various degrees of antioxidant activity	Sadeghi and others (2009)
Peels and seeds	FRAP	Peels showed very high total antioxidant but seed had lower capacity	Surveswaran and others (2007)
Fruits and leaves	DPPH and ABTS	Leaf and peel exhibited very strong antioxidant activity	Zhang and others (2008)
Juice and sour concentrate	Inhibition of peroxidation in linoleic acid system	Sour concentrate present higher antioxidant activity than juice	Orak (2009)

(2007), the mechanism responsible for phenolic toxicity to microorganisms was related to reactions with sulfhydryl groups of proteins and the unavailability of substrates to microorganisms, or interference with bacterial protein secretions. In general, tannins are assumed to be toxic to microorganisms. In solution, tannins create stable complexes, mainly with proteins and, to a lesser extent, with carbohydrates or physiological metal ions (such as Fe and Cu) (Chung and others 1998). The complexation of tannins with enzymes changes their structural conformation, thereby inhibiting enzymatic activity. The formation of complexes with cell wall proteins decreases cell wall permeability and reduces the transport of substrates into the cell. In addition, tannins decrease metal ion availability to bacteria when forming stable complexes with these metal ions. Subsequently, metal depletion may adversely affect the activity of metalloenzymes in microbial cells (Goel and others 2005).

These results provide evidence for the presence of antimicrobial compounds in the crude methanolic extracts of these plants. These findings clearly demonstrate and confirm the effectiveness of pomegranate fruit in inhibiting microbial activity.

Antioxidant Properties

Oxidative deterioration is one of the main culprits of the reduction of the quality and acceptability of food products. This process is initiated by exposure to the enzyme lypoxygenase, heat, ionizing radiation, light, metal ions, and metallo-protein catalysts (Daker and others 2008). Such oxidation leads to a significant loss of a food's nutritional value since it involves a loss of vitamins and essential fatty acids. It also affects the food's sensory quality—changes in color, texture, and taste—which shortens its shelf life and can result in rejection by consumers (Fernández-López and others 2007).

The determination of the antioxidant capacity of pomegranate components and their derivatives is being given greater importance by researchers and those involved in the agro-food industry for use as natural additives to replace synthetic antioxidants, whose use is increasingly restricted due to the secondary effects they may produce (Table 4).

The antioxidant activity of pomegranate components has been the subject of many studies (Naveena and others 2008; Çam and others 2009; Mousavinejad and others 2009; Tezcan and others 2009), most conducted *in vitro* and *in vivo*. All these activities may be related to the diverse phenolic compounds present in pomegranate, including punicalagin isomers, EA derivatives, and anthocyanins (delphinidin, cyanidin and pelargonidin 3-glucosides, and 3,5-diglucosides). These compounds are known for their properties to scavenge free radicals and to inhibit lipid oxidation *in vitro* (Gil and others 2000; Noda and others 2002). However, Tzulker and others (2007) suggested that punicalagin originating from the peels is one of the major phytochemicals contributing to the total antioxidant capacity of pomegranate juice, whilst anthocyanins play only a minor role in this activity.

The action mechanism set in motion by the antioxidant activity of these compounds is still not clearly understood, although it is a known fact that antioxidant mechanisms involved in biological matrixes are quite complex and several different factors may play a role (Çam and others 2009). Madrigal-Carballo and others (2009) suggested that pomegranate polyphenolic molecules undergo redox reactions because phenolic hydroxyl groups readily donate hydrogen to reducing agents. Negi and Jayaprakasha (2003) have also reported a significant increase in the reducing power of pomegranate peel extracts with increases in concentration from 50 to 400 ppm. Reducing properties are generally associated with the presence of reductones (Pin-Der 1998). Gordon (1990) reported

that the antioxidative action of reductones is based on the breaking of the free radical chain by the donation of a hydrogen atom. Reductones also react with certain precursors of peroxides, thus preventing peroxide formation (Naveena and others 2008). However, Amarowicz and others (2004) suggested that the antioxidant activity of phenolic compounds is due to their ability to scavenge free radicals or chelate metal cations.

The antioxidant and sensory qualities of pomegranates depend on several factors, such as cultivar and climatic conditions during fruit maturation and ripening and the part of the fruit used (Borochov-Neori and others 2009). Thus, Singh and others (2002) reported that a methanol extract of pomegranate peel had much higher antioxidant capacity than that of seeds, as demonstrated by using the β-carotene-linoleate and DPPH model systems. Tzulker and others (2007) reported that the homogenates prepared from the whole fruit exhibited an approximately 20-fold higher antioxidant activity than the level found in the aril juice.

Gil and others (2000) reported that pomegranate juice possessed a 3-fold higher antioxidant activity than that of red wine or green tea, and 2-, 6-, and 8-fold higher levels than those detected in grape/cranberry, grapefruit, and orange juices, respectively (Azadzoi and others 2005; Rosenblat and Aviram 2006b).

Seeram and others (2008b) reported that pomegranate juice had the greatest antioxidant potency composite index among such beverages as apple juice, açaí juice, black cherry juice, blueberry juice, cranberry juice, grape juice, orange juice, red wines, and iced tea; and the antioxidant activity was at least 20% greater than any of the other beverages tested.

The next step, in further research, is to try to identify the exactly mechanism or mechanisms by which antioxidant effect occurs, identifying too, the compounds responsible for antioxidant activity.

Other Properties

Preliminary research findings suggest that, in addition to its potential benefits for heart, diabetes, skin, teeth, cancer, and so on, the pomegranate may confer a multitude of other health-promoting effects in the body. However, more conclusive studies are needed to confirm these effects, because, there are very few references present in the scientific literature to substantiate these results.

Antiviral properties

Haidari and others (2009) evaluated the 4 major polyphenols in pomegranate extracts, EA, caffeic acid, luteolin, and punicalagin and identified punicalagin as the anti-influenza component, because this compound blocked replication of the virus RNA, inhibited agglutination of chicken RBC's by the virus, and had viricidal effects. Indeed, it inhibited the replication of human influenza A/Hong Kong (H3N2) *in vitro*. Anti-influenza viricidal activity has also been associated with other flavonoid compounds (Song and others 2005). The pomegranate has been used in phage amplification assays as a viricidal agent (De Siqueira and others 2006). In addition, pomegranate extract has been reported to have microbiocidal effects on HIV-1 (Neurath and others 2005).

Antidiarrheal properties

Pillai (1992) investigated the antidiarrheal activity of aqueous and alcohol extracts of the pomegranate fruit rind in 3 experimental models using albino rats. The extracts exhibited significant activity in rats when compared to loperamide hydrochloride, a standard antidiarrheal drug. Qnais and others (2007) evaluated the antidiarrheal effects of the aqueous extract of pomegranate peels in rats. The results revealed that the extract exhibited a concentration-dependent inhibition of the spontaneous movement of the ileum and attenuated acetylcholine-induced contractions. Olapour and others (2009) evaluated the antidiarrheal effect of pomegranate peel extract in rats given an oral dose of 400 mg/kg. The results showed that pomegranate peel extract decreased the number of defecations and the weight of feces in comparison with the control.

Gut microbiota

The consumption of pomegranate products leads to a significant accumulation of ETs in the large intestine (Seeram and others 2006) where they interact with the complex gut microflora. Bialonska and others (2009) reported that the effect of pomegranate ETs on bifidobacteria was species- and tannin-dependent. The growth of *Bifidobacterium animalis* ssp. *lactis* was slightly inhibited by punicalagins, punicalins, and EA. Pomegranate extract supplementation significantly enhanced the growth of *Bifidobacterium breve* and *Bifidobacterium infantis*.

Sperm quality

Pomegranate juice consumption led to an increase in epididymal sperm concentration, 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 (Türk and others 2008). In a similar study, Türk and others (2010) suggested that EA has a protective effect against testicular and spermatozoal toxicity induced by cyclosporine A. This protective effect of EA seems to be closely involved with the suppression of oxidative stress. Therefore, EA may be used combined with cyclosporine A after transplantation and in autoimmune diseases to improve cyclosporine A-induced injuries in sperm quality and oxidative stress parameters.

Erectile dysfunction

A recent well-controlled trial of pomegranate juice for the treatment of mild-to-moderate erectile dysfunction in men was made by Forest and others (2007). They concluded that subjects were more likely to have improved scores when pomegranate juice was consumed. The randomized, placebo-controlled, double-blind, crossover trial enrolled 53 men with mild-to-moderate impotence. Subjects blindly consumed pomegranate juice, or placebo, for 4 wk. After a 2-wk washout period, they switched treatments. Azadzoi and others (2005) found that, in a rabbit model, long-term pomegranate juice intake (3.87 mL) increased intracavernous blood flow and improved erectile response and smooth muscle relaxation in erectile dysfunction. Indeed, pomegranate juice intake prevented erectile tissue fibrosis.

Obesity

According to the World Health Org., there are currently more than 1 billion overweight adults, 300 million of whom are obese (Mackay and Mensah 2004). Cerdá and others (2003) investigated the effects of pomegranate extract (6% punicalagin) in female rats following exposure to a diet containing 20% of the extract for 37 d. The exposure to pomegranate extract resulted in an intake of 4800 mg punicalagin/kg/d. A significant decrease in feed consumption and body weight of the animals during the early part of the study was noted. Lei and others (2007) investigated the antiobesity effects of pomegranate leaf extract in a mouse model of high-fat diet-induced obesity, finding that the extract inhibited

the development of obesity and hyperlipidemia. The effects appear to be partly mediated by inhibiting pancreatic lipase activity and suppressing energy intake.

Ensuring liver health

Kaur and others (2006) evaluated antioxidant and hepatoprotective activity of pomegranate flowers. The efficacy of extract was tested *in vivo* and it was found to exhibit a potent protective activity in acute oxidative tissue injury animal model: ferric nitrilotriacetate (Fe-NTA) induced hepatotoxicity in mice. These results indicate pomegranate flowers to possess potent antioxidant and hepatoprotective property, the former being probably responsible for the latter.

Safety of Pomegranate

Pomegranate extracts, which incorporate the major antioxidants found in pomegranates, have been developed as botanical dietary supplements to provide an alternative convenient form for consuming the bioactive polyphenols (Heber and others 2007). Despite the commercial availability of pomegranate extract dietary supplements, there have been not too many studies evaluating their safety in human subjects. A variety of recent studies have demonstrated that pomegranate, in various forms, can be included as part of a healthy lifestyle with no risk of toxic reactions. A Cuban study, for example, found that 2 doses of pomegranate extract (0.4 and 1.2 mg/kg of body weight, respectively) given to rats produced no toxic effects in terms of food intake, weight gain, or behavioral or biochemical factors (Vidal and others 2003). Heber and others (2007) carried out a studied to evaluating pomegranate extract dietary supplements, on safety human subjects. Study was designed for safety assessment in 64 overweight individuals with increased waist size. The subjects consumed either 1 or 2 pomegranate extracts capsules per day providing 710 mg (435 mg of gallic acid equivalents, GAEs) or 1420 mg (870 mg of GAEs) of extracts. The researchers conclude that here were no serious adverse events in any subject studied at either site. Another study took these results further, examining still higher doses of pomegranate extract administered orally to rats for 37 d. No significant differences in toxicity were found in the treated rats in any of the blood parameters analyzed, a finding corroborated by analyses of both the liver and kidneys (Cerdá and others 2003). Another study in patients with carotid artery stenosis demonstrated that the consumption of pomegranate juice (121 mg/L EA equivalents) for up to 3 y had no toxic effect on blood chemistry, or on kidney, liver, or heart functions (Aviram and others 2004). Patel and others (2008) reported that the administration of pomegranate extract did not result in any toxicologically significant treatment-related changes in clinical observations, ophthalmic examinations, body weights, body weight gains, feed consumption, clinical pathology evaluations, or organ weights. The hematology and serum chemistry parameters were within the normal laboratory limits and no adverse effects were found.

Conclusions

The consumption of pomegranate has grown tremendously due to its reported health benefits. Pomegranate and derivates, such as juice, peel, and seeds, are rich sources of several high-value compounds with potential beneficial physiological activities. The rich bioactive profile of pomegranate makes it a highly nutritious and desirable fruit crop. Accumulating research offers ample evidence that routine supplementation with pomegranate juice or extract may protect against and even improve several diseases, including diabetes and cardiovascular disease; it may even help to prevent and arrest the development of certain cancers, in addition to protecting the health of the mouth and skin. Side effects are very rare. Using concentrated, low-cost pomegranate juice or standardized pomegranate extract capsules offers consumers a way of reaping the broad spectrum of health benefits of this fruit.

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