

Pomegranate as a Functional Food and Nutraceutical Source

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Abstract

Pomegranate, a fruit native to the Middle East, has gained widespread popularity as a functional food and nutraceutical source. The health effects of the whole fruit, as well as its juices and extracts, have been studied in relation to a variety of chronic diseases. Promising results against cardiovascular disease, diabetes, and prostate cancer have been reported from human clinical trials. The *in vitro* antioxidant activity of pomegranate has been attributed to its high polyphenolic content, specifically punicalagins, punicalins, gallic acid, and ellagic acid. These compounds are metabolized during digestion to ellagic acid and urolithins, suggesting that the bioactive compounds that provide *in vivo* antioxidant activity may not be the same as those present in the whole food. Anthocyanins and the unique fatty acid profile of the seed oil may also play a role in pomegranate's health effects. A more complete characterization of pomegranate components and their physiological fate may provide mechanistic insight into the potential health benefits observed in clinical trials.

Polyphenolic:

a diverse group of natural compounds that contain one or more phenol entities and may possess antioxidant and other potentially health-promoting properties

INTRODUCTION

Pomegranate (*Punica granatum*) and its juices and extracts are currently being widely promoted, with or without scientific support, to consumers as one of the new superfoods, capable of addressing a variety of health ailments. This fruit, which has been consumed and used as a medicinal food in the Middle East for thousands of years, has recently gained popularity in the United States. The potential capabilities of pomegranate as listed on a number of Web sites selling pomegranate products include its use as an antioxidant, an antiinflammatory, an antiviral, an antibacterial, and an antifungal. Specific health benefits listed on these Web sites include anticancer properties, improvement in cardiovascular health, diabetes prevention and management, relief of menopausal symptoms, hormone balance, increased libido in both genders, improved male virility and erectile function, skin nourishment including antiwrinkle effects, and protection against Alzheimer's disease and rheumatoid arthritis. The high antioxidant activity of the fruit and juice as compared with other fruits and antioxidant beverages (Halvorsen et al. 2002, Gil et al. 2000, Stangeland et al. 2007, Wolfe et al. 2008, Seeram et al. 2008a, Chidambara Murthy et al. 2002, Guo et al. 2008) has been the basis for much of the purported health benefits and has stimulated interest in research on potential nutraceutical and functional food applications. Unfortunately, the number of popular press, pomegranate-promoting publications far outweighs the number of significantly supportive scientific studies, as evidenced by the approximately 5,700:1 ratio of internet Google™ hits for "pomegranate health" (2,240,000) as compared with a MEDLINE® search for peer-reviewed journal articles on pomegranate (388). Nonetheless, research on the health-promoting properties of pomegranate has advanced rapidly. In the past two years alone, the number of peer-reviewed journal articles has nearly doubled, and several human clinical trials are in progress. Results from these studies may shed more light on the putative health effects of pomegranate. Although the research on pomegranate as a functional food and nutraceutical source is in its infancy, recently published scientific studies suggest that these phytonutrient-rich products may be beneficial to health. The purpose of this review is to provide an overview of pomegranate chemistry and the potential health effects of pomegranate products.

FUNCTIONAL FOOD AND NUTRACEUTICAL PRODUCTS

In addition to the increased marketing of fresh pomegranate fruit, a number of pomegranate-containing products have recently been introduced into the U.S. market and are being heavily advertised for their health-promoting benefits (**Figure 1**). These products include 100% juices, pomegranate-containing beverages, liquid and powdered polyphenolic extracts of pomegranate plant parts such as leaves, flowers, arils, and peel, pomegranate seed oil, and skin care products containing pomegranate extracts and/or pomegranate seed oil as ingredients. The sales of pomegranate juice alone increased from \$84,507 in 2001 to \$66 million in 2005 in the United States (AC Nielson, http://www.factsfiguresfuture.com/archive/june_2005.htm) illustrating the rapid growth in sales of these products. Recent publications evaluating commercial pomegranate juices and extracts for their phytochemical composition highlight the need for more comprehensive standardization criteria. Commercial juices from 23 manufacturers were tested for authenticity based on anthocyanin composition, the presence of pomegranate-specific ellagitannins, sugar, organic acid and amino acid profiles, and potassium content. Of these, a surprisingly low number (six) met the proposed requirements for authenticity, indicating that several of the juices had been supplemented with other ingredients or diluted (Zhang et al. 2009a). Similarly, 27 commercially available pomegranate extracts were analyzed for ellagitannin content and in vitro antioxidant capacity. Only five contained significant quantities of pomegranate-specific ellagitannins, the punicalins and

punicalagins. Seventeen commercial extracts contained primarily ellagic acid, the currently used standardization compound, and five extracts had very little ellagitannin or ellagic acid content and also exhibited low to no antioxidant activity (Zhang et al. 2009b). Interestingly, the only extracts that contained punicalagins were the ones that were labeled as such, indicating that some companies are taking extra measures to produce standardized pomegranate extracts. In the rapidly growing nutraceutical market, production and sales often precede knowledge and standardization. However, these studies combined with continued research on the specific bioactive components of pomegranate hold promise for future products that can deliver the health benefits as specified.

CHEMISTRY

The high in vitro antioxidant activity of pomegranate products has stimulated studies of its health effects pertaining to a number of chronic diseases thought to be related to oxidative stress. In several studies using multiple antioxidant activity assays, pomegranate fruit and juices have demonstrated antioxidant properties similar to or higher than other foods considered to have high antioxidant activity, including red wine and green tea. (Halvorsen et al. 2002, Gil et al. 2000, Stangeland et al. 2007, Wolfe et al. 2008, Seeram et al. 2008a). The major phytochemical component classes identified to date in pomegranate fruit are anthocyanins and hydrolyzable tannins, specifically ellagitannins, which release ellagic acid when hydrolyzed (Figure 2). Punicalagin, punicalin, gallagic acid, and ellagic acid were found to account for the majority of the ellagitannins in pomegranate juices and homogenates from 29 lines over two growing seasons (Tzulker et al. 2007). Research has shown that the antioxidant activity of pomegranate juices as measured by trolox equivalent antioxidant capacity (TEAC) and ascorbic acid equivalent antioxidant capacity (AEAC) methods was primarily attributable to the concentration of these hydrolyzable tannins, with anthocyanins contributing very little to in vitro antioxidant capacity (Gil et al. 2000). In whole fruit pomegranate homogenates, antioxidant activity was also correlated significantly with total polyphenols ($R^2 = 0.90$, $P < 0.01$), but not with total anthocyanin content ($R^2 = 0.05$, $P > 0.05$) (Tzulker et al. 2007). Nevertheless, anthocyanins have been associated with health effects, including prevention of cardiovascular disease, obesity, and diabetes (He & Giusti 2010) and should not be ignored as potentially bioactive components of pomegranate. The major anthocyanins in pomegranate juice across several Iranian cultivars were delphinidin 3,5-diglucoside, cyanidin 3,5-diglucoside, pelargonidin 3,5-diglucoside, delphinidin 3-glucoside, cyanidin 3-glucoside, and pelargonidin 3-glucoside (Alighourchi et al. 2008, Mousavinejad et al. 2009).

Pomegranate peel extracts have been shown to have higher antioxidant activity than the juice (Kelawala & Ananthanarayan 2004, Zhang et al. 2008) or seed extracts (Zhang et al. 2008, Singh et al. 2002), and were effective at preventing lipid peroxidation (Kelawala & Ananthanarayan 2004, Singh et al. 2002) and ex vivo low-density lipoprotein (LDL) oxidation at levels between 50 ppm and 100 ppm peel extract. Additionally, pomegranate peel extract was a more effective antioxidant than turmeric or ascorbic acid (vitamin C), two food-derived compounds that are known for their antioxidant properties (Kelawala & Ananthanarayan 2004).

Although the seeds have lower polyphenol content and in vitro antioxidant capacity (Zhang et al. 2008, Singh et al. 2002), the oils produced from them contain other components that may contribute health benefits. The seed oil has high phytosterol content and a unique fatty acid profile that includes punicic acid (Figure 3), a conjugated linolenic acid isomer (Kaufman & Wiesman 2007). Across 15 Turkish pomegranate cultivars, punicic acid constituted 70% to 76% of the pomegranate seed oil. The balance of the oil consisted of α -eleostearic, linoleic, oleic, catalpic, palmitic, stearic, β -eleostearic, gadoleic, arachidic, and behenic acids (Kýralan et al. 2009). Other researchers reported a similar fatty acid profile for a commercial cold-pressed pomegranate seed oil

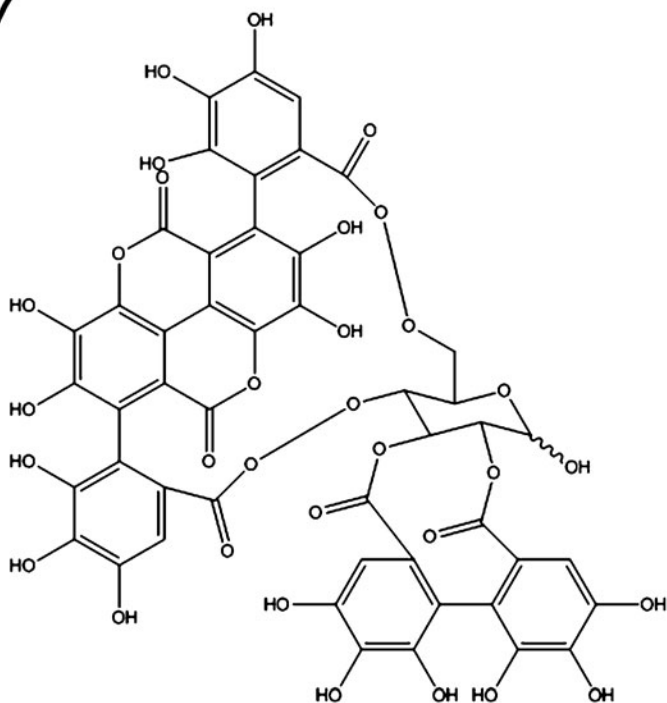
Oxidative stress: an unusually high level of oxidation that may result in damage to vital biomolecules, including protein and DNA, thereby increasing disease risk

Trolox equivalent antioxidant capacity (TEAC): an in vitro estimate of antioxidant properties that uses trolox, a water-soluble vitamin E analog, as a standard

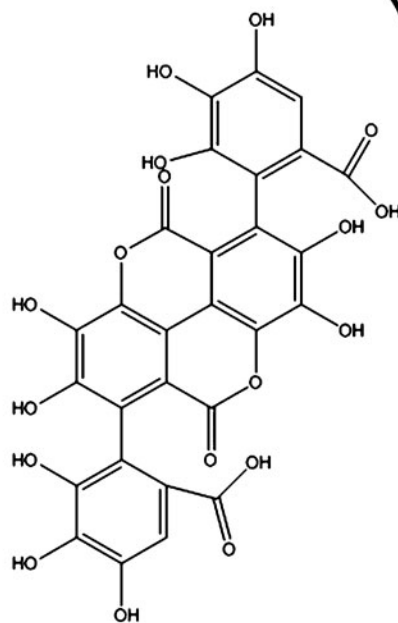
Ascorbic acid equivalent antioxidant capacity (AEAC): an in vitro estimate of antioxidant properties that uses vitamin C as a standard

Ex vivo: laboratory experiments using biological fluids, such as blood or saliva, in order to predict what might be observed if a compound was ingested or otherwise internalized

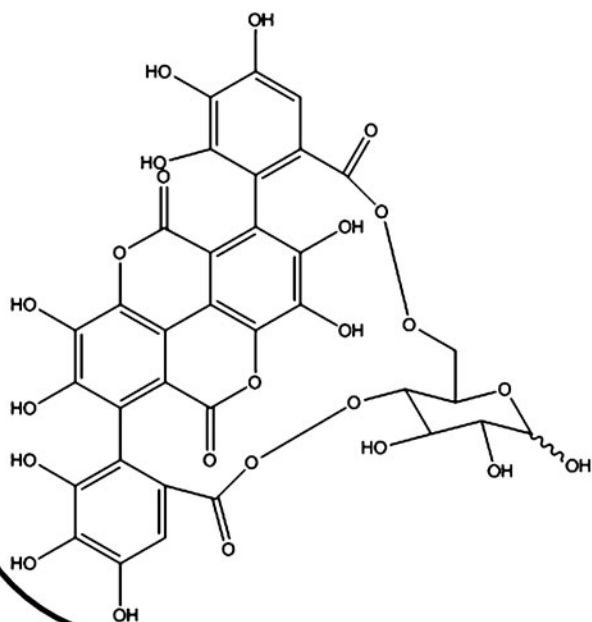
Punicalagins



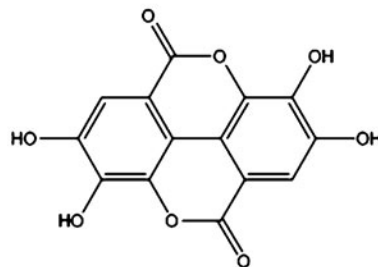
Gallagic Acid



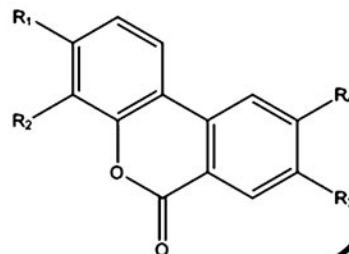
Punicalins



Ellagic Acid



Urolithin Metabolites



with the added detection of minor amounts of vaccenic (C18:1), lignoceric (C24:0), and nervonic (C24:1) acids (Sassano et al. 2009). This unique chemical composition of pomegranate seed oil has stimulated research specific to the healthful effects of the oil, including weight control, skin repair, and alteration of blood lipid profiles in hyperlipidemic individuals.

BIOAVAILABILITY

The high in vitro antioxidant capacity of pomegranate products has been attributed mostly to the high content of polyphenolic compounds, specifically the ellagitannins. However, the bioavailability of ellagitannins must be established in order to provide a link between these compounds and health effects related to in vivo antioxidant activity. In studies of ellagitannin bioavailability in human subjects, ellagic acid and its metabolites were detected in the plasma of individuals post-pomegranate juice consumption (Seeram et al. 2004, 2006). Furthermore, no difference in bioavailability as indicated by plasma ellagic acid or its metabolites was found among pomegranate juice, liquid extract, or powdered extract forms of treatment that contained similar levels of total polyphenols standardized as gallic acid equivalents (Seeram et al. 2008b). In contrast, a second study reported that no ellagic acid, punicalagin, anthocyanins, or their biological degradation products were found in plasma after pomegranate juice consumption (1 liter per day distributed in 5–200 mL bottles), even though the levels of ellagic acid and punicalagin in the juice were higher in this study. Urolithin metabolites were discovered, however, which the authors hypothesized were contributed by colonic microbial metabolism of the pomegranate juice polyphenols based on the timing of the appearance of the metabolites in plasma and urine samples (Cerdá et al. 2004) and their previous work on bioavailability of punicalagin in rats (Cerdá et al. 2003b). It is important to note that the timing of plasma sampling was different between these seemingly contrasting studies, and that since the half life of ellagic acid in the plasma was relatively short, between 0.65–1.79 h, (Seeram et al. 2008b), it may have been cleared from the blood prior to the first sampling in the other study (Cerdá et al. 2004). Thirty-one ellagitannin metabolites were detected using acorn-fed Iberian pigs as a model system, but only urolithin A, urolithin B, dimethyl ellagic acid and their glucuronide derivatives were found in plasma (Espín et al. 2007). Furthermore, urolithin metabolites have been shown to be readily absorbed in mouse models, with the highest levels accumulated in prostate, colon, and intestinal tissues (Seeram et al. 2007). Similarly, urolithin A glucuronide, urolithin B glucuronide, and dimethylellagic acid were the only ellagic acid metabolites detected in human prostate tissues after three days of supplementation with pomegranate juice (González-Sarrías et al. 2010a), indicating that the animal models may be suitable surrogates for studying the bioavailability and metabolism of ellagitannins. Overall, it appears that ellagitannins are hydrolyzed in the stomach where some portion of ellagic acid may be absorbed into circulation. The remaining ellagic acid is metabolized to urolithin derivatives by gut microflora. The less polar of these urolithin derivatives (A and B) are absorbed into circulation and metabolized further to glucuronides. Urolithins A, C, and D have been shown to possess antioxidant activity in a cell-based assay (Bialonska et al. 2009a), and urolithin A was found to have significant anti-inflammatory activity in an in vitro colon fibroblast model (González-Sarrías et al. 2010b). Therefore, it is possible that pomegranate polyphenolic compounds may act in multiple

Bioavailability:

a concept that reflects the ability of dietary components to be both absorbed and utilized in the body

Glucuronide:

a molecule to which glucuronic acid has been added by the liver or kidneys as a means of increasing its ability to be excreted from the body

Figure 2

Chemical structures of pomegranate ellagitannins and microbially derived urolithin metabolites (Urolithin A: R₁ = OH, R₂ = H, R₃ = OH, R₄ = H; Urolithin B: R₁ = H, R₂ = H, R₃ = OH, R₄ = H; Urolithin C: R₁ = OH, R₂ = H, R₃ = OH, R₄ = OH; Urolithin D: R₁ = OH, R₂ = OH, R₃ = OH, R₄ = OH).

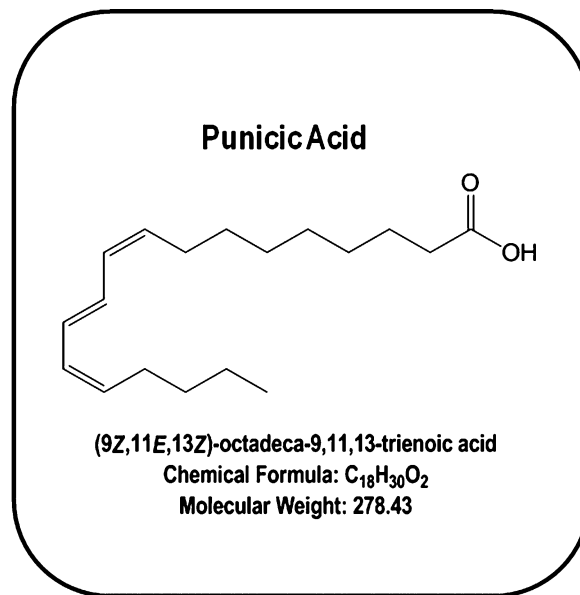


Figure 3

Chemical structure of punic acid, a conjugated linolenic acid isomer unique to pomegranate seed oil.

ways, with some being absorbed and entering the bloodstream to act directly as antioxidants, and the remainder being digested by the colonic microflora to provide other biologically active substances.

HEALTH EFFECTS

Pomegranate has reportedly been used medicinally by the peoples of many cultures for centuries to treat conditions such as diabetes and to combat malarial parasites (Xu et al. 2009, Dell'Agli et al. 2009). However, it is just within the past decade that scientific research related to the health effects of pomegranate has increased substantially. Because of the high in vitro antioxidant activity of pomegranate products, a wide variety of diseases and health conditions that appear to have some relationship to the body's ability to ward off oxidative stresses have been investigated (**Table 1**). Of note, many pomegranate products are being marketed for specific health effects, despite limited scientific data. Human clinical trials are relatively few in number but have shown positive effects of pomegranate juice consumption on prostate cancer prevention and cardiovascular health. Beneficial effects of pomegranate products have also been observed in animal models for prostate, colon, breast, and skin cancers, as well as for hyperlipidemia, atherosclerosis, and diabetes prevention and treatment. Although the weight of evidence is not sufficient for any one health claim, there is some preliminary evidence that shows promise.

Hyperlipidemia:

excessively high cholesterol and/or triglycerides levels, associated with increased cardiovascular disease risk

Cancer

Inhibition of cancer by pomegranate products has been studied for prostate, breast, colon, skin, lung, and cervical cancers, as well as leukemia. Of these, prostate cancer has been the most well studied, and positive effects of pomegranate juice consumption have been demonstrated in humans. Less is known at this time about the beneficial effects of pomegranate toward other cancers.

Table 1 Scientific studies on the potential health effects of pomegranate products

Disease/health claim	Total studies	Human clinical trials (# study subjects)	Animal model studies	Cell culture studies
Cancer	32	1	11	20
-prostate	11	1 (46)		
-colon	6			
-breast	6			
-skin	3			
-lung	2			
-cervical	1			
-leukemia	1			
Cardiovascular disease	22	8 (10, 13, 22, 20, 45, 289, 30)	9	7
Diabetes	11	3 (22, 20, 30)	7	1
Arthritis	3	0	2	1
Antimicrobial	8	3 (60, 60, 32)	0	5
Skin care	14	2 (20, 13)	5	7
Weight control	3	0	3	0
Inflammatory bowel disease	2	0	2	0
Chronic obstructive pulmonary disease	1	1 (30)	0	0
Alzheimer's disease	1	0	1	0
Neonatal neuroprotectant	1	0	1	0
Male infertility	1	0	1	0
Erectile dysfunction	1	1 (53)	0	0
Immune function	1	0	1	0
Menopause	1	1 (351)	0	0

Prostate. In a study of 46 men with rising prostate-specific antigen (PSA) levels following treatment for prostate cancer, consumption of 8 oz per day of pomegranate juice significantly delayed the rise in PSA, increasing the PSA doubling time from 15 months to 54 months based on baseline versus post-treatment measurements. Plasma analysis before and after treatment with pomegranate juice showed the treated subjects' plasma to have higher antioxidant and antiproliferative activities (Pantuck et al. 2006). At the time of publication, these authors indicated that a placebo-controlled trial to study these effects in more detail was underway. Furthermore, several studies in cell culture and animal models have reported inhibition of prostate cancer by pomegranate juice and extracts (Seeram et al. 2005, 2007; Albrecht et al. 2004; Lansky et al. 2005a,b; Malik et al. 2005; Sartippour et al. 2008; Rettig et al. 2008; Hong et al. 2008), and a number of mechanisms have been proposed. In vitro, pomegranate ellagitannins and their urolithin metabolites were shown to inhibit CYP1B1, a cytochrome P450 (CYP450) enzyme associated with prostate cancer initiation and progression. However, only urolithins A and B at higher concentrations inhibited this enzyme in prostate cancer cell cultures (Kasimsetty et al. 2009). Furthermore, urolithin A glucuronide, urolithin B glucuronide, and dimethyl ellagic acid were the only ellagitannin metabolites detected in human prostate tissues after three days of pomegranate juice or walnut consumption prior to fasting for surgery (González-Sarriás et al. 2010a). Given that these ellagitannin entities have been

Prostate-specific antigen (PSA):

a protein associated with prostate cancer progression

Cytochrome P450 (CYP450) enzymes:

enzymes found primarily in the liver and kidneys that serve to metabolize, detoxify, and aid in the excretion of foreign compounds

Apoptosis: an orderly form of cell death often associated with reduced cancer risk

Antiangiogenic: able to prevent the formation of new blood vessels, often associated with reduced risk of the spread of cancer in the body

Nuclear factor-kappa-B (NF- κ B): a transcription regulator, generally present in an inactive form, which, when activated, initiates processes associated with inflammation, immunity, and cell growth

UVB: one of three general types of ultraviolet rays that causes direct DNA damage and is most strongly associated with skin cancer

demonstrated to accumulate in prostate tissues *in vivo*, inhibition assays in cell cultures using these compounds may add to our knowledge of the underlying mechanisms.

Colon. Prevention of colon cancer with pomegranate products is mostly theoretical, with only a few studies in animal models and cell cultures for support. The number of azoxymethane-induced aberrant crypt foci in rats, an animal model for colon cancer, was significantly decreased by consumption of pomegranate juice (Boateng et al. 2007) and punicic acid-rich pomegranate seed oil (Kohno et al. 2004). Additionally, in human colon cell cultures, pomegranate juice inhibited proliferation and induced apoptosis (Seeram et al. 2005), possibly via an inflammatory cell signaling mechanism (Adams et al. 2006). Punicalagin, the primary ellagitannin in pomegranate was shown to release ellagic acid in cell culture media, which actively induced apoptosis of colon cancer-derived Caco-2 cells (Larrosa et al. 2006). It has also been shown that specific ellagitannins from pomegranate and the corresponding urolithin metabolites inhibited proliferation and induced apoptosis of HT-29 human colon cancer cells (Kasimsetty et al. 2010).

Breast. In breast cancer cell cultures, growth was inhibited by pomegranate extracts via apoptosis (Jeune et al. 2005). Similarly, a breast cancer mouse model showed reduction in lesions when treated with fermented pomegranate juice polyphenols, a purified unknown compound from the fermented pomegranate, and pomegranate seed oil (Mehta & Lansky 2004). Further research with these pomegranate components indicated that the inhibition observed in breast cancer models may be due to an antiangiogenic mechanism of action (Toi et al. 2003) and inhibition of nuclear factor-kappa-B (NF- κ B) (Khan et al. 2009). Additionally, differentiation-promoting ability was shown for fermented pomegranate juice and peel extracts in a leukemia cell model (Kawaii & Lansky 2004). Given the intestinal metabolism of pomegranate polyphenols, several ellagitannin metabolites were tested *in vitro* for their antiproliferative and antiaromatase activities. Urolithin B displayed the greatest inhibition of both aromatase (an enzyme that interconverts testosterone and estrogen hormones) activity and proliferation (Adams et al. 2010), indicating that the bioactive components of the polyphenolic pomegranate extracts may be the microbially derived metabolites. Punicic acid, a major component of pomegranate seed oil, also inhibited breast cancer cells, but this effect was dependent on lipid peroxidation (Grossmann et al. 2010). Taken together, there appears to be some evidence in animal and cell culture models that a variety of bioactive compounds may exist in pomegranate extracts and oil that could have anticarcinogenic properties.

Skin. Both pomegranate seed oil and pomegranate fruit extract applied topically to mouse models for skin cancer inhibited the incidence and multiplicity of tumors, as well as delayed their onset (Hora et al. 2003, Afaq et al. 2005b). Sunlight provides UVA, UVB, and UVC radiation, but UVB (290–320 nm) tends to be most carcinogenic. The negative cellular effects of UVB exposure were studied in normal human epidermal keratinocytes in cell culture, and pomegranate fruit extract treatment was found to inhibit changes in NF- κ B and mitogen-activated protein kinase (MAPK) pathways that would normally be stimulated by UVB exposure (Afaq et al. 2005a). Pomegranate juice, extract, and oil applied to reconstituted human skin prior to UVB exposure were equally successful in preventing UVB-mediated damage related to both aging and skin cancer (Afaq et al. 2009). Similarly, pomegranate extract has been shown to inhibit markers for UVB-induced skin damage in cultured human skin fibroblasts (Park et al. 2010, Pacheco-Palencia et al. 2008), with the effects attributed to the content of catechin (Park et al. 2010) and ellagic acid (Bae et al. 2010). Thus, the protective effects of pomegranate extracts on skin cells may be beneficial for both cancer prevention and reduction of photoaging.

Other. Pomegranate fruit extract was demonstrated to have an inhibitory effect that was specific to lung cancer cells, having very little effect on normal bronchial cells in cell culture, and that reduced tumor growth and multiplicity in mouse models (Khan et al. 2007a,b). In contrast, pomegranate extract standardized to 50 $\mu\text{g ml}^{-1}$ gallic acid equivalents was only slightly cytotoxic to cervical cancer cells in vitro and one of the least effective among the fruits tested (McDougall et al. 2008).

Cardiovascular Health

Research on effects of pomegranate products on cardiovascular health has been primarily focused on the prevention of atherosclerosis and the management of hyperlipidemia in diabetic individuals (see below). Several human studies have been conducted, most of which have shown benefits of pomegranate products on cardiovascular health in relation to blood pressure, cholesterol, intima media thickness, and endothelial function. Elderly, hypertensive subjects ($n = 10$) that consumed pomegranate juice containing 1.5 mmol total phenols per day for two weeks experienced a 36% decrease in serum angiotensin II converting enzyme activity and a 5% decrease in systolic blood pressure, both of which are markers for cardiovascular disease risk (Aviram & Dornfeld 2001). After consumption of 50 ml pomegranate juice per day for two weeks, plasma from 13 healthy nonsmoking young men had higher antioxidant activity, decreased lipid peroxides, increased arylesterase activity, and increased resistance to copper sulfate-induced high-density lipoprotein (HDL) oxidation (Aviram et al. 2000). In this same report, it was demonstrated that pomegranate juice consumption decreased the number of foam cells and the size of atherosclerotic lesions by 44% in apolipoprotein E-deficient mice, an animal model for atherosclerosis.

In other human studies, atherosclerotic patients with carotid artery stenosis (a narrowing of the arteries in the neck that supply blood to the brain) that consumed pomegranate juice (50 ml day^{-1}) in addition to their regular medication for one year ($n = 10$) had on average a 30% decrease in intima media thickness (IMT) compared with a 9% increase in IMT in control patients ($n = 9$) (Aviram et al. 2004). In a larger clinical trial ($n = 289$) conducted over an 18-month period, healthy individuals with moderate risk factors for coronary heart disease (CHD) were instructed to consume either a pomegranate juice or placebo beverage daily. There was no overall difference in carotid IMT progression found between placebo and pomegranate juice groups. However, subpopulations that were in the top third of participants for total triglycerides (TG), total cholesterol:HDL cholesterol ratio, TG:HDL ratio, and apolipoprotein B showed significant reduction in carotid IMT progression with pomegranate juice supplementation (Davidson et al. 2009). The authors concluded from these data that individuals at higher risk for CHD benefited from pomegranate juice consumption. Additionally, a placebo-controlled human clinical trial using 45 patients with ischemic CHD found that daily consumption of 240 ml pomegranate juice for three months significantly decreased stress-induced myocardial ischemia ($P < 0.05$), whereas it increased in the placebo group (Sumner et al. 2005). In another study, the short-term benefits of pomegranate juice consumption on cardiovascular health were demonstrated. Endothelial function was significantly improved in adolescents with metabolic syndrome ($n = 30$) after four weeks of supplementation with 240 ml per day of pomegranate juice or grape juice (Hashemi et al. 2010). Overall, it appears that pomegranate juice supplementation may contribute significantly to prevention of cardiovascular diseases, which is consistent with current dietary guidelines that encourage consumption of at least five servings per day of fruits and vegetables.

In a human clinical trial with hyperlipidaemic individuals ($n = 45$), consumption of 400 mg pomegranate seed oil twice daily for four weeks increased HDL cholesterol and decreased the total cholesterol:HDL cholesterol ratio as compared with a placebo (Mirmiran et al. 2010). These

Intima media thickness (IMT): artery wall thickness, associated with cardiovascular disease progression

Metabolic syndrome: simultaneous presence of several risk factors for cardiovascular disease and diabetes-related conditions, including glucose intolerance, large waist size, and hypertension

results indicate that there may be some long-term benefits of pomegranate seed oil consumption on plasma lipid profiles that are associated with cardiovascular health.

Studies in atherosclerotic mouse models have also shown that pomegranate juice consumption significantly reduced the development of atherosclerosis (de Nigris et al. 2005, Kaplan et al. 2001). The antiatherosclerotic activity of pomegranate juice was associated with increased serum paraoxonase activity, decreased macrophage lipid peroxides, and decreased uptake of oxidized low-density lipoprotein (LDL) in macrophage cells (Kaplan et al. 2001). A dose-dependent decrease in cellular oxidative stress and decreased uptake of oxidized LDL in macrophage cells treated with pomegranate juice has been demonstrated in vitro (Fuhrman et al. 2005), and it has been proposed that the decreased cellular oxidative stress observed with pomegranate juice treatment may be at least partially attributed to upregulation of paraoxonase 2 expression (Shiner et al. 2007). Furthermore, a decrease in oxidation-sensitive gene expression and an increase in nitric oxide synthase activity were found in response to pomegranate juice supplementation in both hypercholesterolemic mice and human coronary artery endothelial cells exposed to high shear stress (de Nigris et al. 2005). Pomegranate juice was also shown to increase the bioactivity of nitric oxide synthase in human coronary endothelial cells by inhibiting the oxidation of LDL (oxidized LDL inhibits nitric oxide synthase) and upregulating the expression of endothelial nitric oxide synthase (de Nigris et al. 2006). Therefore, it appears that oxidized cholesterol can contribute to the formation of atherosclerotic lesions (blocking of blood vessels) and also cause vasoconstriction due to a decrease in the vasodilating compound nitric oxide. These animal studies suggest that pomegranate supplementation could attenuate these effects by reducing the uptake of oxidized LDL in macrophages, and maintaining or increasing nitric oxide levels in endothelial cells, thus preventing both atherosclerosis progression and vasoconstriction in partly blocked vessels.

Extracts of pomegranate flowers, peels, arils, and pomegranate juice each decreased atherosclerotic lesions and lipid peroxides in mouse models and cell culture systems, but the seed extracts had no effect (Aviram et al. 2008). Similarly, an extract prepared from pomegranate juice production by-product (the remaining portion of the whole fruit after juicing) reduced atherosclerotic lesion size by up to 57% and decreased markers of oxidative stress in a mouse model (Rosenblat 2006b). Despite questions remaining on the bioavailability and metabolism of pomegranate ellagitannins, an unidentified hydrolyzable tannin isolated from pomegranate juice was also shown to significantly reduce atherosclerotic lesion size, decrease plasma lipid peroxidation, and inhibit macrophage uptake of oxidized LDL in apolipoprotein E-deficient mice (Kaplan et al. 2001). Based on human clinical trials and on animal data, the consumption of pomegranate juice and extracts appear to have promise for maintaining or improving cardiovascular health.

Diabetes

Pomegranate flower extract and pomegranate juices and concentrates have been studied for their roles in management of diabetes in both animal models (Zucker diabetic rats) and humans. Pomegranate flower extract consumed by Zucker diabetic rats, a type II diabetes model, decreased the expected glucose load-induced increase in plasma glucose levels but had no effect on Zucker lean rats (Li et al. 2005, Huang et al. 2005a). Authors hypothesized that this effect was due to increased insulin receptor sensitivity via pomegranate flower stimulation of the peroxisome proliferator-activated receptors (PPAR)- γ (Huang et al. 2005a) or inhibition of intestinal α -glucosidase (Li et al. 2005). In addition to glucose metabolism in diabetic states, pomegranate flower extract has also been shown to decrease triglycerides and total cholesterol (Huang et al. 2005b), decrease cardiac fibrosis (Huang et al. 2005c), and reduce fatty liver via upregulation of fatty acid oxidation (Xu et al. 2009) in Zucker diabetic rat model systems. Pomegranate flower

extract was also shown to increase HDL cholesterol, glutathione, and antioxidant enzymes in streptozotocin-induced diabetic Wistar rats and decrease fasting blood glucose, TG, LDL cholesterol, VLDL cholesterol, and tissue lipid peroxidation (Bagri et al. 2009). This is in agreement with the previous animal studies and provides additional information on the improvement in oxidative state upon treatment with pomegranate flower extract, a traditional antidiabetic medicine. Similarly, pomegranate juice extract consumed for four weeks was able to ameliorate the biochemical and physiological effects of diabetes and hypertension induced in Wistar rats (Mohan et al. 2009).

Hyperlipidemia and oxidative stress in diabetic patients puts them at increased risk for heart disease. Three human clinical trials have been conducted with diabetic patients to study the effect of pomegranate juice consumption on plasma lipid and oxidation profiles. Oxidative stress was decreased by 35% upon consumption of 50 ml per day of pomegranate juice for four weeks and was attributed to increased serum HDL-associated PON1 stability and activity (Rock et al. 2008). After eight weeks of pomegranate juice concentrate (40 g) consumption by 22 diabetic patients, plasma lipid profiles were improved, as evidenced by decreased total cholesterol, LDL cholesterol, and LDL/HDL ratio (Esmailzadeh et al. 2004). Pomegranate juice consumption (50 ml day⁻¹) for three months by diabetic patients and their healthy subject controls decreased serum lipid peroxides by 23%, an indicator of an overall increased antioxidant activity in vivo (Rosenblat et al. 2006a). There were also no negative consequences of pomegranate juice consumption in terms of blood glucose parameters (Rock et al. 2008, Rosenblat et al. 2006a). These clinical results involved only a few patients, but were supported by the animal model work that had been done in this area (Rozenberg et al. 2006, de Nigris et al. 2007).

Arthritis

The effect of pomegranate fruit extract on arthritis has been studied to a limited degree in animal models. Pomegranate fruit extract fed to mice in their drinking water significantly delayed the onset and reduced the incidence and severity of arthritis in a collagen-induced arthritis model, and inflammatory cytokine interleukin 6 (IL-6) was reduced. (Shukla et al. 2008) Similarly, pomegranate juice prevented chondrocyte damage in a mouse model for osteoarthritis in a dose-dependent fashion (Hadipour-Jahromy & Mozaffari-Kermani 2010). Human osteoarthritis cartilage samples (chondrocyte cell cultures) pretreated with an anthocyanin-rich pomegranate fruit extract in vitro resisted interleukin 1- β -induced cytotoxicity, and cartilage degradation was inhibited as evidenced by decreased proteoglycan release (Ahmed et al. 2005) These studies suggest a positive effect of pomegranate consumption on arthritis, thus providing some basis for studying the effects in human clinical trials.

Antimicrobial Applications

Antiviral, antifungal, and antibacterial properties of pomegranate products have been studied to some extent in vitro, but to a very limited degree in animal models or human clinical trials. In screening of fruit juices for inhibition of infection by HIV-1 III_B, pomegranate juice, even from different growing regions, was consistently the most inhibitory. These researchers further isolated the active antiviral component(s) by binding them to corn starch and tested for retention of HIV-specific antiviral activity through development of a potential topical microbicide. Authors proposed that this microbicide could be applied vaginally prior to intercourse to prevent the binding of HIV viral particles to their cell receptors, thus preventing infection (Neurath et al. 2005). Studies to test its efficacy in human populations where control of HIV is difficult may be warranted.

Interleukin-6 (IL-6):

a protein-based cellular signaling molecule involved in communication among immune cells and in the inflammation process

Pomegranate extract was shown to inhibit the influenza virus by blocking its replication, inhibiting agglutination of red blood cells, and possessing virucidal activity (Haidari et al. 2009). Further study of individual polyphenols present in the pomegranate extract showed that punicalagin was responsible for the antiviral activity. A clinical trial to study this effect in humans is currently underway. Given our current knowledge of the intestinal metabolism of punicalagin in animals, it will be of much interest whether the antiviral properties of pomegranate extract can be effectively delivered in humans.

Human clinical trials that investigated the use of pomegranate extracts for topical antibacterial and antifungal treatments in dental hygiene applications suggest some beneficial effects. Twenty-one of thirty patients with denture stomatitis responded to treatment with pomegranate gel extract compared with 27 of 30 patients that received the standard micronazole treatment (Vasconcelos et al. 2003). Although the pomegranate treatment had a lower success rate than the micronazole, a significant proportion of patients responded to this treatment, indicating that there is potential for development of this into a more effective product. Pomegranate extract was also found to be an effective antiplaque rinse, similar in efficacy to chlorhexidene (Menezes et al. 2006), and was suggested for use as a thrice-daily rinse for reduction of gingivitis risk (DiSilvestro et al. 2009).

Desirable antimicrobial activities of pomegranate fruit extracts have been demonstrated in a number of in vitro studies. These include direct antifungal, antibacterial, and antiplasmodial activities (Braga et al. 2005b; Vasconcelos et al. 2006; Dell'Agli et al. 2009; Johann et al. 2010; Bialonska et al. 2009b, 2010) and a synergistic effect with antibiotics for treating methicillin-resistant *Staphylococcus aureus* (Braga et al. 2005a). However, translation of these in vitro activities into therapeutic products for use in humans has yet to be proven.

Skin Care

Skin care products containing pomegranate extracts and seed oil are increasingly available and promise rejuvenation, youthfulness, and beauty. However, research on the ability of pomegranate to act as an effective cosmeceutical ingredient is in the early stages of development. In human cell cultures, pomegranate seed oil extract increased the number of keratinocytes resulting in an increase in thickness of the epidermis and pomegranate peel extract had no effect on keratinocytes, but increased the number of fibroblasts in a dose-response fashion, indicating stimulation of dermal repair mechanisms (Aslam et al. 2006). Whole fruit extracts of pomegranate used to pretreat keratinocyte cells prior to UVA or UVB radiation blocked the oxidative stresses normally observed under those conditions that are commonly associated with aging (Syed et al. 2006, Zaid et al. 2007). Oral supplementation with pomegranate extract provided protection against UV-induced pigmentation in human subjects that were prone to sunburn (Kasai et al. 2006). There was no overall effect of supplementation when the entire group of subjects ($n = 37$) was considered, indicating a need for a larger study to validate the specific effects in susceptible individuals. Pomegranate peel extract has also been studied in a guinea pig model for skin whitening and found to be effective (Yoshimura et al. 2005). Only one study of a pomegranate cosmeceutical product was evaluated in human subjects (Hsu et al. 2007). This study was composed of 20 females aged 35–65 who applied each cream (placebo or treatment) to half of their face twice a day for 60 days. A slight increase in skin smoothness was observed for the pomegranate treatment cream. However, the cream was a blend of pomegranate, green and white teas, and mangosteen, so the effect cannot be distinctly associated with pomegranate from these data. To date, there are limited scientific data to support the cosmeceutical claims for pomegranate. Still, the cell culture work in this area supports a potential protective effect of pomegranate extract on skin cell repair, providing a basis for investigation in human clinical trials.

Other Disease States and Health Claims

Studies related to chronic obstructive pulmonary disease (COPD) (Cerdá et al. 2006), Alzheimer's disease (Hartman et al. 2006), neonatal neuroprotection (Loren et al. 2005), male infertility (Turk et al. 2008), erectile dysfunction (Forest et al. 2007), menopause (Newton et al. 2006), and immune function (Yamasaki et al. 2006) are either limited to a single animal study or have not shown significant improvement in condition upon pomegranate product usage. Two of these, COPD and erectile dysfunction, have been studied in human clinical trials, but no positive effects were observed. Of special note is the fact that pomegranate supplements are currently being marketed on the guarantee to relieve menopausal symptoms, yet the only publication in the scientific literature on this purported health effect is a single human clinical trial that incorporated pomegranate into a multibotanical supplement that included black cohosh and eight other ingredients. Not only was pomegranate not tested independently, the pomegranate-containing multibotanical also had no effect on the vasomotor symptoms of menopause over a 12-month study (Newton et al. 2006). In contrast, there is some preliminary evidence in animal models for weight control using pomegranate extract (Lei et al. 2007) or pomegranate seed oil (Arao et al. 2004, McFarlin et al. 2009) and for anti-inflammatory effects of pomegranate extract against ulcerative colitis in animal models of inflammatory bowel disease (Larrosa et al. 2009, Singh et al. 2009). In summary, these studies represent the initial research on the effects of pomegranate on a variety of health issues. More research is needed in the areas where these preliminary animal models have shown positive effects of pomegranate treatment.

TOXICITY AND POTENTIAL DRUG INTERACTIONS

The human clinical trials that have been conducted to date have mostly involved consumption of a moderate amount of pomegranate juice or a concentrated liquid or powder that is equivalent in polyphenolic content to an 8 oz serving of juice. No adverse side effects have been noted in these studies, and it is generally considered safe to consume the fresh fruit and juice of pomegranates. Owing to the development of concentrated extracts as dietary supplements, toxicity studies have been carried out in rat and mouse models. The lethal dose 50 (LD₅₀) for pomegranate fruit extract standardized to 30% punicalagins was found to be greater than 5 g kg⁻¹ body weight. This group also studied the effect of feeding the pomegranate fruit extract at levels between 0 mg kg⁻¹ and 600 mg kg⁻¹ body weight to Wistar rats for 90 days. At the end of the trial, there were no observed toxic effects even at the highest dose (Patel et al. 2008). In another toxicological study, rat diets were replaced with a 20% pomegranate powder:80% rat chow diet that resulted in 6% punicalagin (equilibrated concentration). This diet was fed for 37 days with no evidence of toxicity (Cerdá et al. 2003a). The safety of POMx brand pomegranate extract powder (1 or 2 capsules daily versus placebo) was demonstrated in a study of 64 overweight individuals who experienced no significant negative effects or changes in renal or liver function parameters over the course of a 28 day treatment period (Heber et al. 2007). The no observable adverse effect level (NOAEL) for pomegranate seed oil was found to be equivalent to 4.3 g kg⁻¹ body weight per day (Meerts et al. 2009). While this evidence is limited in scope, it indicates that a healthy individual may safely consume pomegranate oil, juice, or even powdered extracts in moderation without great risk.

Although it seems that it would take some effort to ingest a toxic dose of pomegranate extract, there may be some effects on cytochrome P450 enzymes that could potentially influence the metabolism of other components in one's system (for example, prescription drugs). Research in rat models has shown that pomegranate juice inhibited cytochrome P450 enzymes CYP2C9

Lethal dose 50 (LD₅₀): the dose at which 50% of the animals given a test compound die

No observable adverse effect level (NOAEL): the dose of a compound at which no detrimental effects occur

(Nagata et al. 2007) and CYP3A (Hidaka et al. 2005) in vitro and increased levels of absorbed tolbutamide and carbamazepine by increasing bioavailability. Interestingly, there was no effect on the clearance of these compounds by the corresponding liver enzymes (Nagata et al. 2007, Hidaka et al. 2005). Consumption of pomegranate juice for four weeks in a mouse model showed an overall decrease in liver CYP450 concentration and an increase in the sleep effect induced by pentobarbital. The decrease in total CYP450 was attributed to decreases in liver CYP1A2 and 3A, and the authors concluded that this may be a mechanism for cancer prevention or a possibility for drug interaction (Faria et al. 2007). One human study with a small number of subjects ($n = 15$) was conducted to test the interference of pomegranate juice consumption with CYP3A and midazolam, a sedative used for short-term treatment of insomnia, as compared with this known drug interaction with grapefruit juice. Although pomegranate juice inhibited CYP3A in vitro, there was no effect on midazolam metabolism post-pomegranate juice consumption (Farkas et al. 2007). More research is needed to fully understand the interaction of pomegranate products with CYP450 enzymes and the implications of those interactions for human health.

CONCLUSIONS AND FUTURE DIRECTIONS

To date, the majority of scientific research studies on the promising health effects of pomegranate have been carried out in cell culture or animal models. Many different potential functional food and nutraceutical applications have been studied, but sufficient depth of knowledge on the effectiveness of many of these proposed uses has not yet been attained. However, the positive results in vitro and in animal models indicate that further study in humans is warranted. Recent human clinical trials have shown significant positive effects of pomegranate juice consumption on lipid profiles in diabetic patients, atherosclerosis reduction, and on PSA levels in prostate cancer patients. Although these human studies are limited in number, they show evidence that regular consumption of pomegranate juice may aid in the prevention or management of chronic diseases.

There are currently 17 registered ongoing human clinical trials testing the potential health effects of pomegranate products (<http://clinicaltrials.gov>). The majority of these studies are related to prostate cancer, a few studies deal with the complications of diabetes, and single studies are listed for cardiomyopathy, lymphoma, intrauterine growth restriction, and influenza. As with previous human studies, the study designs employ a whole foods approach using pomegranate juices or whole fruit polyphenol extracts. A more complete characterization of the bioactive components of pomegranate products and their physiological actions will be required to study the underlying mechanisms for the potential health benefits that have been demonstrated in clinical trials.

SUMMARY POINTS

1. Pomegranates have been used for centuries by Middle Eastern cultures to treat health conditions such as diabetes and parasitic infections.
2. Clinical trials have been conducted examining a wide range of the potential health effects for pomegranate, but the total number of trials is small. The most promising data thus far come from the studies examining the effects of pomegranate on heart disease, diabetes, and prostate cancer.
3. A number of clinical trials are ongoing in the area of prostate cancer, and these could shed further light on the proposed anticancer effects of pomegranate.

4. Pomegranate contains a number of unique ellagitannin-based compounds, including punicalagins, punicalins, and gallic acid, as well as anthocyanins and a distinct fatty acid profile, all of which may contribute to potential and reported health effects.
5. The high in vitro antioxidant activity of pomegranate has been largely attributed to its ellagitannin content, but the bioavailability of these compounds is very low.
6. Although the bioactive components of pomegranate responsible for its observed in vivo effects are yet to be fully elucidated, it is possible that the health effects of pomegranate are due to its metabolites (e.g., urolithins) rather than the components of the intact fruit per se.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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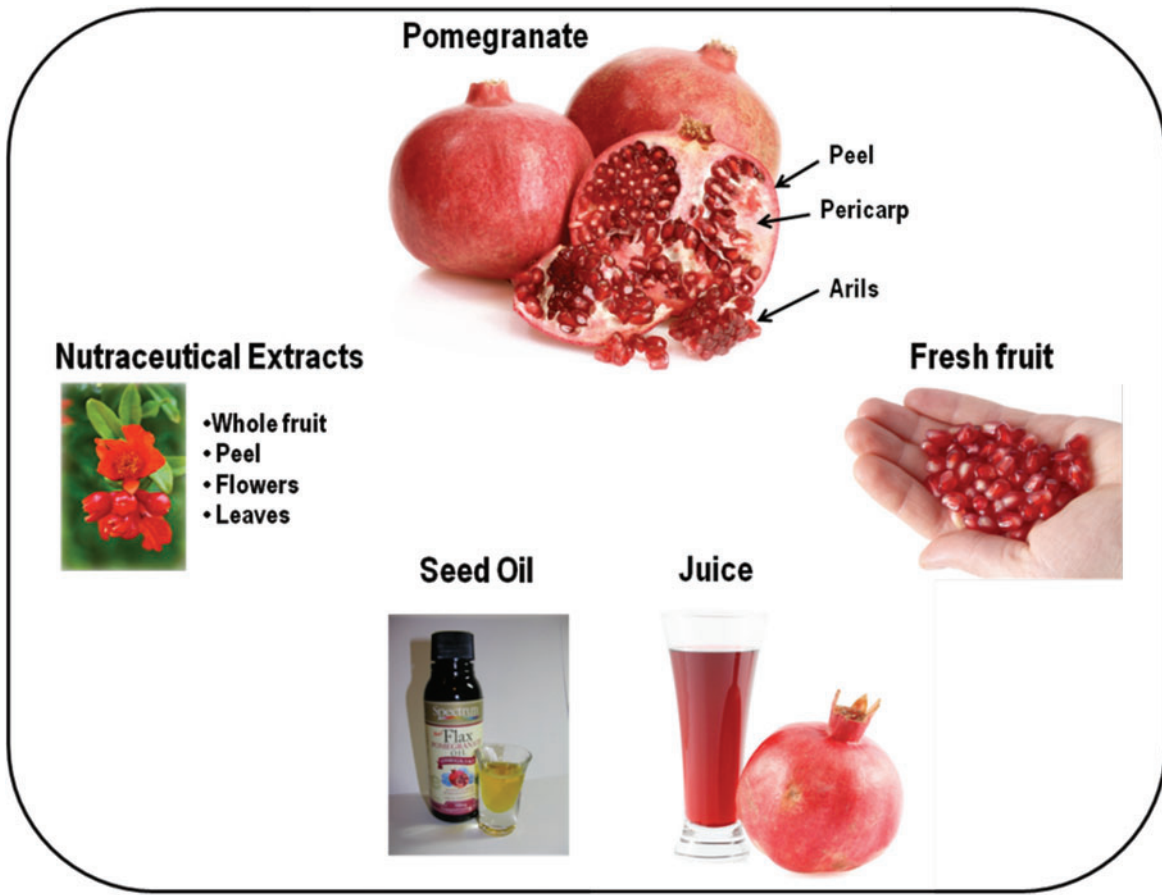


Figure 1

Pomegranate products studied for their health effects.



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Errata

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