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Pomegranate Phytochemicals: Nutraceutical and Therapeutic Values

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ABSTRACT

Pomegranate tree is the oldest domesticated tree for its countless health benefits, known even before the 21st Century. Folk medicines make use of all parts of this tree. Various researchers have identified about 153 phytochemicals, including their derivatives in pomegranate. Polyphenols are the major class of phytochemicals, extracted from almost all parts of pomegranate tree, but are most abundant in fruits. Flavonoids, hydrolysable tannins and condensed tannins are the major pomegranate polyphenols. Anthocyanins, which impart red colour to the arils, are most abundant and responsible for potential health benefits. Workers have reported more than 18 hydrolysable tannins in pomegranate leaves, bark and fruits, among which gallotannins, ellagitannins, punicalgin and punicalin have attracted most attention among researches, and which are pomegranate's most powerful antioxidants. Other phytochemicals reported in pomegranate include catechin and procyanidins, organic acids, phenolic acids, sterols, terpenoids, fatty acids, triglycerides, alkaloids and some other compounds. The prophylactic and curative potential of these bioactive compounds has been proved against cardiovascular diseases, hypertension, all types of cancers, inflammations, hyperlipidemia, diabetes, ageing, Alzheimer's disease, etc., and are, in addition, antibacterial, antifungal, antiviral, anthelmintic, vermifugal tenicidal and molluscidal agents. Pomegranate juice contains 3-fold more antioxidants than green tea and red wine as well as several common fruits like apples, grapes, etc. Researchers have used various technologies to extract, purify and analyse these phytochemicals for chemical characterization and evaluation of their antioxidant capacities. Research in this area is expanding rapidly because of an understanding of the fact that naturally available phytonutrients offer the best protection against many diseases.

Keywords: antimicrobial, antioxidant, bioactivity, bioavailability, cancer, cardiovascular, hypertension, nutritive, polyphenol, toxicity

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INTRODUCTION

It has been firmly established and documented that the dietary intake of several berry fruits belonging to species of *Rubus*, *Vaccinium*, *Fragaria*, *Ribes*, etc. have a profound impact on human health (Seeram 2008). Recently there has been a surge in the consumption of an exotic berry type fruit, the pomegranate (*Punica granatum* L., family Punicaceae). Researches have proved beyond doubt that pomegranate fruits or their processed products prevent disease and have a positive and profound impact on human health.

Pomegranate is the most historic fruit tree domesticated for its innumerable health benefits, is as old as human life, and is a food medicine of great importance since folk medicines have been using all parts of this tree for a long time (Longtin 2003) and its use in modern-day medicine continues. People in the Middle East, Iran and India have used it as medication for its antimicrobial activity. Ancient physicians used pomegranate for curing numerous diseases. It is believed to be a symbol of fertility resulting from the seeds (Langely 2000).

The epithets – the ancient fruit, the exotic fruit, the power house of energy, the super fruit, the symbol of bounty and fertility – used from time to time by various authors (Langely 2000; Daniells 2007; Smulevitz 2010; Starling 2010), aptly describe the importance of pomegranate in human health. Researchers have conducted various studies on chemicals having nutritive, medicinal and/or harmful effects in several horticultural and agricultural crop plants but pomegranates are one of the fruit crops that store several important chemicals and have immense economic value. All its parts, namely roots, stems, leaves, bark, flowers, fruits, seeds, rind, etc. are being exploited in pharmacy, the leather or dye industry or for decorative value. It is a powerhouse of energy due to its immense nutritive value; in addition, it has several beneficial phytochemicals, which earn

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Invited Review

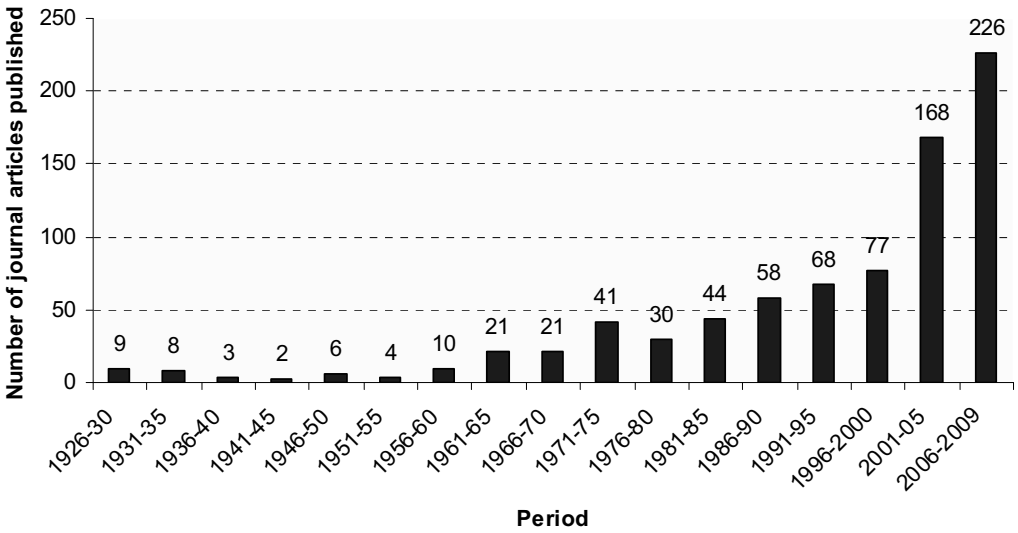

Fig. 1 Popularity of *Punica granatum* over time as shown by number of research articles on pomegranate between 1926-2009 [Source: Australian New Crops,The articles listed in 'Listing of Interesting Plants of the World- *Punica granatum* - covering Biological abstracts and Biosis Previews – available on www.australiannewcrops@gmail.com, have been plotted for every five year, except 2006-09 for four years which includes references of 2008-09 available collected from various sources.]

it the name 'super fruit'. It is because of these bioactive chemicals that today nutraceutical industries are having proliferating business with pomegranate as the most preferred food/food product in the European, American and some Asian markets (statistics not avialable).

In this review, the nutraceutical and therapeutic values of pomegranate are not discussed under separate headings; nutraceutical infact is a term combining the words 'nutrition' and 'pharmaceutical.' It is a food/food product providing health benefits, including prevention and treatment of disease. The term nutraceutical according to the latest edition of the *Merriam-Webster Dictionary* is, 'a foodstuff (fortified or a dietary supplement), that provides health benefits'. Hence, we consider here, nutraceutical food, as a food having 'nutrition' as well as 'therapeutic' values. Phytochemicals are complex secondary plant metabolites that have human health benefits but are not essential nut-rients. Seeram *et al*. (2006) reported 122 and Lansky and Newman (2007) reported 102 phytochemicals with their derivatives and chemical structures. There are as many as 153 phytochemicals, excluding essential nutrients, reported by various groups in different parts of the tree (**Tables 1-6**).

HISTORICAL ACCOUNT: MEDICINAL PROPERTIES OF POMEGRANATE

Lloyd (1897) has given a good account of the historical references on therapeutic uses of pomegranate. According to this report medicinal properties of different parts of pomegranate plant have been clearly reported by Greek authors – Theophrastus and Dioscorides, Roman authors – Cato Censorius, Pliny, Celsus, and others much before the first century and Tragus and Bauhinus in the middle ages.

The bark also contains mannite and a yellow coloring matter. The rind of the fruit contains about 19 % tannic acid and wild fruits have higher astringency. The flowers also have tannic acid (Dioscorides in the middle of 1st century)

The rind of pomegranate fruit was used as tanning material by Greeks (Pliny 23-79 AD), Later Moors introduced tanning into Spain, and their finest Moroccos were tanned with rind of this fruit (Osborne 1861). Tunis and Japan also used it for tanning. Since time immemorial, India and Afghanistan used rind for dyeing clothes (Pliny 23-79 AD). The mention of medicinal properties of pomegranate roots as a tenifuge in *Charaka-Samhita* - the oldest medical work in the world, is not clear however, the ancient people of more proximate historical age knew the anthelmintic properties of the root and rind. The Chinese, Romans (Censorius 234-149 BC, Pliny 23-79 AD, Celsus 25 BC-50 AD) and Arabians also knew this property. Since time immemorial, India used the root of the pomegranate tree with miraculous success to treat tapeworm infestations and an English physician Buchanan confirmed this fact after a long gap in 1807. He cited two successful cases treated by him and later Dr. Gomez successfully treated 14 persons in Lisbon for tapeworm in 1822 (Mérat and De Lens 1833). Later Wackenroder (1824) reported 22% tannic acid in the bark of the root. Tanret (1878, 1880) studied several alkaloids in the root-bark of pomegranate and reported pelletierine being the most prominent alkaloid found, that later proved to possess anthelmintic property. It was in the nineteenth century that the literature on pomegranate chemicals started enriching. The rising popularity of pomegranate among researchers is visible with increasing number of journal articles particularly, from 2000 onwards (**Fig. 1**). The number of research articles would be much higher for the period 2005-2010, as seen from **Fig. 1**, that for 2006-2009 (4 years), number of articles was 226 vs 168 in the previous five years (2000-2005).

PHYTOCHEMICALS RESEARCH IN THE 20th AND 21st CENTURIES

Researchers all over the Globe have compiled and reviewed the constituents of different parts of pomegranate tree and their therapeutic values (Lloyd 1897; Seeram 2006; Lansky and Newman 2007; Jurenka 2008).

Phytochemicals reported in pomegranate

Polyphenols – phenolic ring compounds, with multiple hydroxyl groups -are the major class of phytochemicals reported in pomegranate and extractable from almost all parts of pomegranate tree, however are most abundant in fruits. The fruits are the major source of dietary polyphenols. Flavonoids, hydrolysable tannins and condensed tannins are the major pomegranate polyphenols and the first two mainly extracted into pomegranate juice (PJ) from whole fruits (Gill *et al.* 2000). Among the various flavonoid polyphenols packed in pomegranate fruits, anthocyanins are in abundance. These are water-soluble pigments and impart red colour to the fruit arils as well as the characteristic flavour having mild astringency. These anthocyanins are responseble for the antioxidant properties, having potential health benefits. Fortunately, these are the major polyphenols studied in pomegranate. The other flavonoids are present in

fruit peel (Van Elswijk *et al.* 2004).

Hydrolysable tannins include ellagitannins and gallotannins and ellagic acid derivatives found in peel, membranes and seeds of the fruit though are also present in bark and leaves (Haddock *et al.* 1982; Tanaka *et al.* 1985, 1986a, 1986b; Satomi *et al.* 1993; Mavlyanov *et al.* 1997; Hussein *et al.* 1997; el-Toumy *et al.* 2001; el-Toumy and Rauwald 2002). The ellagitannins yields ellagic acid and glucose and gallotaninis yields gallic acid and glucose (Haslam 1989). These are the predominant polyphenols found in PJ and account for 92% of its antioxidant activity (Gil *et al*. 2000) and 50% of this antioxidant activity in Juice is contributed by punicalagin. The soluble polyphenol content is only 0.2 to 1.0% (Narr *et al.* 1996). These tannins are esters of gallic and ellagic acids and the core molecule consists of polyphenols such as sugars.

More than 18 hydrolysable tannins have been reported (Tanaka *et al*. 1985, 1986a, 1986b) in pomegranate leaves, bark and fruits. Gallotannins, ellagitannins, punicalgin and punicalin among which have attracted more researches due to their beneficial effects. The tannins are the most powerful antioxidants in various pomegranate tree parts. Recently, use of pomegranate fruit fresh or processed products has increased as herbal medicine and/or dietary supplements. The PJ extracts have both polyphenol and fatty acid constituents.

The other phytochemicals reported in pomegranate include catechin and procyanidins, organic acids, phenolic acids, sterols, terpenoids, fatty acids, triglycerides, alkaloids and some other compounds.

These bioactive compounds have been proved to have prophylactic and curative potentials for dreaded diseases like heart strokes, atherosclerosis, all types of cancers, inflammations, hyperlipidemia, diabetes, hypoxia, ischemia, ageing, Alzheimer disease and in addition are antibacterial, antifungal, antiviral, anthelmintic, vermifugal and tenicidal agents.

Distribution of phytochemicals in various plant parts

Tables 1-6 summarize various phytochemicals reported in different parts of pomegranate tree. The various phytochemicals reported in pomegranate fruit include predominantly anthocyanins, anthocyanidins, catechin and procyanidins (Santagati *et al*. 1984; Mavlyanov *et al*. 1997; Hernández *et al*. 1999). The fruit juices have organic acids (Artik *et al*. 1998; Poyrazoglu *et al*. 2002). The seed and seed oil have ellagic acid derivatives (Chen *et al*. 2003; Wang *et al*. 2004), fatty acids (Chen *et al*. 2003), triglycerides (Yusuph and Mann 1997; Fatope *et al*. 2002), sterols and terpenoids (Brieskorn and Keskin 1955; Batta and Rangaswami 1973; Ahmed *et al*. 1995; El Wahab *et al*. 1998). The fruit peel and pericarp are rich in ellagitannins and gallotannins (Tanaka *et al*. 1986; Satomi *et al*. 1993; Mavlyanov *et al*. 1997), ellagic acid (Satomi *et al*. 1993; Nawwar and Hussein 1994), flavonols (Mavlyanov *et al*. 1997; Artik *et al*. 1998; Chauhan and Chauhan 2001; Lugasi and Hovari 2002; Van Elswijk *et al*. 2004). The tree bark and heartwood are source of ellagitannins and gallotannins (Tanaka *et al*. 1986a, 1986b; Mavlyanov *et al*. 1997; el-Toumy *et al*. 2001), ellagic acid (Nawwar and Hussein 1994; el-Toumy *et al*. 2001; el-Toumy and Rauwald 2002), flavonols (Chuahan and Chuahan 2001), gallyol derivatives (el-Toumy *et al*. 2001), sterols and terpenoids (Fayez *et al*. 1963), mannitol (Fayez *et al*. 1963) and alkaloids (Neuhoerfer *et al*. 1993), whereas in root bark only two alkaloids- hygrine and nonhygrine have been reported (Neuhoerfer *et al*. 1993). The leaves also have several phytochemicals belonging to ellagitannins and gallotannins (Haddock *et al*. 1982; Tanaka *et al*. 1985; Hussein *et al*. 1997; el-Toumy and Rauwald 2002), flavonols (Nawwar *et al*. 1994; Srivastava *et al*. 2001), gallyol derivatives (Nawwar and Hussein 1994; Hussein *et al*. 1997) and alkaloids (Nawwar *et al.* 1994).

The entire pomegranate plant, including roots, is a rich source of polyphenols. el-Toumy and Rauwald (2002) reported that the polyphenol concentrations in the extract of pomegranate tree parts was highest in bark, and reduced in stem, whole fruit juice and leaves in decreasing order. The soluble polyphenol content varies within the limits of 0.2 to 1.0% and includes mainly ellagic tannins, gallic and ellagic acids, anthocyanins and catechins (Narr *et al*. 1998; el-Toumy *et al*. 2001).

The pomegranate flower powder extract in ethanol also contained polyphenols (45 nmoles of total polyphenols/mg flower weight). Among the various pomegranate fruit constituents – aril juice, skin (red), membrane (white) and seeds contain polyphenol with the highest concentration observed in the membrane fraction and the lowest concentration in the seed aqueous extract (Noda *et al*. 2002). Anthocyanins and tannin fractions were isolated from the skin, membrane, aril juice and seeds. These phytochemical classes contained the highest polyphenol concentration and were the most potent antioxidant with the lowest weight concentrations required for the inhibition of copper ion-induced low-density lipoprotein (LDL) by 50%. The antioxidant activity was higher in juice extracted from whole fruit than that of juice obtained from arils only, suggesting that while processing, some of the hydrolysable tannins present in the rind are extracted into the juice. Arils contain substantial amount of polyphenols such as gallic acid, protocatechinuie acid, chlorogenic acid, caffeic acid, ferulic acid, coumaric acids and catechin (Poyrazoglu *et al.* 2002). Punicalagin was isolated from pith and carpellary membrane of pomegranate fruit (Kulkarni *et al*. 2004). Two new compounds coniferyl 9-*O*-[α-D-apiofuranosyl(1->6)]-*O*-β-D-glucopyranoside and sinapyl 9-*O*-[β-D-apiofuranosyl(1->6)]-*O*-β-D-glucopyranoside, were isolated from the seeds of *P. granatum*, together with five known compounds, 3,3'-di-*O*-methylellagic acid, 3,3',4'-tri-*O*-methylellagic acid, phenethyl rutinoside, icariside D1, and daucosterol (Wang *et al*. 2004)

It was demonstrated that the aqueous extracts of pomegranate membrane had more powerful antioxidants in comparison to the aril juice (Noda *et al*. 2002), based on an equal polyphenol concentration. Guo *et al*. (2003) also found that pomegranate peel had the highest antioxidant activity among the peel, pulp and seed fractions of 28 kinds of fruits commonly consumed in China. The contents of total phenolics, flavonoids and proathocyanidins were also higher in peel extract than in pulp extract. The large amount of phenolics contained in peel extract was responsible for its antioxidant ability. The results showed that pomegranate peel extract had markedly higher antioxidant capacity than the pulp extract in scavenging superoxide anion, hydroxyl and peroxyl radicals as well as inhibiting LDL oxidation (Li *et al*. 2006). Extracts from whole fruit exhibited an approximately 20-fold higher antioxidant activity than the level found in the juice from arils alone (Tzulker *et al*. 2007). The antioxidant activities of fruit parts (peel, juice, and seed) and extracts of three pomegranate varieties in China were investigated by Guo *et al.* (2007) and found peel extract of red pomegranate had the best effect on the scavenging ability of superoxide anion and the seed extract of white pomegranate could scavenge hydroxide radical most effectively. In a study based on 10 cultivars grown in Iran, the pomegranate peel extract had markedly higher antioxidant capacity than the pulp extract. The peel extract of the sweet white peel cultivar appeared to have more potential as a health supplement rich in natural antioxidants compared to the pulp and peel extracts of other pomegranate cultivars (Hajimahmoodi *et al.* 2008). Pomegranate peel extract were found to have the highest total polyphenols and and total flavonols and also exhibited superior antioxidant activity followed by apple peel, citrus peel, banana peel and 5 other agricultural wastes (Bushra 2008).

The most investigated part of pomegranate fruit is the seed that yield seed oil, which has above 60% punicic acid (Kohno *et al.* 2004). Seed oil has other fatty acids like arachide, linolic, oleic, palmitic, stearic and palmitoleic acid (Melgarejo *et al.* 1995). Presence of sex hormones such as estrone and cocumestrol in pomegranate seed have been re-

Table 1 Phytochemicals reported in pomegranate juice.

Phytochemical	Chemical class	Reference
Cyanidin	Anthocyanins	Santagati *et al.* 1984; Mavlyanov *et al.* 1997; Artik *et al.* 1998; Hernández *et al.* 1999
Cyanidin-3-rutinoside		
Delphinidin		
Cyanidin 3-*O*-glucoside		
Cyanidin 3,5-di-*O*-glucoside		
Delphinidin 3-*O*-glucoside		
Delphinidin 3,5-di-*O*-glucoside		
Pelargonidin 3-*O*-glucoside		
Pelargonidin 3,5-di-*O*-glucoside		
Succinic acid	Alphatic oganic acids	Poyrazoglu *et al.* 2002
Tartaric acid		
Fumaric acid		
Citric acid		
L-Malic acid		
Gallic acid	Hydroxy benzoic acids	Artik *et al.* 1998; Amakura *et al.* 2000b; Wang *et al.* 2004; Huang *et al.* 2005b
Ellagic acid		
Protocatechuic acid		
Caffeic acid	Hydroxy cinnamic acid	Artik *et al.* 1998; Amakura *et al.* 2000a
Chlorogenic acid		
o-Coumaric acid		
p-Coumaric acid		
Quinic acid		
Cinnamic acid		
Flavan-3-ol	Flavan-3-ols	de Pascual Teressa *et al.* 2000
Catechin		
Epicatechin		
Epigallocatechin 3-gallate		
Quercetin	Flavonols	Artik *et al.* 1998; Rena *et al.* 2009
Isoquercetin		
Rutin		
Oxalc acid	Flavonol glycosides	
Ferulic acid		
Glucose	Simple sugars	Gabbasova and Abdurazakova 1969; Cui *et al.* 2004
Fructose		
Sucrose		
Proline	Amino acids	Seppi and Franciosi 1980; Velioğlu *et al.* 1997
Valine		
Methionine		
Tryptamine	Indoleamines	Artik *et al.* 1998; Badria 2002
Serotonin		
Melatonin		
Quinic acid	Cyclitol carboxylic acids	Artik *et al.* 1998; Amakura *et al.* 2000a
(-)-Catechin	Catechin and procyanidins	Artik *et al.* 1998
Procyanidin B 1		
Procyanidin B 2		

ported (Moneam *et al.* 1988; Melgarejo *et al.* 1995), however, a recent paper did not detect presence of estrol, estradial and testosterone in it or fruit juice (Choi *et al.* 2006).

Pomegranate *vis-à-vis* other fruit juices and beverages

Pomegranates are an excellent dietary source of polyphenolic antioxidants. They contain 11.33 m mol of total antioxidants/100 g of edible part, whereas wild bilberries (*Vaccinium mycitillus*) has only 8.23 m mol, grapes (*Vitis vinifera*) 2.42 m mol and tomatoes (*Lycopersicom esculentum*) 0.34 m mol/0.34 (Halvorsen *et al.* 2002). PJ contains three folds higher antioxidant as compared to green tea and red wine (Gil *et al.* 2000; Surh 2003).

Studies have shown that cold-pressed seed oil from pomegranate fruits showed antioxidant activity close to that of butylated hydroxylanisole and green tea, and significantly greater than that of red wine (Schubert *et al.* 1999; Gil *et al.* 2000). Pomegranate wine also significantly reduced oxidative stress induced by tumor necrosis factor-alpha (TNF-∞) in endothelial cells as well as the activation of nuclear factor-kappa beta NF-Kβ (Schubert *et al.* 2002).

The antioxidant activity of 19 fruits and five fruit juices used in Indian diet was evaluated. Second highest phenolic content was recorded in anthocyanin-rich fruits like red pomegranate (270 mg/100 g), out passed by only *Amla* (*Phyllanthus officinalis*) fruits which had the highest phenol content (290 mg/100 g), highest antioxidant activity (56.8 mM), β-carotene lineolate system (92%) and super-oxide anion scavenging activity (85%). Appreciably high phenols were present in fruits like plums (250 mg/100 g), *Jamun* (*Syzygium cumini*; 215 mg/100 g) and black grapes (192 mg/100 g). Processing in the form of juices resulted in a significant increase in total phenols and antioxidant activity (Kaur and Kapoor 2005).

Among five most common fruits grown in Turkey, tested for antioxidant activity, pomegranate had the highest (62.7%) antioxidant activity, followed by quince (60.4%), grape (26.6%), apple (25.7%) and pear (13.7%). Total phenolic and flavonoid contents in fruits varied from 326 to 4306 mg catechin/kg and from 282 to 2115 mg catechin/kg, respectively. A highly significant correlation between antioxidant activity and total phenolic content was determined in fruits (r^2 = 0.9307). Total phenolic content is the major contributor to the antioxidant activity of fruits (Karadeniz *et al.* 2005).

Drogoudi *et al.* (2005) evaluated twenty pomegranate (*Punica granatum* L.) accessions – collected from different regions in northern Greece – under uniform conditions for

Table 2 Phytochemicals reported in pomegranate seed and seed oil.

Phytochemical	Chemical class	Reference
Seed		
Ellagic acid	Ellagic acid derivatives	Wang *et al.* 2004
3,3'–di-*O*-methyl ellagic acid	(hydroxybenzoic acids)	
3,3, 4'-tri-*O*-methyl ellagic acid		
Asiatic acid	Triterpenoids	Batta and Rangaswami 1973
Betulinic acid		
Daucosterol	Sterols	Brieskorn and Keskin 1955; Brieskorn and
Cholesterol		Keskin 1994; Ahmed *et al.* 1995; Wahab *et al.*
β-Sitosterol		1998; Wang *et al.* 2004
Camesterol		
Stigmasterol		
17-α-Estradiol	Sex steroids	Heftmann *et al.* 1966; Dean *et al.* 1971; Wahab
Estrone		*et al.* 1998; Kim *et al.* 2002; Lansky *et al.*
Testosterone		2005a
Estriol		
Tocopherol	Tocopherols	Kim *et al.* 2002
Di-*O*-punicyl-*O*-octadeca-8Z-11Z-13E-trienylglycerol	Phenyl aliphatic glycosides	Wang *et al.* 2004
Coniferyl 9-*O*-[β-D-apiofuranosyl-(1-6)]-*O*-β-D-glucopyranoside		
Sinapyl 9-*O*-[β-D-apiofuranosyl-(1-6)-β-D-glucopyranoside		
Phenylethyl rutinoside		
Icariside D1		
Seed oil		
Linoleic acid	Non-conjugated fatty acids	Hopkins and Chisholm 1968; Schubert *et al.*
Linolenic acid		1999; Hornung *et al.* 2002; Chen *et al.* 2003
Oleic acid		
Palmitic acid		
Stearic acid		
Eicosenoic acid		
Punicic acid (*cis*-9, *trans*-11, *cis*-13 octadecatrienoic acid)	Conjugated fatty acids	Schubert *et al.* 1999
1-*O*-trans, *cis*, *trans*, octadecatrienol glycerol	Triglycerides	Fatope *et al.* 2002
1-*O*-isopentyl-3-*O*-octadec-2-enoyl glycerol		
Tri-*O*-punicylglycerol		Yusuph and Mann 1997
Cerebroside	Glycolipids	Tsuyuki *et al.* 1981
Coumestrol	Coumestan	Micheli *et al.* 1962; Moneam *et al.* 1988

physical and chemical characters. A negative coorelation existed between the fruit weight, fruit hue and total anthocyanin content. They found that small and red pomegranate had higher antioxidant activity.

It has also been demonstrated that PJ contains higher concentration of total polyphenols (5 mmol/L) in comparison to other fruit juices such as orange, grapefruit, grape, cranberry, pear, pineapple, apple and peach, which contain only 1.3 to 4 mmol/L of total polyphenols (Rosenblat and Aviram 2006). The antioxidant capacity was estimated on the basis of antioxidant potency, ability to inhibit LDL oxidation, and total polyphenol content of the commonly consumed polyphenol-rich beverages in the United States. The PJ showed maximum antioxidant capacity followed by red wine, Concord grape, blueberry juice, black cherry juice, ac'ac juice, cranberry juice, orange juice, iced tea beverages, apple juice (Seeram 2008).

Wolfe *et al*. (2008) studied cellular antioxidant activity, total phenolic contents, and oxygen radical absorbance capacity of 25 common fruits consumed in United States. They found that pomegranate and berries (wild blueberry, blackberry, raspberry, and blueberry) had the highest cellular antioxidant activity values, whereas banana and melons had the lowest, however apples were found to be the largest contributors of fruit phenolics due to its highest consumption. The PJ was potentially better than apple juice in improving antioxidant function in the elderly consuming 250 ml/day of either of the juices for 4 weeks (Guo *et al*. 2008). They did not find significant differences in plasma ascorbic acid, vitamin E, and reduced glutathione contents between the two fruits hence, they concluded that the phenol compounds in PJ accounted for the improved antioxidant activity.

Among 35 Ugandan fruits and vegetables tested for total antioxidant activity, the highest antioxidant activity per serving size was in pomegranate, African black olive (*Canarium schweinfurthii*), guava (*Psidium guajava*), mango (*Mangifera indica*) and tree tomato (*Cyphomandra betacea*) in decreasing order with values ranging from 8.91 to 3.00 mmol/serving (Stangeland *et al*. 2009). Antioxidant values in the range of 47.25 to 0.77 mmol/100 g fresh weight were reported earlier (Stangeland *et al*. 2007).

TECHNIQUES USED FOR STUDYING PHYTOCHEMICALS

Researchers working on phytochemicals have developed technology for the extraction of phytochemicals in suitable solvents; their purification through chemical methods such as hydrolyses followed by analysis using various chromatographic techniques, mass spectrometry and nuclear magnetic resonance.

Extraction

Various workers have used solvents like – chloroform, ethanol, methanol, water, etc. for the extraction of phytochemicals from various parts of the pomegranate tree. Pomegranate peels were powdered and extracted with ethyl acetate, acetone, methanol, and water for 1 hr each at room temperature, and methanol was best for extraction of polyphenols (Negi and Jayaprakash 2003). Methanol extract exhibited stronger radical-scavenging effect than others did. Bushra and his coworkers (2008) found 80% methanol extracts were best for extracting antioxidants from pomegranate peels. Alkaline extraction of esterified ferulic acid was done from pomegranate peel and response surface methodology (RSM) was used for optimization of esterified ferulic acid extracts, which resulted in a 1.3-fold increase as compared to the unoptimized conventional extraction technique (Tilay *et al.* 2008).

Table 3 Phytochemicals reported in pomegranate fruit peel and pericarp.

Phytochemical	Chemical class	Reference
Casuarinin	Ellagitannins	Tanaka *et al.* 1986a; Tanaka *et al.* 1986b; Satomi *et al.* 1993; Nawwar and Hussein 1994; Gil *et al.* 2000
Pedunculagin		
Punicalin		
Punicalagin		
Corilagin		
Gallagyldilacton		
Granatin A		
Granain B		
Terminalin/gallyldilacton		
Tellimagrandin		
2,3-(s)-hexahydroxydiphenoyl-D-glucose		
Methyl gallate	Gallyol derivative	Rena *et al.* 2009
Ellagic acid	Hydroxybenzoic acids	Amakura *et al.* 2000b; Wang *et al.* 2004; Huang *et al.* 2005b
Gallic acid		
Caffeic acid	Hydroxycinnamic acids (phenylpropanoids)	Artik *et al.* 1998; Amakura *et al.* 2000a
Chlorogenic acid		
p-Coumaric acid		
Quinic acid	Cyclitol carboxylic acids and their salts	Artik *et al.* 1998; Amakura *et al.* 2000a
Kaempferol	Flavonols	Mavlyanov *et al.* 1997; Artik *et al.* 1998; Chauhan and Chauhan 2001; Lugasi and Hovari 2002; Van Elswijk *et al.* 2004
Quercetin		
Myricetin		
Quercimeritrin		
Quercetin-3-*O*-rutinoside		
Quercetin-3,4′-dimethyle ether 7-*O*-α-L-arabinofuranosy-(1-6) β-D-glucoside		
Peelletierine	Pelletierine alkaloids	Neuhofer *et al.* 1993; Vidal *et al.* 2003
Luteolin	Flavones	Van Elswijk *et al.* 2004
Rutin	Flavonol glycosides	Artik *et al.* 1998; Van Elswijk *et al.* 2004
Kaempferol 3-*O*-glycoside		
Kaempferol 3-*O*-rhamnoglycoside		
Flavan-3-ol	Flavan-3-ols	de Pascual Teresa *et al.* 2000
Catechin		
Epicatechin		
Epigallocatechin 3-gallate (ECGC)		
Naringin	Flavanone glycoside	Kim *et al.* 2002
Delphinidin	Anthocyanidins	Noda *et al.* 2002
Cyanidin		
Pelargonidin		

Purifications

Sample purification using chemical methods is an important step for analysing complex structures of pomegranate phytochmeicals. Sample purification using acidic, basic or enzymatic hydrolysis with tannase has been reported (Tanaka *et al*. 1986a, 1986b).

Analysis

The hydrolysates after purification can be analysed for complex structures of the various phytochemicals specially polyphenols using chromatographic techniques like absorption and adsorption chromatography, high performance liquid chromatography (HPLC) and medium performance liquid chromatography (MPLC) (Tanaka *et al*. 1985, 1986a, 1986b; Seeram *et al*. 2005; Bushra *et al.* 2008; Noe Aguilar *et al.* 2008; Tanner *et al*. 2008). Negi and Jayaprakash (2003) used HPLC using 1,1-diphenyl-2-picrylhydrazyl for comparing radical-scavenging activity of dried ethyl acetate, acetone, methanol and water extracts of pomegranate peels with butylated hydroxyanisole at 5, 10, 25, and 50 ppm. Advanced technologies like mass spectrometery (Krueger *et al.* 2000; Porter *et al.* 2001; Krueger *et al.* 2003, 2004; Reed *et al.* 2005).has provided a more reliable tool for the investigation of polyphenols. Application of matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) recently has assisted in the detection of hydrololysable tannins in pomegranate arils (Mullen *et al.* 2003; Afaq *et al.* 2005; Seeram *et al.* 2005). They also found that coupling of HPLC with tandem mass spectrometry (LC-MS^n) was useful for differentiating ellagic acids and quercetin aglycons in pomegranate. Lipid soluble phytochemicals found in seed and seed oil of pomegranate such as fatty acids, triglycerides etc. were identified by Schubert *et al.* (1999) (Schubert *et al.* 1999) using gas chromatography (GC) along with flame ionization and mass spectrometric detectors (GC-MS). Tanaka (1985, 1986a, 1986b) confirmed, absolute structures of hydrolysable tannins and related compounds along with their isomers – ^{1}H and ^{13}C–NMR (nuclear magnetic resonance). Spectroscopic data analysis elucidated the structures of two glucopyranosides isolated from pomegranate seed (Wang *et al*. 2005).

Lu *et al*. (2008) reported a new process for ellagic acid production from pomegranate husk by extraction of tannins using various solvents, acid concentration and reaction time for acid hydrolysis and the volume of methanol used for purification and then recrystallization. This method produced high-purity ellagic acid, is easy to scale up and hence, useful for industrial applications as well as for laboratory experiments. The cost of production is also low. The production of ellagic acid is easier and the yield and purity of ellagic acid produced in this way are higher than earlier methods.

The total phenolic content was determined using Folin-Ciocalteu method by Allam and Bassiuny (2002). Noe-Aguilar and co-workers (2008) evaluated the content of proteins, crude fibres, lipids, reducing and total sugars following the Association of Analytical Chemists (AOAC), International methods. Tannins were analyzed using a spectrophotometric method, biodegradation of ellagitannins was monitored kinetically and the accumulation of gallic and ellagic acids was determined by HPLC. Tilay and fellow researchers (2008) analyzed ferulic acid by means of HPLC

Table 4 Phytochemicals reported in pomegranate bark and heartwood.

Phytochemical	Chemical class	References
Stem bark		
Castalgin	Ellagitannins and gallotannins	Tanaka *et al.* 1986a, 1986b; El-Tounmy *et al.* 2001
Casuariin		
Punicacortein A		
Punicacortein B		
Puniglucoin 2-*O*-galloyl-4,6(S,S) gallagoy-D-glucose		
Punicacortein C		
Punicacortein D		
Casuarinin		
Pedunculagin		
Punicalin		
Punicalagin		
Punigluconin 2,3-di-*O*-galloyl-4,6-(*S*)-hexahydroxydiphenoylgluconic acid		
Ellagic acid	Ellagic acid	Nawwar and Hussein 1994
Humarian	Dimeric gallic acid glucoside	Tantray *et al*. 2009
Quercetin-3,4′-dimethyle ether 7-*O*-α-L-arabinofuranosy-(1-6) β-D-glucoside	Flavonols	Chuhan and Chuhan 2001
Friedooleanan-3one	Sterols and terpenoids	Fayez *et al.* 1963
Pelletierine	Pelletierine alkaloids	Neuhofer *et al.* 1993; Vidal *et al.* 2003
N-methyl pelletierine		
Pseudopelletierine		
Nor-pseudopelletierine		
Sedridine	Piperidine alkaloids	Neuhofer *et al.* 1993
2,3,4,5-tetrahydro-6-propenyl-pyridine	Pyridine alkoloids	Neuhofer *et al*. 1993
3,4,5,6-tetrahydro-amethyl-2pyridine ethanol		
Manitol	Other compounds	Fayez *et al.* 1963
Root bark		
Peelletierine	Pelletierine alkaloids	Neuhofer *et al.* 1993; Vidal *et al.* 2003
N-Methylpelletierene		
Pseudopelletierene		
Hygrine	Pyrrolidine alkaloid	Neuhofer *et al.* 1993
Norhygrine		
Sedridine	Piperidine alkaloids	Neuhofer *et al.* 1993
2-(2-Hydroxypropyl)Δ^1- piperideine		
2-(2-Propenyll)Δ^1- piperideine		
Punicalin	Ellagitannins	Tanaka *et al.* 1986a; Gil *et al.* 2000
Punicalagin		
Punicacortein A		
Punicacortein B		
Punicacortein C		
Punicacortein D		
Punigluconin 2,3-di-*O*-galloyl-4,6-(*S*)-hexahydroxydiphenoylgluconic acid		
Heartwood		
Corilagin	Gallotannins	Mavlyanov *et al.* 1997; El-Toumy *et al.* 2001
Ellagic acid, 3'-*O*-methyl-3,4-methylene	Ellagic acid derivative	El-Toumy *et al.* 2001; El-Toumy and Rauwald 2002
Eschweilenol C		
Diellagic acid rhamnosyl (1-4) glucoside		
Methyl gallate	Simple gallyol derivatives	El-Toumy *et al.* 2001

having 50.89% purity. He further purified it by adsorption chromatography using Amberlite XAD-16 followed by preparative high-performance thin-layer chromatography (HPTLC). The recovery of Amberlite XAD-16 purified ferulic acid was 57.97% (1.35-fold) and after preparative HPTLC 95.35% (2.53-fold) as compared to 50.89% with HPLC.

Evaluation of antioxidant activity

Kelawala and Ananthanarayan (2004) used *in vitro* method involving the measurement of oxidation of linoleic acid by fluorimetry for determining the antioxidant activity of selected natural food materials. The antioxidant activities of pomegranate peel, juice, and seed and extracts of three pomegranate varieties in China were investigated by using a chemiluminescence method *in vitro* (Guo *et al*. 2007). Seeram *et al*. (2008) applied 4 methods for evaluating antioxidant potency – Trolox equivalent antioxidant capacity, total oxygen radical absorbance capacity, free radical scavenging capacity by 2,2-diphenyl-1-picrylhydrazyl (DPPH), and ferric reducing antioxidant power (FRAP). For testing of antioxidant functionality i.e., inhibition of LDL, he used oxidation by peroxides and malondialdehyde methods and evaluated total polyphenol content using gallic acid equivalents (GAEs)] of polyphenol-rich beverages.

Wang *et al.* (2004) evaluated the antioxidant activity of chemicals isolated from seed by measuring LDL susceptibility to oxidation and by determining *in vitro* malondialdehyde levels in the rat brain.

Gil *et al.* (2000) and Mustafa *et al.* (2009) evaluated the antioxidant activity of PJs by using 4 different methods: 2,2'(3-ethylbenzothiazoline)-6-sulfonic acid; α,α-diphenyl-β-pycryhydrazil; *N*,*N*-dimethyl-*ρ*-phenylenediamine and FRAP (ferric reducing ability of plasma). FRAP and trolox equivalent antioxidant capacity assays were also used by Özgen *et al.* (2008) and Cam *et al.* (2009) in addition used *o*-carotene-linoleate model system.

Radical-scavenging activity of dried ethyl acetate, acetone, methanol, and water extracts of pomegranate peels were compared with butylated hydroxyanisole at 5, 10, 25, and 50 ppm by high-performance liquid chromatography method using 1, 1-diphenyl-2-picrylhydrazyl (Negi and Jayaprakash 2003). The scavenging ability of pomegranate

Table 5 Phytochemicals reported in pomegranate leaves.

Phytochemical	Chemical class	Reference
Punicalin	Ellagitannins	Haddock *et al.* 1982; Tanaka *et al.* 1985, 1986a, 1986b; Satomi *et al.* 1993; Nawwar *et al.* 1994b; Hussein 1997; Gil *et al.* 2000; El-Toumy and Rauwald 2002
Punicalagin		
Corilagin		
Punicafolin		
1,2,3-Tri-*O*-galloyl-4C1-glucose		
Cyclic 2,4:3,6-bis(4,4',5,5',6,6'-hexahydroxy [1,1'-biphenyl]-2,2'-dicarboxylate) 1-3(3,4,5-trithydroxybenzoate)		
Apigenin	Flavones	Nawwar *et al.* 1994a
Punicafolin	Flavonols	Nawwar *et al.* 1994; Srivastava *et al.* 2001
Strictinin		
Tercatain		
5-*O*-galloy-punicacortein D		
Tellimagrandin I		
Eriodictyol-7-*O*-α-L-arabinofuranosy (1-6) β-D-glucoside		
Naringenin 4′-methylether 7-*O*-α-L-arabinofuranosy (1-6) β-D-glucoside		
Apigenin-4′-*O*-β-D-glucopyranoside	Flavone glycosides	Nawwar *et al.* 1994a
Luteolin-4′-*O*-β-D-glucopyranoside		
Luteolin-3′-*O*-β-D-glucopyranoside		
Luteolin-3′-*O*-β-D-Xylopyranoside		
Brevifolin carboxylix acid	Cyclitol carboxylic acids and their salts	Hussein *et al.* 1997
Brevifolin carboxylic acid-10 monopotassiumsulphate		
Brevifolin	Simple gallyol derivatives	Nawwar and Hussein 1994; Hussein *et al.* 1997; Wang *et al.* 2005
1,2,3-Tri-*O*-galloy-β-glucose		
1,2,4-Tri-*O*-galloy-β-glucose		
1,2,6-Tri-*O*-galloy-β-glucose		
1,4,6-Tri-*O*-galloy-β-glucose		
1,3,4-Tri-*O*-galloy-β-glucose		
1,2,3,4,6-Pent-*O* –β-galloyl		
1,2,3,4,6-Pent-*O*-Galloyl- β-D-glucose		
3,4,8,9,10-pentahydroxy-dibenzol [b,d] pyran-6-one		
N-(2′,5′-dihydroxyphenyl) pyridium chloride	Piperidine alkaloids	Nawwar *et al.* 1994; Schmidt *et al.* 2007

Table 6 Phytochemicals reported in pomegranate flowers.

Phytochemical	Chemical class	Reference
Gallic acid	Hydroxybenzoic acids	Amakura *et al.* 2000b; Huang *et al.* 2005b
Ursolic acid	Triterpenoids	Batta and Rangaswami 1973; Ahmed *et al.* 1995; Huang *et al.* 2005c
Oleanolic acid		
Maslinic acid		
Asiatic acid		
Punicaflavone	Flavone	Ali and Sharma 2006

extracts on super oxide anion, hydroxide radical, and hydrogen peroxide was determined by the pyrogallol-luminol system, the $CuSO_4$-Phen-Vc-H_2O_2 system, and the luminol-H_2O_2 system, respectively (Guo *et al*. 2007).

Seeram *et al*. (2004) employed rapid plasma extraction procedure utilizing acidic precipitation of proteins, followed by HPLC-UV analyses, for studies on bioavailability.

HEALTH BENEFITS

Although many phytochemicals have positive effect on health, very many can be toxic and harmful, however, plants containing the most harmful phytochemicals are usually not treated as foods. The major health benefits of pomegranate are because of its anthocyanin contents, which are present in appreciably large quantities and have antioxidant properties. Andreu *et al*. (2008) recently reviewed composition of pomegranate fruit juice, beneficial health effects, including association with anti-carcinogenicity and anti-inflammatory properties.

Antioxidant properties

The antioxidant agents reduce oxidative damage (damage due to oxygen) such as that caused by free radicals, which are highly reactive chemicals and attack molecules by capturing electrons and thus modifying chemical structures. Oxidative damage (oxidation) to the cells is partly responsible for the effects of ageing and certain diseases. Cells produce free radicals that are deficient in electron. In order to stabilize these free radicals react by taking electrons from certain key components in the cell and in the process, they damage these cells. Antioxidants divert this damage by donating electrons to the free radicals and stabilize them, thus, saving cell components from the scavenging effect of free radicals. The environment is also a source of free radicals caused by ultraviolet radiation or airborne pollutants, such as cigarette smoke. It is a well known fact that most free radical damage is repaired naturally; a fraction may however, remain unrepaired. This free radical damage may reduce or takeover the body's natural defense. Increase in cell damage with lapse of time leads to ageing and diseases like cancers, cardiovascular problems and some other problems. In a study on ageing mice by Zhang and Xu (2007), PJ when given at 20 ml/kg wt had significant antioxidant activity, suggesting possible role in ageing. Cataracts might develop partly because of oxidation of proteins in the lens of the eye, and some studies have shown that antioxidants might be effective in reducing age-related macular degeneration and the resulting vision loss. Polyphenols and vitamins, which have antioxidant properties, in one's diet help in countering some of the damage. Polyphenols especially anthocyanins and vitamins, present in appreciably large quantities in pomegranate (**Table 7**) can play an important role in benefiting human health.

Protection against cardiovascular diseases

Antioxidant in general lower risk of cardiovascular events by inhibiting LDL-oxidation, promotion of atherosclerosis plaque stability, improved vascular endothelial function and decreased tendency for thrombosis (Hannum 2004). Antioxidant phenols in vegetables and fruits reduce cardiovascular and age related diseases (Halliwell *et al.* 2005). Seve-

Table 7 Antioxidant activity and phenol contents of pomegranate *in comparison to* other fruits and beverages.

Parameter	Fruit	Quantity reported	Reference
Antioxidant activity	**Pomegranate arils**	11.33 mmol/100 g	Halvorsen *et al*. 2002
	Wild bilberries	8.23 mmol/100 g	
	Grapes	2.42 mmol/100 g	
	Tomatoes	0.34 mmol/100 g	
	Pomegranate fruit	62.7%	Karadeniz *et al*. 2005
	Quince	60.4%	
	Grape	26.6%	
	Apple	25.7%	
	Pear	13.7%	
	Pomegranate arils	47.25	Stangeland *et al*. 2007
	African black olive, guava, mango and tree tomato	< 47.25 to 0.77 mmol/100 g fresh weight	
	Pomegranate arils	8.91	Stangeland *et al*. 2009
	African black olive, guava, mango and tree tomato	< 8.91 to 3.00 mmol/serving	
Phenol contents	**Pomegranate fresh juice**	2117 mg/l	Gil *et al.* 2000
	Red wine	2036 mg/l	
	Green tea	1029 mg/l	
	Red pomegranate	270 mg/100 g	Kaur and Kapoor 2005
	Amla (*Phyllanthus officinalis*)	290 mg/100 g	
	Plums	250 mg/100 g	
	Jamun (*Syzygium cumini*)	215 mg/100 g	
	Black grapes	192 mg/100 g	
	Pomegranate juice	5 mmol/l	Rosenblat and Aviram 2006
	orange, grapefruit, grape, cranberry, pear, pineapple, apple and peach juice	1.3 to 4 mmol/l	

ral *in vitro* studies, animal experiments (Maron 2004; Halliwell *et al.* 2005) and clinical trials (Arts and Hollman 2005) have proved the health benefits of flavonoids and other phenolic compounds present in foods. The studies conducted by Gil *et al*. (2000) and Noda *et al*. (2002) have demonstrated that daily ingestion of PJ rich in phyphenol antioxidants including flavonoids and ellagic acid has benefits related to cardiovascular diseases by slowing progression and onset of atherosclerosis and dyslipidemia (Aviram *et al.* 2000; Kaplan *et al.* 2001; Aviram *et al.* 2002). It also reduces blood pressure in hypertensive patients (Aviram *et al.* 2004), reduces blood clotting (Loren *et al.* 2005), gives neuro-protection from brain ischemia (Loren *et al.* 2005) and increases antioxidant status of brain (Sweeny *et al.* 2002).

Fuhrman and Aviram (2006) studied the effect of PJ consumption in a patient with carotid artery stenosis for a year, recording data at an interval of 3 months. A gradual increase in arterial wall thickness resulted in control patients not consuming PJ and the increase was 10% after 1 year; where as a gradual decrease occurred in patients consuming one glass of PJ everyday and it decreased by 43% in the same period. They observed reduction in the peak systolic velocity by 12 and 28%, respectively, in the left and right carotid arteries. They also reported that continuing a diet of PJ after a stroke was also beneficial.

In an *in vitro* study with cultured human coronary artery endothelial cells exposed to high shear stress and hypercholesterolemic mice, PJ concentrate reduced the activation of redox-sensitive genes (ELK-1 and p-JUN) and increased endothelial nitric oxide synthase expression – which decreased by perturbed shear stress-in cultured endothelial cells and in atherosclerosis-prone areas of hypercholesterolemic mice. Moreover, oral administration of PJ to hypercholesterolemic mice at various stages of disease reduced significantly the progression of atherosclerosis (de Nigris *et al*. 2005). PJ significantly reduced atherosclerotic lesion areas in immune-deficient mice and intima media thickness in cardiac patients on medications (Basu and Penugonda 2009).

Pomegranate flower extract improved hyperglycemia, hyperlipidemia and fatty heart in Zucker diabetic fatty rats. These rats were a genetic animal model of type 2 diabetes and obesity. The study concluded that pomegranate flower extract and its phytochemicals oleanolic acid, ursolic acid and gallic acid inhibited lipopolysaccharide-induced nuclear factor-kappaB activation in macrophages and could reduce cardiac fibrosis in Zucker diabetic fatty rats (Huang *et al*. 2005).

Nishigaki *et al*. (2008) demonstrated, *in vitro*, that pomegranate fruit extract could inhibit lipid peroxide and enhance the antioxidant enzyme status in glycated fetal bovine serum-iron chelate exposed endothelial cells by suppressing reactive oxygen species generation, thereby, limiting the effects of the advanced glycation end-products (AGEs) to a cell-surface receptor for AGEs interaction. Pomegranate fruit extracts may therefore have therapeutic potential in the prevention and treatment of vascular complications in diabetic patients. Diabetes increases heart fibrosis resulting in increased risk for impaired cardiac function. Fibrosis formation is regulated by endothelin-1 and nuclear factor-kappaB.

Protection against hypertension

Antioxidants vitamin C, E, β carotene and coenzyme Q10 have hypertensive protection (Aviram 2000). It is hypothesized that, LDL cholesterol damages the lining of the arteries when it oxidizes. Vitamin C, vitamin E and carotenoids may help protect against the oxidation of LDL cholesterol by neutralizing free radicals (Klouche *et al*. 2004: Winklhofer-Roob *et al.* 2004).

The consumption of PJ for 1 year by carotid artery, stenosis patients resulted in reduction of systolic blood pressure from 174 ± 22 to 143 ± 17 mm Hg (18%), however diastolic blood pressure that remained 81 ± 2-3 mm Hg before or after the treatment, did not change, (Kitiyakara and Wilcox 1998; Singh *et al*. 1999). It was found that blood serum angiotensin converting enzyme (ACE) activity in the blood serum of hypertensive patient decreased significantly (36%) within 2 weeks of PJ consumption. The effect was attributed to antioxidants such as tannins present in PJ. The PJ has inhibitory effect on serum ACE activity as well as cytochrome pysoenzymes activity that metabolize 'ACE' inhibition (He *et al.* 1998; Aviram *et al.* 1999). ACE activity enhances blood pressure and accelerates atherosclerosis hence PJ reduces the hypertension. Studies also proved that PJ also reduced significantly (up to 11% in 2 weeks) collagen induced platelet aggregation, responsible for enhanced atherogensclerosis atherogenicity (Aviram *et al.* 2000). Studies were conducted on effect of PJ consumption on serum lipid profile in diabetic patients with hyper-

lipidemia having cholesterol level higher than 5.2 m mol/l and triglyceroids levels higher than 2.3 m mol/l (Esmaillzadeh *et al*. 2004). After 8 weeks LDL-cholesterol significantly reduced, however HDL-cholesterol or serum in glyceroids did not reduce significantly. Later in a study, total cholesterol, LDL cholesterol/high-density lipoprotein-cholesterol and total cholesterol significantly reduced after consumption of 40 g concentrated fruit juice for 8 weeks by type II diabetic patients with hyperlipidaemia having total cholesterol or triglycerides ≥ 200 mg/dl (Esmaillzadeh *et al*. 2004). Concentrated PJ consumption could therefore, modify heart disease risk factors in these hyperlipidaemic patients.

Two weeks of PJ consumption resulted in a small but highly significant, decrease of 16% in susceptibility to free radical induced lipid pre oxidation in human plasma. This further decreased to 21% when PJ was given for additional 2 weeks, however once PJ intake was stopped plasma lipid per oxidation returned to higher values within 4 weeks (Fuhrman and Aviram 2001). It also reduces a serum oxidative status and thus inhibited plasma lipid per oxidation in patients with carotid artery stenosis. The susceptibility to the patient's plasma to free radical induced oxidation decreased after 12 months of PJ consumption by 62% (from 20 ± 18 at baseline to 79 ± 6 nmol of peroxides/ml). Basu and Penugonda (2009) reported decreased lipid per oxidation in patients with type 2 diabetes, and systolic blood pressure and serum angiotensin converting enzyme activity in hypertensive patients (Aviram and Dornfeld 2001).

Pomegranate peel extracts also possess significant antioxidant activity (Chindambara *et al.* 2002). Patients with carotid artery stenosis resulted in a significant reduction in the basal level of LDL-associated lipid peroxides by 43, 86, 89 and 90% after 3, 6, 9 and 12 months of PJ consumption, respectively and simultaneously increased the resistance of LDL to copper ion induced oxidation (Aviram *et al.* 2004). PJ inhibits oxidized LDL uptake and the cholesterol biosynthesis in macrophages, exhibiting direct anti atherogenic effects (Fuhrman *et al.* 2005). Pomegranate fruit juice and seed oil administration inhibited atherosclerosis development in hypercholesterolaemic rabbit aortas without any significant effects on lipid profile (Radjabian *et al.* 2008).

Rosenblat *et al.* (2006) reported that pomegranate fruit peel administration to apolipoprotein E-deficient mice attenuates atherosclerosis development because of decreased macrophage oxidative stress and reduced cellular uptake of oxidized LDL.

Anticancer potential

Many phytochemicals have an anti- carcinogenic (anti-cancer) action as they slow cell proliferation (division) by interfering with the cell cycle, induce apoptosis (cell suicide) inhibit phase 1 enzymes – that convert harmless substances into carcinogens and induce phase 2 enzymes – enzymes that can attach carcinogens to molecules that facilitate speedy excretion (Best 2006).

The possible anti carcinogenic effects of the pomegranate extract have been explored. The pomegranate extract has shown, to induce programmed cell death and to inhibit tumor invasion, proliferation and angiogenesis. The molecular targets of pomegranate include several proteins viz. matrix metalloproteinases, vascular endothelial growth factor, Lipoxygenase, nitrogen activated protein Kinase, migration inhibitory factor, C-Jun-N-terminal Kinase, and extracellular signal related kinase (Shishodia *et al*. 2006). They also reported role of ellagic acid found in pomegranate fruit in the prevention and therapy of cancer.

The fruit juice, peel and oil possess anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion and angiogenesis (Lansky and Newman 2007).

Pomegranate seeds are rich in sugars, polyunsaturated (n-3) fatty acids, vitamins, polysaccharides, polyphenols minerals and high antioxidant activity. The seed oil has 80% punicic acid, the 18-carbon fatty acid along with the isoflavone- genistein, the phytoestrogen coumestrol and the sex steroid estrone. Among the various botanicals studied the pomegranate has the highest known concentration of estrone (17 ms/kg dried seed) as reported by (Heftmann *et al.* 1996). A wide variety of plants produce phytoestrogen that are secondary metabolites. Controversies on use of pharmacological hormone replacement therapy (HRT) for the treatment of menopausal symptoms necessitate identification of natural sources of estrogen (Jordan 2003) and pomegranate was identified the best known source. In fact, pomegranate tree is one of the only plants in nature known to contain estrone (Van Elswijk *et al.* 2004). The seed coat contains delphinidin-3-glucoside, delphinidin-3,5-diglucoside, cyanidin-3-glucoside, cyanid-3,5-diglucoside, pelargonidin-3-glucoside and pelrgenidin-3,5-diglucoside, with delphinidin 3,5-diglucoside, being the major anthocyanin in PJ (Halvorsen *et al.* 2002).

Edible oil produced from pomegranate seeds contain linolenic acid (18:3) reported to be the predominant fatty acid (64-83%), and punicic acid (18:3: 9-*cis*, 11-*trans*, 13-*cis*) being the major isomer. A very high concentration of Phytosterols was found in the seed oil (4089–6205 mg/kg), about 3−4-fold higher than in soybean oil. The major phytosterols are β-sitosterol, campesterol, and stigmasterol (Kaufman and Weisman 2007). Because of its unique composition, seed-oil is a powerful health-benefiting agent, due to its antioxidative, anticancer, and antilipidemic properties.

The extrogenic compounds luteolin, quercetin and kaempferol have been identified in pomegranate (Van Elswijk *et al*. 2004). Studies have shown possible role of phytoestrogens in preventing range of diseases. Other major components ellagic acid, caffeic acid and punicic acid found in pomegranate fruit are having known anticancer activities. Anthocyanidins (delphinidin, cyaniding and pelargonidin) in pomegranate fruit contribute to antioxidant activity. The base of most of the information on anticancer potential of pomegranate is the *in vitro* studies. The *in vitro* studies support the therapeutic application of pomegranate in human cancers. Pomegranate extracts have shown enough potential against tumors in numerous preclinical studies to warrant clinical trials. The polyphenols in the fermented PJ have anticancer effects on human breast cancer cell *in vitro* (Van Elswijk *et al.* 2004)

The micronutrients in PJ have *in vitro* anticancer activity against breast cancer (Kim *et al.* 2002), leukemia (Kawaii and Lansky 2004) prostate cancer (Albrecht *et al.* 2004; Seeram *et al.* 2005) oral and colon cancer (Seeram *et al.* 2005).

Estrogenicity and breast cancer

Medical explorations have shown that pomegranate hull and/or root extracts prevent both fertility and abortion and treat various gynecological conditions (Lansky *et al.* 2000).

The extracts from peel, seed, the seed oil and fermented/unfermented fruit juice all have suppressive effect on human breast cancer cells *in vitro* (Settheetham *et al.* 1995). Bingham *et al*. (1998) had reported that diets rich in phytoestrogens protect against breast, prostrate, colon cancer as well as cardiovascular disease and osteoporosis (Bingham *et al.* 1998) however, in certain sections phytoestrogen could increase disease risk, particularly with dietary supplements providing high levels of phytoestrogens (Katzenellenbogen and Muthyala 2003). The whole pomegranate seed oil is more chemopreventive for breast cancer (Mehta and Lansky 2004). The fermented PJ polyphenols in comparison to fresh juice recorded approximately twice the antiproliferative activity and inhibited cancerous lesion formation induced by a popular carcinogen (Kim *et al.* 2002).

The ingredients found in pomegranate extracts having potential estrogenic activities include the steroids–estradial, estrone and estriol; coumentan: the counestral; the stigmasterol and sitosterol; flavone-Luteolin; the flavonols-kaemp-

ferol; quercetin and rectin; the flavenol-narigngin, ellagitannin-ellagic acid and the anthocyanidin-cyanidin (Heftmann *et al*. 1966; Dean *et al.* 1971; Moneam *et al.* 1988; Kim *et al.* 2002; Van Elswijk *et al.* 2004).

Several *in vitro* studies in mice and other animal models have proved estogenic activity of complex extracts of pomegranate (Sharaf and Nigm 1964) and pomegranate seed oil (Heftmann *et al.* 1966) and observed inhibition of in cell proliferation of breast cancer (Kim *et al.* 2002; Mehta and Lansky 2004). Bioavailability and maximal intake of pomegranate supplements juice extracts for getting protein response in breast cancer or other menopausal problems however require investigation.

A study of estrogenic effects in the postmenopausal woman in the age group of 52-63 was carried out (Warren *et al.* 2006) and a significant increase in estrone was reported but at a nonphysiologic level in postmenopausal women after a week of PJ supplementation. They concluded that with long term use of PJ, a mild estrogenic activity might be possible due to cumulative effect.

Tanner *et al*. (2008) in a study found that PJ may be a useful nutrient-based, non-chemotherapeutic treatment alternative for the inhibition of estrogen receptor negative breast cancer cell proliferations of feline and human breast cancer cell types.

In vitro and *in vivo* studies show that flavonoid rich polyphenol fractions from pomegranate fruit have anti proliferative, anti-invasive, anti-eicosanoid and proapoptotic effects on breast and prostate cancer cell (Settheetham and Ishida 1995; Bond *et al.* 1998; Toi *et al.* 2003; Afaq *et al.* 2005; Ahmed *et al.* 2005; Lansky *et al.* 2005).

Prostate cancer

The various biochemicals in pomegranate fruit have super additive complementary and synergestic effect against proliferation, metastatic potential and phospholipase A2 expression of human prostrate cancer cells *in vitro* (Lansky *et al.* 2005). Several *in vitro* and *in vivo* studies in mice have been done (Albrecht *et al.* 2004; Freeman *et al.* 2004; Fuhrman *et al.* 2005; Malik *et al.* 2005) which suggest chemopreventive as well as chemotherapeutic effect of PJ on human prostrate cancer. Hong *et al.* (2008) found inhibition of gene expression for key androgen-synthesizing enzymes and androgen receptor, most consistently in the LNCaP-AR cell line by pomegranate polyphenols, ellagitannin-rich extract and whole juice extract.

Pantuck *et al.* (2006) reported the first successful clinical trial of PJ in human patients with prostrate cancer. 35% of patients achieved a decrease in prostrate specific antigen during treatment with PJ and the 83% patients' average prostrate specific antigen doubling time, a surrogate marker of cancer progression, increased from 15 months to 37 months after the therapy.

In clinical studies, PJ administration led to a decrease in the rate of rise of prostate-specific antigen after primary treatment with surgery or radiation (Heber 2008).

Colon cancer

PJ, ellagic acid, punicalgin and pomegranate tannins show apoptosis in specific colon cell (Larrosa *et al*. 2006). Pomegranate seed oil which is composed of 70% of conjugated linolenic acid, suppress colon carcinogenesis hence, dietary pomegranate seed oil significantly inhibits incidence of adeno carcinomas (Kohno *et al.* 2004). In a study by Saruwatari *et al.* (2008), the results indicated that the inhibition of sulfotransferase activity by punicalagin in Caco-2 cells was responsible for the reductions seen in 1-naphthyl sulfate accumulation. They also suggested that constituents of PJ, most probably punicalagin, impair the enteric functions of sulfoconjugation and that this might have effects upon the bioavailability of drugs and other compounds present in food and in the environment. These effects might be due to the anticarcinogenic properties of PJ.

Skin cancer

Exposure to ultraviolet (UV) radiation has been associated with several acute and chronic conditions. The UV-B component may cause sunburn, hyperpigmentaion, edema, hyperplasia, immunosuppression, photo ageing, and skin cancer whereas UV-A may be responsible for tumor formation. The role of naturally occurring phytochemicals in the prevention of such UV-related conditions has captured increased interest. The biochemicals delphinidin, cyaniding and pelargonidin, (anthocyanidins), Punicalin, pedunculagin, punicalagin and gallagic and ellagic acid esters of glucose (hydrolysable tannins) in pomegranate are strong antioxidants and antinflamatory agents these compounds which account for 92% of the antioxidant of the whole fruit (Afaq *et al.* 2005), protect from ultraviolet radiation. Ultraviolet A is responsible for the formation of benign and malignant tumors. Pomegranate fruit extract contains antioxidants and anti-inflammatory phytochemicals that can treat human epidermal keratinocytes. Fruit extracts provided protection against Ultraviolet A mediated activation of signal transducers and activators of transcription. The pomegranate fruit extract reduces damage induced by ultraviolet-A, by modulating cellular pathways. (Deeba *et al.* 2006) The Studies on effect of pomegranate seed oil on skin tumors in mice have shown that PJ extracts are safe and effective chemo preventive against skin cancer (Hora *et al.* 2003). Pacheco-Palencia *et al*. (2008) demonstrated protective effects of standardized polyphenolic extracts from pomegranate in ultraviolet-irradiated human skin fibroblasts, their studies demonstrated the protective effects of pomegranate extract against UVA- and UVB-induced cell damage and the potential use of pomegranate polyphenolics in topical applications.

Lung cancer

Studies conducted on effect of pomegranate fruit extract on lung cancer (Ahmad *et al.* 1999; Hadi *et al.* 2009) suggest that pomegranate fruit extract may have chemopreventive as well as cancer chemotherapeutic effects against lung cancer in humans. Continued translational research on the chemopreventive potential of pomegranate ellagitannins is ongoing.

Administration of 70% methanolic extract of *P. granatum* fruit rind (250 mg/kg and 500 mg/kg) shows inhibition of gastric ulceration in treated groups of animals, The histopathological examination of the stomach of the ulcerated animals shows severe erosion of gastric mucosa, sub-mucosal oedema and neutrophil infiltration where as these symptoms were absent in treated groups. The present investigation revealed the gastro protective activity of the pomegranate peel extract through antioxidant mechanism (Ajaikumar *et al*. 2005).

Antimicrobial and other bioactivities

1. Antibacterial, antifungal and antiviral activities

The unique healing powers of pomegranate tree find references in the Bible and Roman mythology. People of some countries chew its bark, petals and peel to treat conditions of dysentery and diseases of the mouth and gum (Jemal *et al.* 2005) caused by antimicrobial agents.

Several studies have documented the antimicrobial activities of the extracts from pomegranate indicating presence of some metabolic tannin or broad spectrum antibiotic compounds. In the majority of the plants, phenols and tannins were the most common active ingredients (Tanaka *et al.* 1991). Pomegranate has several phenols, tannins present in its various parts and plant alkaloids have antimicrobial activity (Gibbons 2004).

Pomegranate extracts from different parts have antimicrobial activity (Aynechi *et al.* 1982; Avirutnant and Pogpan 1983; Cáceres *et al.* 1987; Lee and Watson 1998) varying

Table 8 Antimicrobial and other activities of pomegranate extracts.

Plant part* used for extract	Effective extract conc.	Microorganism affected	Microbial activity/diseases affected	Reference
Plant	Not stated	*Candida albicans*	Antifungal	Ahmad and Beg 2001
Plant	0.01% v/v (delayed growth) 1% v/v (bactericidal) 0.05% v/v (inhibited enterotoxin production)	*Staphylococcus aureus*	Antibacterial/food-borne diseases (*in vitro*)	Braga *et al.* 2005
Fruit	12.5 62.5 µg/ml	*S. aureus*, *Candida* spp.	Antibacterial and antifungal	Holetz *et al.* 2002
Pulp	2.5 mg/disc	*Salmonella typhi*, *S. paratyphi*	Antibacterial/typhoid fever bacteria (*in vitro*)	Ravi and Rajasekharapandian 2005
Pulp	2.5 mg/disc	*S. typhi*, *S. paratyphi*	Antibacterial/typhoid fever (*in vitro*)	Sharma *et al*. 2008
Aril	30 and ≥ 90 µg/mL	*S. aureus*, *Corynebacterium xerosis*, *Escherichia coli*, *Enterococcus faecalis*, *Micrococcus luteus*, and 3 fungi (*Kluvyeromyces marxianus*, *Rhodotorula rubra*, *C. albicans*)	Antibacterial and antifungal	Duman *et al*. 2009
Juice	Not stated	*Candida mycoderma*	Antifungal	Kirilenko *et al*. 1978
Juice	80-200 µg/ml	*Streptococcus mutans*	Antibacterial/tooth decay	Alsaimary 2009
Rind	100 mg/Kg (orally in rabbits)	Increased antibody titer of typhoid-H antigen	Immunomodulatory	Gracious *et al.* 2001
Peel	Not stated	*S. aureus*, *Pseudomonas aeruginosa*	Antbacterial	Opara *et al*. 2007
Peel	65-1000 µg/ml	*Salmonella typhimurium* (16 strains)	Antbacterial / gastro-intestinal infections	Choi *et al.* 2009
Peel	4 mg/ml	*S. enteritidis*	Diseases caused by the emergence of multi-drug resistant pathogens	Al-Zoreky 2009
Peel	4 mg/ml	*Listeria monocytogenes*	Food-borne diseases such as listeriosis	Al-Zoreky 2009
Pericarp	10.0 ml/plate	*Ascaris galli*, *A. lumbricoides*, *Pheritima posthuma*, *Taenia solium*	Anthelmintic (*in vitro*)	Raj 1975; Hukkeri *et al*. 1993
Pericarp	Not stated	Herpes simplex virus type 2	Inhibited replication genital herpes virus	Zhang *et al*. 1995
Pericarp	Not stated	*S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans*	Antibacterial and antifungal	Navarro *et al.* 1996; Machadoa *et al.* 2002
Pericarp	0.8%	*S. aureus*, *S. Mutans*, *Lactobacillus* spp.	Antibacterial against human oral pathogens	Chulasiri *et al*. 1995a
Pericarp	25 mg/well	*B. cereus*, *E. faecalis*, *E. coli*, *Klebsiella pneumoniae*, *P. aeruginosa* and *S. aureus*	Antibacterial (*in vitro*)	Chulasiri *et al.* 1995b, 1995c
Pericarp	Not stated	Hepatitis B virus	Antiviral (*in vitro*)	Goto *et al*. 1996
Pericarp	60.0 µg/ml	*Proteus mirabilis*, *Haemophilus influenzae*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *Candida albicans*	Antibacterial and antifungal (*in vitro*)	Alkofahi *et al.* 1996
Pericarp	25 µg/ml	*Chrysomya albiceps*	Larvicidal	Morsy *et al*. 1998
Pericarp	5%	*Trichophyton tonsurans, T. rubrum*, *T. simii*, *Trichosporon beigelii*, *Microsporum fulvum*, *M. gypseum*, *C. albicans*	Antifungal growth (*in vitro)*	Dutta *et al*. 1998
Pericarp	Not stated	*S. aureus*, *E. coli*	Antibacterial	Prashanth *et al.* 2001
Pericarp	0.78 mg/ml (inhibitory) 0.19-0.39% (bactericidal)	*E. coli*	Antibacterial	Voravuthikunchai *et al*. 2004, 2005
Pericarp	2.5 mg/disc	*S. aureus*, *E. coli*, *S. typhimurium*, S. *typhi*, *Shigella dysenteriae*, *S. flexneri*, *Vibrio cholerae*	Gastro Intestinal Tract infection causing bacteria (*in vitro*)	Pradeep *et al*. 2008
Pericarp	100 µg/ml	hepatitis C virus	Antiviral (*in vitro*)	Anonymous 2009
Seeds	Not stated	*B. subtilis*, *E. coli*, *Saccharomyces cerevisiae*	Antibacterial	De *et al*. 1999
Leaf	Not stated	*S. paratyphi*, *S. aureus*, *S. epidermidis*, *E. aerogenes P. aeruginosa* and *B. subtilis*	Antibacterial	Nair and Chanda 2005
Root	10 µg tannin in extract/ml	*Entamoeba histolytica*	Amoebic dysentry and diahorrea	Segura *et al.* 1990
Root	100 µg tannin in extract/ml	*E. invadens*	Amoebic dysentry and diahorrea	Segura *et al.* 1990
Root	1.5-2.5 mg/disc	*Bacillus subtilis*, *S. aureus*, *Staphylococcus epidermidis*, *E. coli*, *E. faecalis*, *C. albicans*	Skin, venereal, nervous and respiratory diseases (*in vitro*)	Duraipandiyan *et al.* 2006
Bark	25.0 mg/well	*Bacillus cereus*, *E. faecalis*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*	Antibacterial (i*n vitro*)	Nimri *et al*. 1999
Bark	22.42 mg/l	*Lymnaea acuminata*	Molluscicidal	Tripathi and Singh 2000

*as mentioned in the original paper/abstract

with variety, contents of phenolic compounds, pigments and citric acid (Kirilenko *et al.* 1978) and extraction solvents. **Table 8** summarizes antimicrobial and other activities of pomegranate extracts along with their inhibitory concentrations. Aqueous extracts of pomegranate seeds were inhibitory to *Bacillus subtilis*, *Escherichia coli* and *Sacharomyces cerevisiae* (De *et al.* 1999). Extracts of pericarp prepared in ethanol, methanol, acetate, water etc. by different workers inhibited *Staphylococcus aureus*, *E. coli*, *Pseudomonas aeruginosa* and *Candida albicans* (Navarro *et al.* 1996; Thelma *et al*. 2002; Machado *et al.* 2003; Pradeep *et al*. 2008). Extract of peels hulls, fruits in different extraction

solvents have antibacterial activity against *Salmonella typhi*, *Vibrio cholera*, *S. aureus*, *E. coli*, *Klebsiella pneumeniae*, *Proteus vulgaris*, *B. subtilis*, *S. typhi*, *C. albicans*, *Mycobacterium tuberculosis*, *B. cerus*, *B. coagulens*, *P. aeruginosa* (Ferara *et al.* 1989; Pérez and Anesini 1994; Guivara *et al.* 1994; Navarro *et al.* 1996; Prashanth *et al.* 2001; Asres *et al.* 2001; Holetz *et al.* 2002; Negi and Jayaprakasha 2003; Machado *et al.* 2003; Voravuthikunchai *et al.* 2004; Rani and Khullar 2004; Opara *et al*. 2007; Pradeep *et al*. 2008; Al-Zoreky 2009; Choi *et al.* 2009; Duman *et al*. 2009). Pomegranate peel extracts also have antifungal activity against *Candida myoderma*, *C. albicans*, *Penicillium citrinum*, *P. patulum*, *P. roquefortii*, *Aspergillus ochraceus* (Azzouz and Bullerman 1982; Burapadaja and Bunchoo 1995; Jia and Zia 1998; Jassim 1998; Pereira 1998; Ahmad and Beg 2001; Vasconcelos *et al.* 2003; Duman *et al*. 2009). Antiviral/viricidal activity is reported against Herpes Simplex Virus type 1 (HSV-1), Human Respiratory Syncytial Virus (RSV), Influenza Virus, Genital Herpes Virus (HSV-2), Poliovirus and Aids Virus-HIV (Zhang *et al.* 1995; Ma *et al.* 1998; Kinjo *et al.* 2000; Peña 1998; Mavlyanov *et al.* 1999; Caballero *et al*. 2001, Cheng *et al*. 2002; Li *et al.* 2004) and hepatitis virus C (Anonymous 2009). Neurath *et al.* (2004) tested a selected complex from pomegranate phytochemicals for inhibition of infection by primary HIV-1 isolates. HIV-1 entry inhibitors from PJ adsorb onto cornstarch. This complex blocks virus from binding to specific cells and inhibits infection by primary virus clades. The results obtained suggest the possibility of producing an anti-HIV-1 microbicide from PJ. Tanins in the extract have antiviral activity (Li *et al.* 2004). Haidari and co-workers (2009) demonstrated that pomegranate peel extract suppressed replication of influenza virus-A, was viricidal, inhibited viral RNA replication and that punicalagin was effective anti-influenza polyphenol component.

Since, the pomegranate extract are having antibacterial, antifungal and antiviral properties, the pomegranate extracts have been utilized for the cure of dysentery, diarrhea, stomatitis and food borne diseases (Kritikar and Basu 1975; Cáceres *et al.* 1987; Nagaraju and Rao 1990; Al-Zoreky 2009; Choi *et al.* 2009).

2. Anthelmintic, vermifugal, tanicidal, antiparasitic and molluscidal activities

The entire pomegranate tree including, the fruit, hull and roots posses anthelmintic, vermifugal (worm killer) or tanicidal (expeller) properties. The alkaloids belonging to piperidine group namely plletierine, pseudopelletierine isopelletierine and methyl isopelletierine found in fruit peel and bark of pomegranate tree, are responsible for above mentioned properties (Hukkeri *et al.* 1993) and among these alkaloids iso-pelletierine is the most potent tanicide. These alkoloids cause the tapeworm to relax its grip on the wall of the intestine allowing the parasite to expel as such or by another drug (Caius and Mhaskar 1923; Prakash *et al.* 1980; Zhicen 1987; Kapoor 1990; Naovi *et al.* 1991).

The extracts from the fruit hulls posses' antiparasitic activity against *Giardia* (Ponce Macotela 1994). *In vitro* as well as *in vivo* studies prove that bark extracts have molluscidal activity, against harmful snails – *Lymnaea acuminata*, the vector for *Fasciola hepatica* and *F. gigantica* responsible for endemic fascioliasis in the cattle population (Tripathi and Singh 2000, 2001). The mortality in snails is because of several metabolic changes in its body.

Other therapeutic uses

1. Protection against hepatotoxicity

Flowers extract of *Punica granatum* possesses potent antioxidant activity and protects against Fe-NTA induced hepatotoxicity (Kaur *et al.* 2006).

2. Osteoarthritis

In a study using mice, a single intra-articular injection of mono-iodoacetate induced fast and progressive damage to articular cartilage, which exactly mimicked human osteoarthritis. Administration of PJ to different group of mice prevented the negative effects of iodoacetate, in a dose-dependent manner. Chondrocyte damages were significantly prevented and proteoglycane less affected, especially in a group receiving high amount of juice and no cell proliferation and inflammatory cell were detected in synovium. They concluded that PJ was effective in the improvement of histopathological damages and had chondro protective effects *in vivo* (Jahromy *et al.* 2007; Jahromy and Kermani 2009).

3. Alzheimer's disease

Pomegranates are rich sources of polyphenols and polyphenols are neuroprotective in different model systems. Researchers feel that PJ can help in slowing progression of Alzheimer's disease. Hartman *et al.* (2006) studied two groups of genetically engineered transgenic mice, to express a protein that eventually leads to Alzheimer's disease. They divided mice between the age group of 6 and 12.5 months into 2 groups: The diet of one group was plain and that of the second supplemented with diluted PJ concentrate, equivalent in strength to commercially sold PJs. They found that the significantly less (approximately 50%) accumulation of soluble Abeta42 and amyloid deposition in the hippocampus of the brain of the mice consuming PJ, resulting in 35% faster learning and swimming.

BIOAVAILABILITY OF POMEGRANATE POLYPHENOLS

Researchers have demonstrated beyond doubt that, the polyphenols present in high quantities in the PJ have high biological activity, however, in order to investigate its role in human health, various workers carried out its bioavailability and tissue distribution investigations both in animals and in volunteer human beings.

Animal studies

A rapid absorption and metabolism of ellagic is reported by Doyle and Griffiths in rats (Doyle and Griffiths 1980) however, poor absorption and rapid elimination of the compound in animals was reported by Smart *et al.* (1986) and Teel and Martin (1998) and in monkeys and goats (Van Tassel 41973) where diet naturally contains ellagic acid. The studies on bioavailability of pomegranate ellagitannins in pomegranate husk using rat as test animals was conducted and absorption of instant punicalagic and detection in plasma was reported (Gil *et al.* 2000; Cerdá *et al.* 2003a; Manach *et al.* 2005). They detected only traces of punicalagen metabolites in liver or kidney and none in lung, brain or heart (Cerdá *et al.* 2003a, 2003b).

Espín *et al*. (2007) demonstrated the whole metabolism of ellagitannins for the first time in Iberian pig used as a model. He found that ellagitannins release ellagic acid in the jejunum, then the intestinal flora metabolizes ellagic acid sequentially to yield tetrahydroxy- (urolithin D), trihydroxy- (urolithin C), dihydroxy- (urolithin A), and monohydroxy- (urolithin B) dibenzopyran-6-one metabolites, which were absorbed preferentially when their lipophilicity increased. The presence of EA metabolites in bile and in urine and its absence in intestinal tissues suggested its absorption in the stomach. Urolithin A was the only metabolite detected in faeces, together with its derivative glucuronide, which was the most abundant metabolite in urine. No metabolites accumulated in any organ analyzed.

Free gallic acid, a compound in pomegranate extracts has one of the largest bioavailability of the food phenolic compounds (Manach *et al.* 2005). Studies on bioavailability

of anthocyanins indicate that anthocyanin 3 glucosides present in juice can be absorbed intact and excreted as such in urine, but at very low rates (0.1-06% of the intake depending on structures) and the anthocyanins are partly metabolized to methyl ether derivatives or glucoronides before excretion (McGhie *et al.* 2003; Talavéra *et al.* 2005). The metabolism of anthocyanins is largely in the large intestine by the colon microflora to give simpler phenolics that can be absorbed (Manach *et al.* 2005). Lacueva *et al.* 2005 gave convincing proof of distribution of anthocyanin to various brain regions responsible for learning and memory in rats. The bioavailability of procyanidins and flavan-3-ols, depends on the structure of the flavonol hydroxylation pattern and on the degree of polymerization (Lacueva *et al.* 2005), however, direct evidence of the bioavailability of pomegranate procyanidins and flavon-3-ols is lacking. Catechin and epicatechin belong to the most bioavailable polyphenols described so far (1-30% of ingested amount, excreted in urine). The bioavailability of galloylated derivatives is very low (Manach *et al.* 2005).

Human studies

In pharmacokinetic studies at university of California when volunteers were administered PJ concentrate at 180 ml/person. They detected ellagic acid in human plasma at a maximum concentration after 1 hr post ingestion, which was rapidly eliminated by 4 hr (Seeram *et al.* 2004, 2006).

The bioavailability studies were conducted in which 1 L of PJ was given orally for 5 days to healthy volunteers, punicalagin and ellagic acid present in juice were not detected either in plasma or in urine, however 3 microbial ellagitanin derivatives (metabolic products) were detected with great interindividual variability 1 day after juice consumption (Cerdá *et al*. 2004).

In another study results indicated that ellagic acid from the pomegranate extract is bioavailable metabolites urolithin-A, urolithin-B, hydroxyl-urolithin-A, urolithin A-glucuronide, and dimethyl ellagic acid-glucuronide were identified in the plasma. The antioxidant capacity increased with a maximum effect of 32% after 0.5 h, whereas the generation of reactive oxygen species did not affect. The inflammation marker was not significantly affected 4 h after the consumption of the extract (Mertens-Talcot *et al*. 2006).

Studies conducted on bioavailability of anthocyanins in humans using anthocyanins present in pomegranate but obtained from other food sources, proved that, anthocyanins are absorbed with poor efficiency and eliminated rapidly (Lapidot *et al.* 1998; Wu *et al.* 2002; Felgines *et al.* 2003). The study also demonstrated that anthocyanins were glucuro- and sulfo-conjugated anthocyanins in humans and that the main metabolite in human urine found was monoglucuronideof pelargonidin (Felgines *et al.* 2003).

The understanding of metabolism of procyanidins in human is only partial; however, evidence is available for relatively fast absorption and excretion of flauvonols (Williamson and Manach 2005). In a study by Cerdá *et al*. (2006), none of the polyphenols present in PJ were detected in plasma or in urine of volunteer human beings consuming PJ for 5 weeks. The colonic microflora of human volunteers metabolized the most abundant polyphenols- ellagitannins, to yield two major metabolites in both plasma and urine (dibenzopyranone derivatives) with no antioxidant capacity.

NUTRITIVE VALUE OF POMEGRANATE FRUIT

Mineral nutrients are natural component of many fruits and play an important role in maintaining fruit quality and determining nutritive value. Pomegranate is a rich source of these bioactive compounds. Nutrients in a fruit may change during the development of the tree, during fruit maturation, under different environmental and cultivation conditions and between pomegranate cultivars.

Pomegranate is a source of all essential nutrients, digested easily and refreshes physically or mentally tired people too. It is a diet full of nourishment for growing children, ageing/elderly or sick persons and pregnant women. It has the power to cure hunger, quench thirst and refresh the drunkard. The fresh juice contains 85% water, 10% total sugars, 1.5% pectin, ascorbic acid and polyphenolic flavonoids (El-Nemr *et al*. 1990). Its aril juice is rich in vitamin C and provides in 100 ml about 15% of the daily requirement of an adult (USDA National Nutrient Database 2009). The major sugars as reported by Özgen (2008) were fructose (6.4 g/100 ml) and glucose (6.8 g/100 ml); the major acids were citric (1.78 g/100 ml) and malic (0.12 g/100 ml). They further reported that pomegranate is a rich source of vitamin C, vitamin K, vitamin B6 and pantothenic acid (vitamin B5). It also consists of vitamin A, vitamin E, thiamin and riboflavin in small amounts. In addition to these, niacin and folate are present in traces. Pomegranate is a rich source of minerals like potassium and copper and is very low in sodium, hence useful in the control of hypertension. Iron is present in small quantity, while traces of magnesium, phosphorus, zinc and selenium are also there. Ascorbic acid (vitamin C) varies with varieties. In a study it was reported to vary between 52.8 to 72.0 mg/100 g fresh weight (fw) for arils and 76.8 to 118.4 mg/100 g fw for peels and it was found significantly higher in peels than the arils, with differences ranging from 24.4 to 97.0% depending on variety (Opara *et al.* 2009).

PJ is considered beneficial for diabetics, despite the juice containing significant sugar concentrations. The explanation given in support of this is that, "In most juices, sugars are present in free and harmful forms but in PJ, however, the sugars are attached to unique antioxidants - the polyphenols forming a complex, which actually make these sugars protective against atherosclerosis" (Rock *et al*. 2008). Rozenbers *et al.* (2006) concluded from their study that PJ consumption by diabetic patients does not worsen their diabetic parameters but contributes to serum paraoxonase-1 stabilization, increased association with HDL cholesterol, and enhanced catalytic activities, leading to retardation of atherosclerosis development in diabetic patients.

The fruit is low in fats (< 0.12 g/100 g arils) and sweet varieties have almost half the fat content than that of bitter/sour varieties (Hernández *et al*. 2001). The seed oil has five fatty acids. The highest levels (about 90%) were those of polyunsaturated fatty acids and out of which between 60-80% were C18:3 fatty acids called punicic acids (El-Shaarawy and Nahapetian 1983; Melgarejo *et al*. 1995; Hernández *et al*. 2001; Kaufman and Weisman 2007), which are good for health. Waheed *et al.* (2004) reported, low concentration of 19 minerals in PJ including Fe, Ca, Cu, K, Mg, Mn, Mo, Zn, etc.

National Research Centre on Pomegranate, Solapur, Maharashtra, India, has reported the essential nutrients available in the edible part of pomegranate fruit in the two main cultivars- Bhagawa and Ganesh, grown in India (Annual Report 2007-08 and 2008-09). The nutrient composition of pomegranate fruit as reported by USDA database is summarised in this review (**Table 9**).

TOXICITY AND DRUG INTERACTIONS

Toxicity

Pomegranate fruit though considered mostly safe, extracts of other parts or even rind may have some toxic effects if taken in large doses, however, much remains unexplored in this field with reference to pomegranate. Squillaci and Di Maggio (1946) had reported that due to presence of both tannins and alkaloids, decoction of tree bark and some times of fruit pericarp may cause gastric inflamation or may prove fatal. Oesophageal cancer and allergic reactions are reported from eating of fruits/seeds (Ghadirian 1987; Ghadirian *et al.* 1992).

The water-soluble ellagitannin 'punicalagin' is toxic to cattle and as this polyphenol is very abundant in PJ (≥ 2 g/l) it may have toxic effects. Cerdá *et al*. (2003a) evaluated its

Table 9 Nutritive value of pomegranate fruit/100 g edible portion.

Nutrients	Value/100 g
Water (%)	77.93 (80.97)
Energy (kcal)	83 (68)
Protein (g)	1.67 (0.95)
Carbohydrate (g)	18.70 (17.17)
Lipid (fat) (g)	1.17 (0.30)
Dietary fibre (g)	4.0 (0.6)
Ash (g)	0.53 (0.61)
Minerals	
Calcium (mg)	10.0 (3.0)
Selenium (µg)	0.5 (0.6)
Iron (mg)	0.30 (0.3)
Manganese (mg)	0.12 (-)
Magnesium (mg)	12.0 (3.0)
Copper (mg)	0.16 (0.70)
Phosphorus (mg)	36.0 (8.0)
Zinc (mg)	0.35 (0.12)
Sodium (mg)	3.0 (3.0)
Potassium (mg)	236 (259)
Vitamins	
Ascorbic acid -Vitamin C (mg)	10.2 (6.1)
Thiamin -Vitamin B1 (mg)	0.07 (0.03)
Riboflavin-Vitamin B2 (mg)	0.05 (0.03)
Niacin -Vitamin B3 (mg)	0.29 (0.30)
Pantothenic acid -Vitamin B5 (mg)	0.38 (0.596)
Pyridoxine -Vitamin B6 (mg)	0.08 (0.105)
Folate (µg)	38.0 (6.0)
Choline – Nitrogen containing alcohol having vitamin related activity (mg)	7.6 (-)
Phylloquinone - Vitamin K (µg)	16.4 (-)
Folic acid, Vitamin A and E not found, however, how reported in traces by	
Sugars	
Total (g)	13.67
Glucose (g)	6.80*
Fructose (g)	6.40*
Sucrose	Nil-0.1% of total
Acids	
Citric acid (g)	1.78*
Malic acid (g)	0.128*
Oxalic acid, boric acid, succinic acid, tartaric acid	Traces
Lipids (fatty acids)	
Saturated (g)	0.12
Monounsaturated (g)	0.09
Polyunsaturated (g)	0.08
Cholesrol (mg)	- (0.0)
Phytosterol (mg)	- (17.0)

Note: Values in parenthesis are the ones given in USDA Nutrient Database for Standard Reference (2001), and have been given to show the variation in values which may be due to methodology used for analysis, variety, season or other factors.

* Values given by Özgen (2008)

Sign '-' not reported

Source: USDA National Nutrient Database (2009) Fruit Facts: http://www.fruits-fruits.com/2010/01/fruit-facts-pomegranate-nutrition-facts.html

possible toxic effects on Sprague-Dawley rats. High oral doses of pomegranate having 6% punicalagin, supplied to rats for 37 days did not produce any toxic effect studied in eight hematological parameters and 16 serobiochmical parameters, though 5 of its metabolites were identified in liver and kidney of fed rats (Cerdá *et al*. 2003a). Pomegranate fruit extracts were studied for potential adverse effects, if any, following subchronic administration in rats with the extracts standardized to 30% punicalagins – the major antioxidant in the PJ. Administration of the extract up to 90 days did not reveal any treatment-related gross or histopathology findings in any of the treatment-related changes in clinical, ophthalmic, pathological, hematology, serum chemistry parameters etc even at 600g/body wt. – the highest dose tested (Patel 2008).

The peels of eight kinds of fruits commonly consumed and grown in Thailand were explored for the potential of fruit waste materials as sources of powerful natural antioxidants. Top three extracts from peels having markedly high free radical-scavenging power were from *Punica granatum* (pomegranate), *Nephelium lappaceum* (rambutan), and *Garcinia mangostana* (mangosteen). The extract of mangosteen peel showed moderate toxicity to Caco-2 cells and high toxicity to peripheral blood mononuclear cells, Pomegranate peel extracts also stimulated both cell types but to a lesser extent, whereas, rambutan exhibited non-toxic activity to the cells (Okonogi *et al.* 2007).

In vitro cytotoxic studies against three cell lines, namely, Vero (normal African green monkey kidney cell line), Hep-2 (human larynx epithelial cancer cell line), and A-549 (human small cell lung carcinoma cell line) showed that this polyphenol is toxic only at higher concentration (Kulkarni *et al*. 2007).

Drug interaction

Pomegranate fruit juice considered exotic because of the several phytochemicals having potential health benefits, in a recent report was found to interact with Rosuvastatin (TN Crestor) belonging to a group of medicines called HMG-CoA reductase inhibitors or 'statinss'. The interaction in the patient being medicated resulted in the development of symptoms of rhabdomyolysis a serious condition that causes the breakdown of muscle fibers and may lead to kidney failure (Sorokin *et al.* 2006). This report should caution scientists and doctors to understand drug interactions with pomegranate fruit juice, which is getting immense popularity among consumers. PJ and grapefruit juice both block the cytochrome P450 3A4 enzyme systems in the intestines, which may increase concentration of many medications in the blood to a level that many lead to serious complications in the patient (Hidaka *et al.* 2005). Some potential pomegranate drug interactions include interactions with drugs belonging to the group of medicines -antiarrhythmics, calcium channel blockers, statinss, immunosuppressants and protease inhibitors (Kim *et al.* 2006). Contrary to this, Dr. Farkas *et al*. (2007) from Department of Pharmacology and Experimental Therapeutics at Tufts University reported that PJ does not produce drug interactions with oral or intravenous medication in human beings. The conducted studies with the drug Midazolam, an established test drug used to assess CYP3A activity in healthy human volunteers, and hence they concluded that it was safe to take PJ with medicines. The differences in observations by various workers could be due to various factors- such as volume of juice consumed/day, number of days juice consumed, dose of drug, etc. Hence, before arriving at any conclusion intensive studies are required for knowing whether medications are in any way, interacting with PJ, as only limited evidences are available about the potential drug interactions.

Pomegranate allergy

Zoccatelli (2007) isolated and identified two lipid transfer proteins in pomegranate, which can explain the role of these proteins as elicitors of allergy to pomegranate.

CONCLUSION

Considering the enormous health benefits and nutritive value, consumption of fresh fruits of pomegranate is very popular world over, especially in countries where it is cultivated commercially or where it is imported in large quantities. With the campaigning of its health benefits a large number of its products-juices, wine, jam, jellies, candies etc. have also come up in the commercial market. Apart from the processed products, pomegranate is also available as botanical extracts/ingredients in dietary, supplements, cosmetics, etc. Given here are few such products having high rating in the market: Pomegranate power caps by Mother

nature, Cardioedge by Douglas Labs, Cardio Gramale & Estra Granals by Pomegranates Health, pomAgic by Trialco, PJ Concentrate from Jarrow Formulas, Pomegranate Standardized from Nature's Way, Herbal Plus Pomegranate from GNC, Pomegranate Extract from Puritan's Pride, Pomegranate Fruit from Nature's Herbs. Pomegranate from Vitabase, PomActiv Pomegranate Extract from Nutraceutical Sciences Institute, Slice of Life Vitamin C + Antioxidant from Hero Nutritionals, Pomegranate from Vitabase, Pomegranate Fruit from Nature's Herbs. The European markets are flooded with several such products however, the safety of these products should be ensured, before it comes to the market. The product should be evaluated for its quality, safety, bioavailabity and its interaction with other drugs.

Even our ancestors knew the concept of phytonutrients and their role in human health; however, they are much better known and understood today. Thanks to the modern tools and technology, which have enabled scientists to identify such fruits, explore and understand the phytochemicals found in them and harness their beneficial effects. Research in this area is expanding rapidly because of the understanding of the fact that naturally available phytonutrients offer the best protection we know of against the dreaded diseases that plague millions across the world. The day is not far when the physicians of coming generations would prefer to prescribe pills of phytochemicals. Once we understand well the tissue-specific way in which these nutrients work to target specific diseases, phytonutrient pills made from pomegranate and other super fruits, which are storehouse of several well-known phytonutrients, would be flooding the market and shelves of the medical stores. The American and European markets are already marketing such pills.

To conclude, we can say we known much on pomegranate phytochemals, yet a lot more remains to be done. Chemistry of most phytochemals available in this fruit is now well known, however, the role of these phytochemicals is yet ambiguous, as the focus of research remained on polyphenols and most studies done were *in vitro* or using animal subjects. Bioavailability of these bioactive compounds in humans and their role in specific diseases is not yet convincingly proved, to harness the goodness of these super fruits, which are gaining so much significance. Reports on toxicity-drug interaction though few, warrant casual use of pomegranate as a nutraceutical food and direct us to carry out intensive research, on all aspects of these phytochemicals before advocating them as a boon for human health.

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