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Review

Punica granatum (pomegranate) and its potential for prevention and treatment of inflammation and cancer

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Abstract

The last 7 years have seen over seven times as many publications indexed by Medline dealing with pomegranate and *Punica granatum* than in all the years preceding them. Because of this, and the virtual explosion of interest in pomegranate as a medicinal and nutritional product that has followed, this review is accordingly launched. The pomegranate tree, *Punica granatum*, especially its fruit, possesses a vast ethnomedical history and represents a phytochemical reservoir of heuristic medicinal value. The tree/fruit can be divided into several anatomical compartments: (1) seed, (2) juice, (3) peel, (4) leaf, (5) flower, (6) bark, and (7) roots, each of which has interesting pharmacologic activity. Juice and peels, for example, possess potent antioxidant properties, while juice, peel and oil are all weakly estrogenic and heuristically of interest for the treatment of menopausal symptoms and sequellae. The use of juice, peel and oil have also been shown to possess anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion and angiogenesis. These may be associated with plant based anti-inflammatory effects, The phytochemistry and pharmacological actions of all *Punica granatum* components suggest a wide range of clinical applications for the treatment and prevention of cancer, as well as other diseases where chronic inflammation is believed to play an essential etiologic role.

Keywords: *Punica granatum*; Cancer; Eicosanoid; Inflammation; Pomegranate

Contents

Abbreviations: AA, arachidonic acid; ABTS, 2,2-azinobis(3-ethylbenzathiazoline-6-sulfonic acid); Akt, (protein kinase B); AOM, azoxymethane; CA, carbonic anhydrase; CAI, carbonic anhydrase inhibitor; COX, cyclooxygenase; cdk, cyclin dependent kinase; DMBA, 7,12-dimethyl-benz[*a*]anthracene; DMPD, *N*,*N*-dimethyl-*p*-phenylendiamine; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EA, ellagic acid; FAS, a death receptor ligand; FRAP, ferric reducing antioxidant potency; HAEC, human aorta endothelial cells; HDL, high density lipoprotein; HETE, hydroxyeicosatetraenoic acid; HODE, hydroxy-9,11-octadecadienoic acid; HPLC, high pressure liquid chromatography; IL, interleukin; J, ethyl acetate extract of fresh pomegranate juice; LDL, low density lipoprotein; LTA, leukotriene A; LTB, leukotriene B; LOX, lipoxygenase; MAPK, mitogen-activated protein kinase; MIF, migration inhibitory factor; MMOC, mouse mammary organ culture; MMP, matrix metalloproteinase; NF-κB, nuclear factor *kappa* B; NO, nitric oxide; NOS, nitric oxide synthase; NSAID, non-steroidal anti-inflammatory drug; O, polyphenol fraction of PSO; ODC, ornithine decarboxylase; P, pomegranate peel extract; PFE, pomegranate flower extract; PGD, prostaglandin D; PGE, prostaglandin E; PGF, prostaglandin F; PGG, prostaglandin G; PGH, prostaglandin H; PGI, prostaglandin I; PGI_2, prostacyclin; PGJ, purple grape juice; PGO, pomegranate (seed) oil; PJ, pomegranate juice; PSA, prostate specific antigen; PSE, aqueous/ethanolic pomegranate seed extract; PSO, pomegranate seed oil; ROS, reactive oxygen species; SESCO, supercritical CO_2-extracted pomegranate seed oil; TEAC, Trolox equivalent antioxidant capacity; TPA, 12-*O*-tetradecanoylphorbol 13-acetate; TPT, total pomegranate tannin; TXA, thromboxane A; UV-b, ultraviolet b; VEGF, vascular endothelial growth factor; W, fermented pomegranate juice; WPFE, acetone extract of whole pomegranate fruits

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1. Introduction

It has been 8 years since we published in this Journal the first report of antioxidant and antieicosanoid activities of pomegranate fractions *in vitro*. Medline now cites 138 new scientific papers relating to health effects of pomegranate, compared to only 25 between 1950 and summer 1999. Many of these new papers have focused on antioxidant actions *in vitro*, *ex vivo* and *in vivo*, while other work has elaborated on the ability of pomegranate juice, seed oil, peel or flower extracts, and their derivatives to kill bacteria and viruses, or to fight vascular disease, diabetes and cancer. In everything from improving erectile insufficiency in rabbits to healing ethanol induced stomach ulcers in rats, antioxidant action is given as the leitmotif and root of the observed beneficial effects. Driven by such studies, sales of pomegranate juice are soaring worldwide, with even pomegranate seed oil beginning to appear in the marketplace.

The enthusiasm for health effects of pomegranate, however, may be only partially justified. For one thing, the straight line that many ascribe between *in vitro*, *in silico* and even *in vivo* antioxidant effects on the one hand, and protection against neurological damage, ulcers, high cholesterol, cancer, arterial plaques and impotence on the other, has not been solidly established. Although redox status may serve as a trigger of inflammation-modulating cytokines (Flohe et al., 1997) or of angiogenesis (Rojas et al., 2006), its precise role in regulating disease is still unclear. Secondly, research into the effects of pomegranate derivatives on human health is still at a very early stage. Few well controlled clinical trials have yet been completed, and the toxicology of pomegranate fractions, particularly their potential for mutagenesis, is only now beginning to be addressed. Much deeper investigation into this rapidly growing field is thus required to assess the overall value and safety of pomegranate as an intact fruit or of various extracts derived from pomegranate components.. In order to facilitate such research, the present review is needed and accordingly, offered.

Punica granatum (Fig. 1) shares its botantical family only with *Punica protopunica*, the latter restricted in occurrence to Socotra, an island off the Yemeni coast. Over 1000 cultivars of *Punica granatum* exist (Levin, 1994), originating from the Middle East, extending throughout the Mediterranean, eastward to China and India, and on to the American Southwest, California and Mexico in the New World. While the pomegranate plant is considered either a small tree or a large shrub, its fruit is often deemed to be a large berry. The fruit is delimited by a leathery pericarp, contained within are numerous *arils*, each a single seed surrounded by a translucent juice-containing sac. Thin acrid-tasting membranes extend into the interior of the fruit from the pericarp, providing a latticework for suspending the arils. Thus, the fruit itself gives rise to three parts: the seeds, about 3% of the weight of the fruit, and themselves containing about 20% oil, the juice, about 30% of the fruit weight, and the peels (pericarp) which also include the interior network of membranes. Other useful parts of the plant include the roots, bark, leaves, and flowers.

The history of pomegranates with respect to development of mankind is impressive. An 800-year old Kabbalistic text, *Sefer ha Rimon*: *The Book of the Pomegranate*, equates pomegranate with *Shekinah*, the female aspect of Creation, and Its Creator (Wolfson, 1988). Pomegranates feature prominently in Judaism, Christianity, Islam, Buddhism and Zoroastrianism. Pomegranates appear in the coats of arms of several British med-

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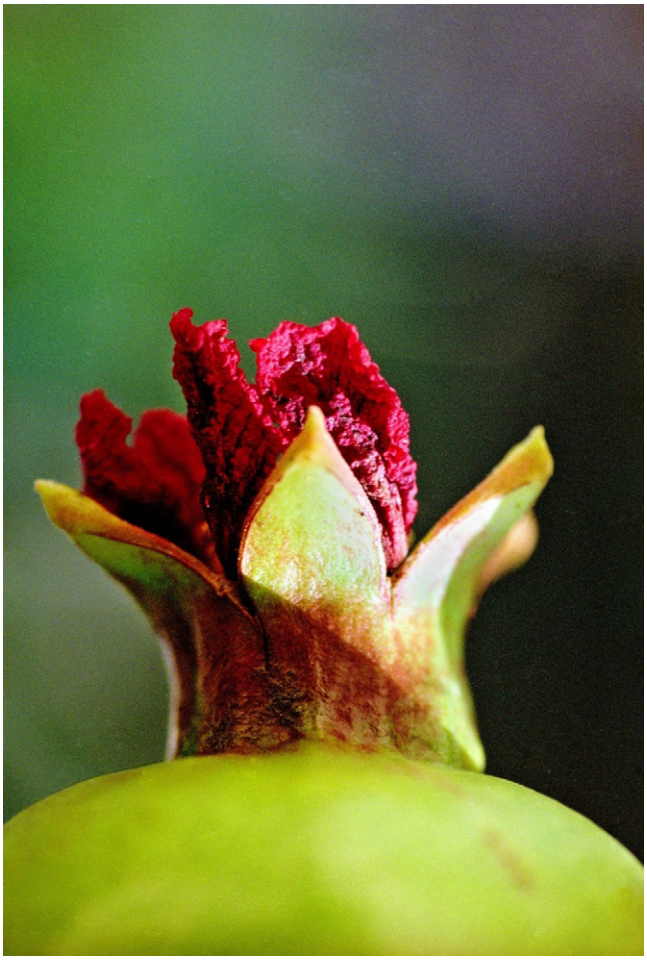

Fig. 1. The apex of a pomegranate fruit with a portion of its vestigial flower. The fruit, which contains hundreds of juice encapsulated seeds, or arils (Hebrew legend fixes the number at exactly 613, while other reports range from around 200–800 in a mature fruit), is literally gestated within the flower, as the flower becomes the fruit. The distinctive crown (the inspiration for the crowns of kings and queens), is developed from the flower's calyx (photo by Dr. Menachem Granat).

ical societies (Langley, 2000). The pomegranate is a symbol of life, longevity, health, femininity, fecundity, knowledge, morality, immortality and spirituality, if not Divinity (Mahdihassan, 1984). In Ayurvedic medicine the pomegranate is considered "a pharmacy unto itself," the bark and roots believed to have anthelmintic and vermifuge properties (Naovi et al., 1991), the peels a powerful astringent and cure for diarrhea and oral aphthae, and the juice a "refrigerant" (Arseculeratne et al., 1985) and "blood tonic" (Lad and Frawley, 1986). From India (Nagaraju and Rao, 1990), Tunisia (Boukef et al., 1982), and Guatemala (Caceres et al., 1987), dried pomegranate peels are decocted in water and employed both internally and externally for numerous problems demanding astringents and/or germicides, especially for aphthae, diarrhea and ulcers. Mixtures of pomegranate seed, juice and peel products paradoxically have been reported to not only prevent abortion (Ramirez et al., 1988) but also conception (Gujral et al., 1960; Jochle, 1971; Zhan, 1995). In Unani medicine, a Middle Eastern traditional medical system that later took root in India (Izhar, 1989), pomegranate flowers serve as a remedy for diabetes mellitus (Saxena and Vikram, 2004). Modern uses of pomegranate derived products now include treatment of acquired immune deficiency syndrome (AIDS) (Lee and Watson, 1998), in addition to use for cosmetic beautification (Kawamada and Shimada, 2002; Moayadi, 2004) and enhancement (Curry, 2004), hormone replacement therapy (Lansky, 2000), resolution of allergic symptoms (Watanabe and Hatakoshi, 2002), cardiovascular protection (Shiraishi et al., 2002; Aviram and Dornfeld, 2003), oral hygiene (Kim and Kim, 2002), ophthalmic ointment (Bruijn et al., 2003), weight loss soap (Guojian, 1995), and as an adjunct therapy to increase bioavailability of radioactive dyes during diagnostic imaging (Il'iasov, 1975; Amorim et al., 2003).

Over the past few decades scientific investigations have laid a credible basis for some of the traditional ethnomedical uses of the pomegranate. These studies, most completed in the past 5 years, may be divided into several general areas. For example, pomegranate mediated antioxidant activity can be considered a means of lowering the threshold for inflammation. Antioxidant activity, as well as suppression of inflammation, may contribute to chemotherapeutic and chemopreventive utility against cancer. Investigations of the pharmacology and health benefits claimed from use of pomegranate components to these three broad, but interconnected areas (antioxidant, anti-inflammatory and anti-cancer) as well as an introduction to the chemical constituents of *Punica granatum*, will be discussed in this review.

2. Chemistry

While detailed knowledge of relationships of the chemical content of pomegranates and their desirable pharmacologic endpoints has yet to be obtained, significant progress has been made over the past 8 years toward a much more comprehensive understanding of some of the important pharmacologic components of pomegranate. These are summarized, with their structures, in Table 1. In addition to the more common anthocyanins shown in the table, pentose glycosides of malvidine and pentunidin have been described in the pericarp and juice (Sharma and Seshadri, 1955). Although some limited knowledge of the abundance of selected compounds does exist, e.g., Vitamin C in the juice at 0.47 mg/100 g (Veres, 1976), in general such quantitative knowledge is lacking, and hence has been left out.[1]

2.1. Seed

Pomegranate seed oil (PSO) comprises 12–20% of total seed weight. The oil consists of approximately 80% conjugated

[1] This particular case cited here about ascorbic acid at 0.47 mg/100 g juice (Veres, 1976) is taken as an example of quantification, but not as a model. Qualitative as well as quantitative ambiguity is common around the pomegranate. For example, alkaloids were found and not found in peels (by Dragendorff and Mayer assays, respectively) by one group (Vidal et al., 2003). Reliable quantification of most of the compounds described herein in pomegranate fruits, with appropriate ranges and error consideration, is lacking, and hence omitted rather than risk such numbers being committed to memory as *de facto* standards rather than the single estimations or extrapolations that they more probably represent.

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Table 1
Selected compounds of *Punica granatum*

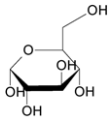
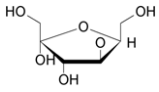
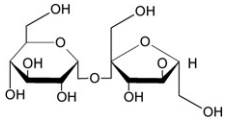
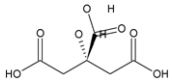
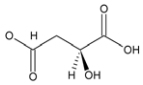
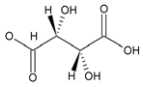
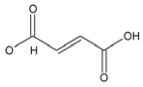
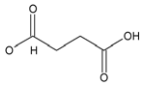
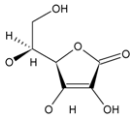
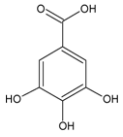
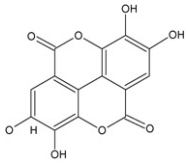
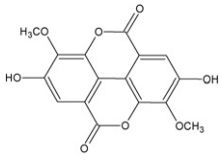
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Simple sugars	Glucose		J	Cui et al. (2004)
Simple sugars	Fructose		J	Cui et al. (2004)
Simple sugars	Sucrose		J	Gabbasova and Abdurazakova (1969)
Aliphatic organic acids	Citric acid		J	Poyrazoglu et al. (2002)
Aliphatic organic acids	Malic acid		J	Poyrazoglu et al. (2002)
Aliphatic organic acids	Tartaric acid		J	Poyrazoglu et al. (2002)
Aliphatic organic acids	Fumaric acid		J	Poyrazoglu et al. (2002)
Aliphatic organic acids	Succinic acid		J	Poyrazoglu et al. (2002)
Enolic furanolactone	Ascorbic acid		J	Veres (1976)
Hydroxybenzoic acids	Gallic acid		J, P, F	Amakura et al. (2000b), Huang et al. (2005b)
Hydroxybenzoic acids	Ellagic acid		J, P, S	Amakura et al. (2000b), Wang et al. (2004)
Hydroxybenzoic acids	3,3′-Di-*O*-methylellagic acid		S	Wang et al. (2004)

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Table 1 (*Continued*)

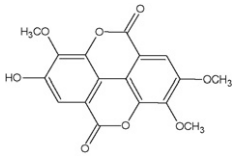
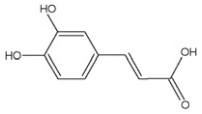
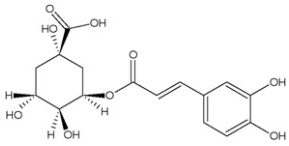
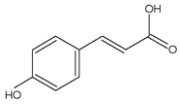
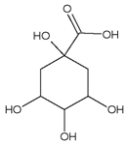
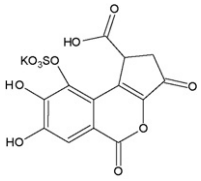
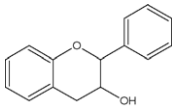
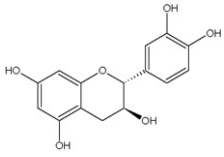
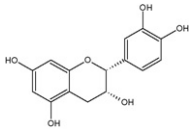
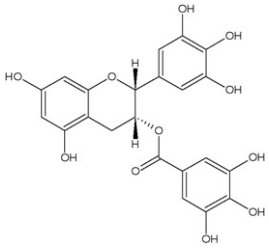
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Hydroxybenzoic acids	3,3′,4′-Tri-*O*-methylellagic acid		S	Wang et al. (2004)
Hydroxycinnamic acids (phenylpropanoids)	Caffeic acid		J, P	Artik (1998), Amakura et al. (2000a)
Hydroxycinnamic acids (phenylpropanoids)	Chlorogenic acid		J, P	Artik (1998), Amakura et al. (2000a)
Hydroxycinnamic acids (phenylpropanoids)	*p*-Coumaric acid		J, P	Artik (1998), Amakura et al. (2000a)
Cyclitol carboxylic acids and their salts	Quinic acid		J, P	Artik (1998), Amakura et al. (2000a)
Cyclitol carboxylic acids and their salts	Brevifolin carboxylic acid 10-monopotassium sulphate		L	Hussein et al. (1997)
Flavan-3-ols	Flavan-3-ol		J, P	de Pascual-Teresa et al. (2000)
Flavan-3-ols	Catechin		J, P	de Pascual-Teresa et al. (2000)
Flavan-3-ols	Epicatechin		J, P	de Pascual-Teresa et al. (2000)
Flavan-3-ols	Epigallocatechin 3-gallate (ECGC)		J, P	de Pascual-Teresa et al. (2000)

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Table 1 (*Continued*)

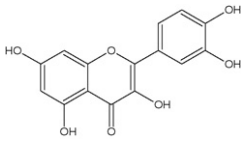
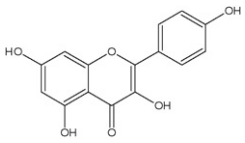
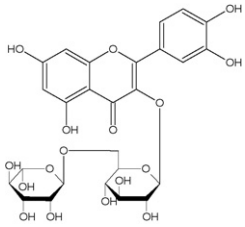
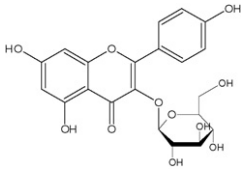
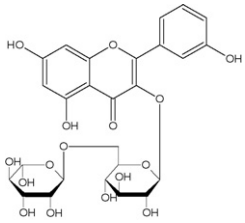
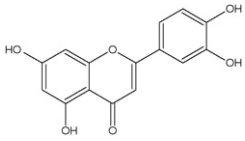
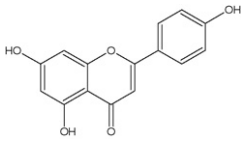
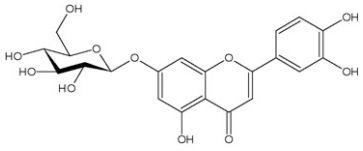
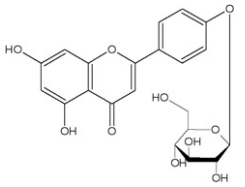
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Flavonols	Quercetin		J, P	Artik (1998)
Flavonols	Kaempferol		P	van Elswijk et al. (2004)
Flavonol glycosides	Rutin		P, J	Artik (1998)
Flavonol glycosides	Kaempferol 3-*O*-glycoside		P	van Elswijk et al. (2004)
Flavonol glycosides	Kaempferol 3-*O*-rhamnoglycoside		P	van Elswijk et al. (2004)
Flavones	Luteolin		P	van Elswijk et al. (2004)
Flavones	Apigenin		L	Nawwar et al. (1994a)
Flavone glycosides	Luteolin 7-*O*-glycoside		P	van Elswijk et al. (2004)
Flavone glycosides	Apigenin 4′-*O*-β-glucopyranoside		L	Nawwar et al. (1994a)

Table 1 (*Continued*)

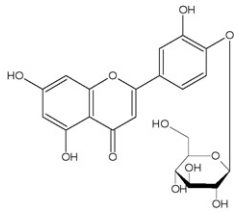
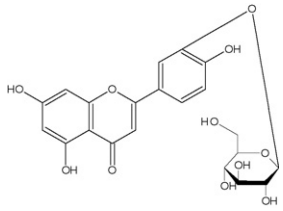
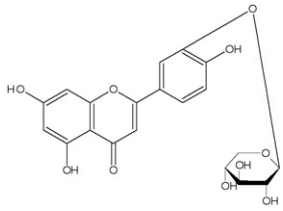
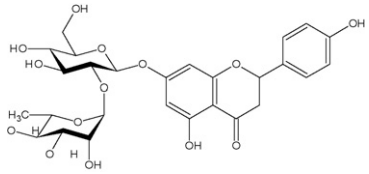
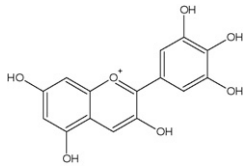
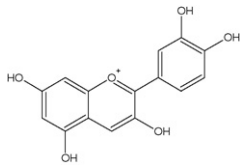
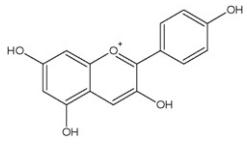
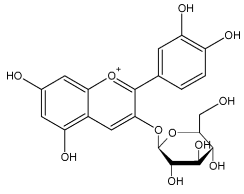
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Flavone glycosides	Luteolin 4′-*O*-β-glucopyranoside		L	Nawwar et al. (1994a)
Flavone glycosides	Luteolin 3′-*O*-β-glucopyranoside		L	Nawwar et al. (1994a)
Flavone glycosides	Luteolin 3′-*O*-β-xylopyranoside		L	Nawwar et al. (1994a)
Flavanone glycoside	Naringin		P	Kim et al. (2002)
Anthocyanidins	Delphinidin		P	Noda et al. (2002)
Anthocyanidins	Cyanidin		P	Noda et al. (2002)
Anthocyanidins	Pelargonidin		P	Noda et al. (2002)
Anthocyanins	Cyanidin 3-*O*-glucoside		J	Hernandez et al. (1999)

Table 1 (*Continued*)

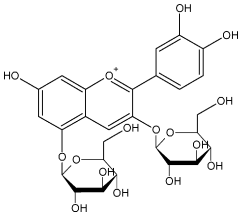
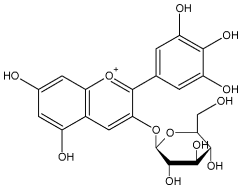
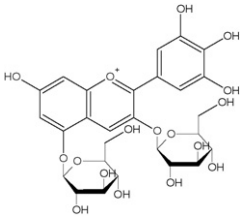
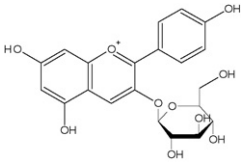
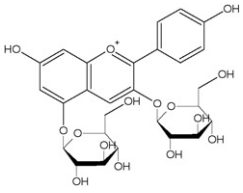
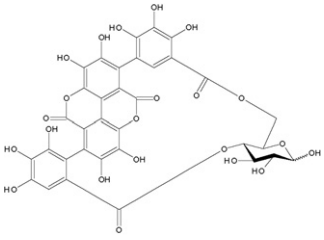
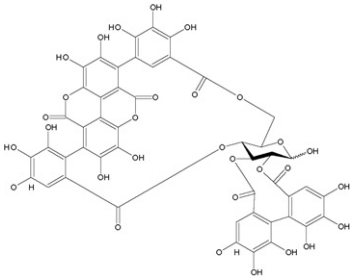
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Anthocyanins	Cyanidin 3,5-di-*O*-glucoside		J	Hernandez et al. (1999)
Anthocyanins	Delphinidin 3-*O*-glucoside		J	Hernandez et al. (1999)
Anthocyanins	Delphinidin 3,5-di-*O*-glucoside		J	Hernandez et al. (1999)
Anthocyanins	Pelargonidin 3-*O*-glucoside		J	Hernandez et al. (1999)
Anthocyanins	Pelargonidin 3,5-di-*O*-glucoside		J	Hernandez et al. (1999)
Ellagitannins	Punicalin		P, L, B, R	Tanaka et al. (1986a), Gil et al. (2000)
Ellagitannins	Punicalagin		P, L, B, R	Tanaka et al. (1986a), Gil et al. (2000)

Table 1 (*Continued*)

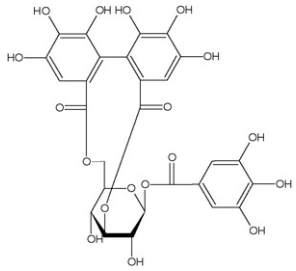
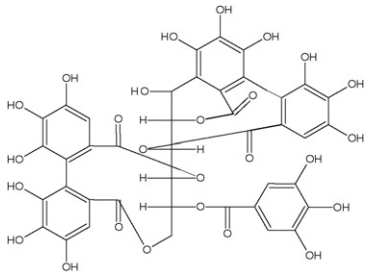
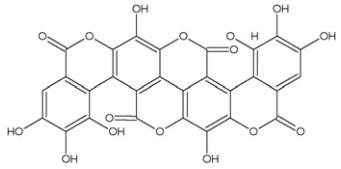
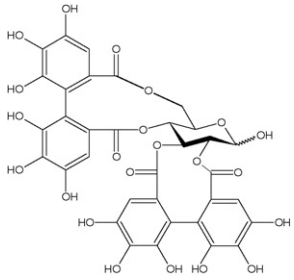
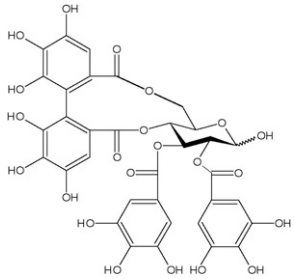
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Ellagitannins	Corilagin		P, L	Satomi et al. (1993), Nawwar et al. (1994b)
Ellagitannins	Casuarinin		P	Satomi et al. (1993)
Ellagitannins	Gallagyldilacton		P	Satomi et al. (1993)
Ellagitannins	Pedunculagin		P	Satomi et al. (1993)
Ellagitannins	Tellimagrandin		P	Satomi et al. (1993)

Table 1 (*Continued*)

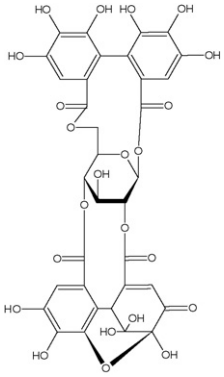
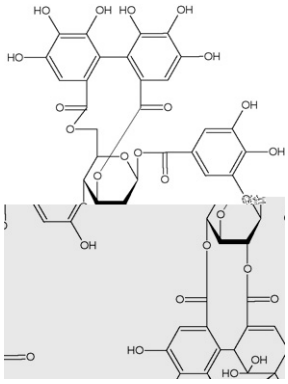
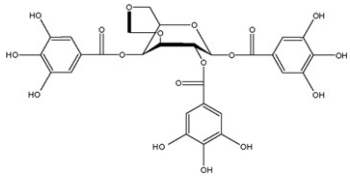
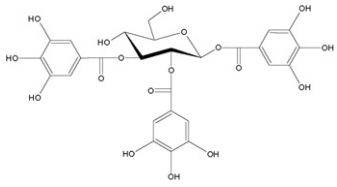
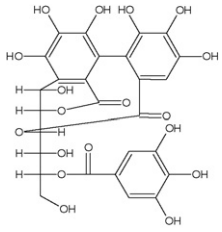
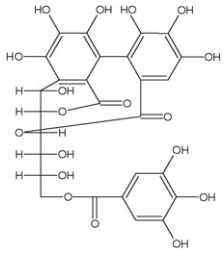
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Ellagitannins	Granatin A		P	Tanaka et al. (1990)
Ellagitannins	Granatin B		P	Tanaka et al. (1990)
Ellagitannins	Punicafolin		L	Nawwar et al. (1994b)
Ellagitannins	1,2,3-Tri-*O*-galloyl-β-^{4}C1-glucose		L	Nawwar et al. (1994b)
Ellagitannins	Punicacortein A		B, R	Tanaka et al. (1986b)
Ellagitannins	Punicacortein B		B, R	Tanaka et al. (1986b)

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Table 1 (*Continued*)

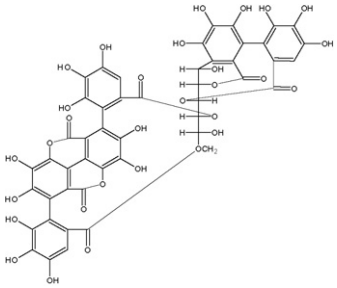
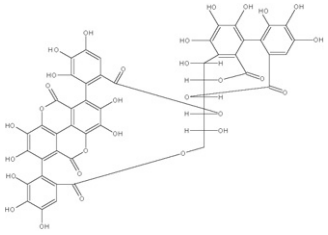
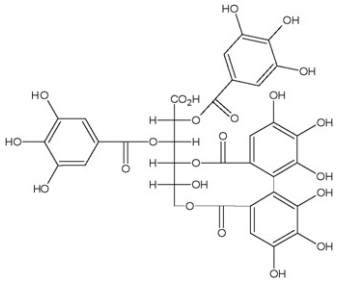
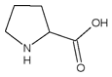
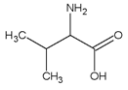
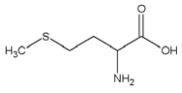
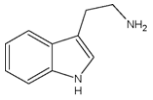
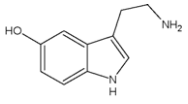
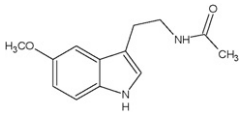
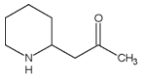
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Ellagitannins	Punicacortein C		B, R	Tanaka et al. (1986b)
Ellagitannins	Punicacortein D		B, R	Tanaka et al. (1986b)
Ellagitannins	Punigluconin 2,3-di-*O*-galloyl-4,6-(*S*)-hexahydroxydiphenoylgluconic acid		B, R	Tanaka et al. (1986b)
Amino acids	Proline		J	Velioglu et al. (1997)
Amino acids	Valine		J	Seppi Ak Franciosi (1980)
Amino acids	Methionine		J	Seppi Ak Franciosi (1980)
Indoleamines	Tryptamine		J	Badria (2002)
Indoleamines	Serotonin		J	Badria (2002)
Indoleamines	Melatonin		J	Badria (2002)
Pelletierine alkaloids	Peelletierine		P, B, R	Neuhofer et al. (1993), Vidal et al. (2003)

Table 1 (*Continued*)

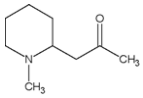
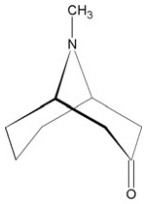
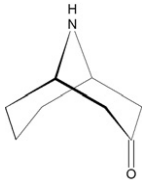
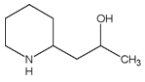
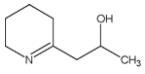
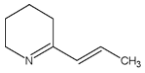
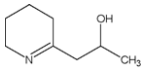
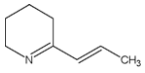
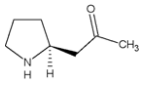
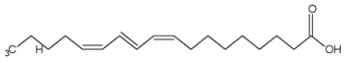
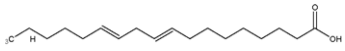
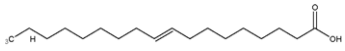
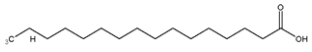
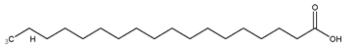
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Pelletierine alkaloids	*N*-Methylpelletierene		B, R	Neuhofer et al. (1993)
Pelletierine alkaloids	Pseudopelletierene		B, R	Neuhofer et al. (1993)
Pelletierine alkaloids	Norpseudopelletierene		R	Neuhofer et al. (1993)
Piperidine alkaloids	Sedridine		R	Neuhofer et al. (1993)
Piperidine alkaloids	2-(2′-Hydroxypropyl)Δ^1-piperideine		R	Neuhofer et al. (1993)
Piperidine alkaloids	2-(2′-Propenyll)Δ^1-piperideine		R	Neuhofer et al. (1993)
Piperidine alkaloids	*N*-(2′,5′-Dihydroxyphenyl) pyridium chloride		L	Nawwar et al. (1994a)
Pyrrolidine alkaloid	Hygrine		R	Neuhofer et al. (1993)
Pyrrolidine alkaloid	Norhygrine		R	Neuhofer et al. (1993)
Conjugated fatty acids	Punicic acid (*cis*-9, *trans*-11, *cis*-13 octadecatrienoic acid)		S	Schubert et al. (1999)
Non-conjugated fatty acids	Linoleic acid		S	Hopkins and Chisholm (1968), Schubert et al. (1999), Hornung et al. (2002)
Non-conjugated fatty acids	Oleic acid		S	Schubert et al. (1999)
Non-conjugated fatty acids	Palmitic acid		S	Schubert et al. (1999)
Non-conjugated fatty acids	Stearic acid		S	Schubert et al. (1999)

Table 1 (*Continued*)

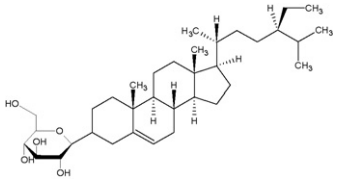
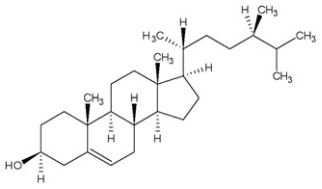
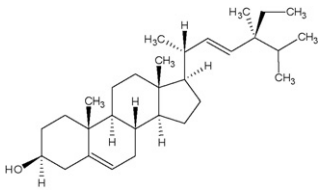
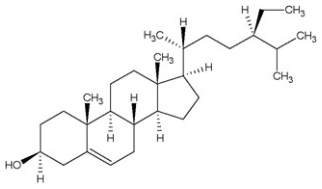
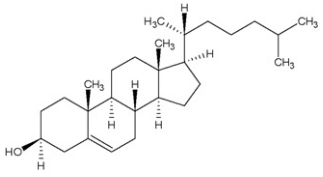
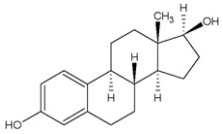
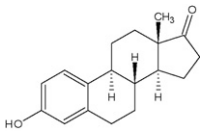
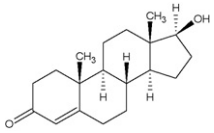
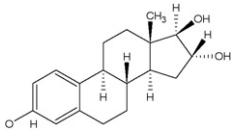
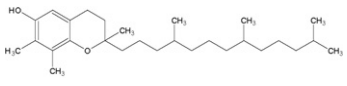
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Sterols	Daucosterol		S	Wang et al. (2004)
Sterols	Camesterol		S	Abd El Wahab et al. (1998)
Sterols	Stigmasterol		S	Abd El Wahab et al. (1998)
Sterols	β-Sitosterol		S	Abd El Wahab et al. (1998)
Sterols	Cholesterol		S	Abd El Wahab et al. (1998)
Sex steroids	17-α-Estradiol		S	Kim et al. (2002), Lansky et al. (2005a)
Sex steroids	Estrone		S	Heftmann et al. (1966), Dean et al. (1971), Abd El Wahab et al. (1998)
Sex steroids	Testosterone		S	Abd El Wahab et al. (1998)
Sex steroids	Estriol		S	Abd El Wahab et al. (1998)
Tocopherols	γ-Tocopherol		S	Kim et al. (2002)

Table 1 (*Continued*)

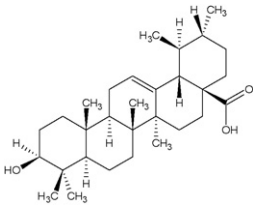
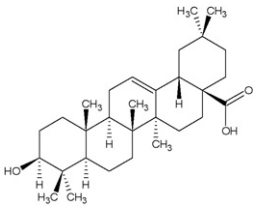
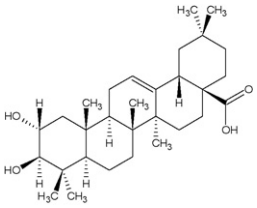
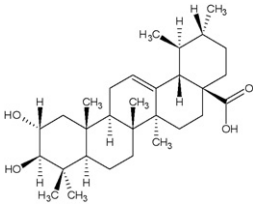
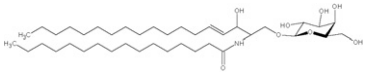
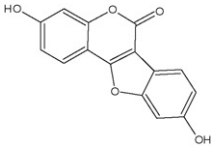
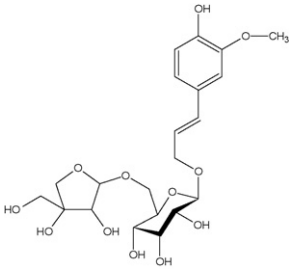
Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Triterpenoids	Ursolic acid		S, F	Ahmed et al. (1995), Huang et al. (2005c)
Triterpenoids	Oleanolic acid		F	Huang et al. (2005a)
Triterpenoids	Maslinic acid		F	Batta and Rangaswami (1973)
Triterpenoids	Asiatic acid		F	Batta and Rangaswami (1973)
Glycolipids	Cerebroside		S	Tsuyuki et al. (1981)
Coumestan	Coumestrol		S	Moneam et al. (1988), Micheli et al. (1962)
Phenyl aliphatic glycosides	Coniferyl 9-*O*-[β-D-apiofuranosyl(1 → 6)]-*O*-β-D-glucopyranoside		S	Wang et al. (2004)

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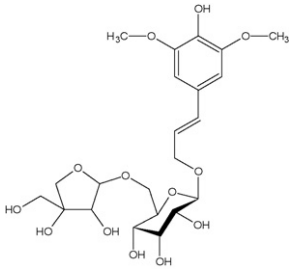
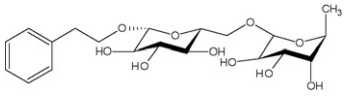
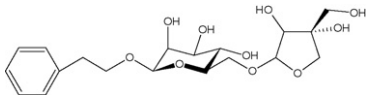
Table 1 (*Continued*)

Chemical class	Compound name	Compound structure	Plant part: J: juice, P: leaf, F: flower, L: leaf, S: seed, B: bark of tree, R: bark of tree root	References
Phenyl aliphatic glycosides	Sinapyl 9-*O*-[β-D-apiofuranosyl(1 → 6)]-*O*-β-D-glucopyranoside		S	Wang et al. (2004)
Phenyl aliphatic glycosides	Phenethyl rutinoside		S	Wang et al. (2004)
Phenyl aliphatic glycosides	Icariside D1		S	Wang et al. (2004)

octadecatrienoic fatty acids, with a high content of *cis* 9, *trans* 11, *cis* 13 acid (i.e. punicic acid), synthesized *in situ* from non-conjugated octadecadienoic fatty acid, linoleic acid (Hopkins and Chisholm, 1968; Hornung et al., 2002), itself about 7% of PSO. The fatty acid component of PSO comprises over 95% of the oil, of which 99% is triacylglycerols. Minor components of the oil include sterols, steroids, and a key component of mammalian myelin sheaths, cerebroside (Tsuyuki et al., 1981). Seed matrix includes lignins (Dalimov et al., 2003), fusion products of cell wall components and hydroxycinnamic acids, and potently antioxidant lignin derivatives (Wang et al., 2004).

2.2. Juice

Anthocyanins, potent antioxidant flavonoids, provide pomegranate juice with its brilliant color, which increases in intensity during ripening (Hernandez et al., 1999), and declines after pressing (Perez-Vicente et al., 2002; Miguel et al., 2004). Minerals in the juice and seed include Fe, relatively prevalent, but not in so high concentrations as in watermelon, and Ca, Ce, Cl, Co, Cr, Cs, Cu, K, Mg, Mn, Mo, Na, Rb, Sc, Se, Sn, Sr, and Zn (Waheed et al., 2004).

2.3. Pericarp (peel, rind, hull are synonymns)

Both flavonoids and tannins are more abundant in the peels of wild-crafted compared to cultivated fruits (Ozcal and Dinc, 1993). Complex polysaccharides from the peels have been studied and partially characterized (Jahfar et al., 2003). The presence of alkaloids (e.g., pelletierine) in the peel is equivocal, positive by Dragendorff assay, but negative by Mayer assay (Vidal et al., 2003).

2.4. Leaf

Unique tannins occur in pomegranate leaves, as well in peel. Leaves also contain glycosides of apigenin, a flavone with progestinic (Zand et al., 2000) and anxiolytic (Paladini et al., 1999) properties. With respect to chemical elements, N is high in medium age, K in young age; Ca and Fe in old leaves. In July and August in the Northern Hemisphere, N and K are both low during flowering and fruit-setting, N further declines during fruit maturity, along with Mg, Fe and Zn (Munde et al., 1980, 1981).

2.5. Flower

The flowers contain compounds also found in peels (e.g. gallic acid) and seed (e.g. ursolic acid), and quite possibly unique, distinctive compounds as well (Huang et al., 2005c). Further study is in process to elucidate the chemistry of these flowers that have also been ethnomedically employed.

2.6. Tree bark and roots

Extracts prepared from the rougher parts of the tree also have potent physiological effects and a long medical history. Their chemistry is notable against that of other tree parts mainly for the extensive presence of alkaloids.

Table 2 highlights of some of the major chemical components of pomegranate seeds, juice, pericarp, bark and leaf, and their pharmacologic activity in mammalian cells relevant to the prevention and/or treatment of malignant cell growth. While multiple mechanisms reflect the fruit's chemical complexity, major themes of increased apoptosis, decreased inflammation, decreased metastasis and invasion, as well as a decrease in drug

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Table 2
Key compounds in pomegranate and their known anticancer or anti-inflammatory 1 actions

Plant component	Compounds or compound classes with known anti-cancer or anti-inflammatory effects	Therapeutic activities of relevance to inflammation, cancer prevention and treatment	Recent references
Seed	γ-Tocopherol	Inhibits sphingolipid synthesis	Jiang et al. (2004)
		Inhibits COX-2 activity in PC	Jiang et al. (2000)
		Apoptosis in cancer cells, not in normal cells	Campbell et al. (2006), Vraka et al. (2006)
	Ursolic acid	Apoptosis in MCF-7 via p-53 upregulation	Zhang et al. (2005)
		Apoptosis in endometrial cancer cells via caspase 3 pathway	Achiwa et al. (2005)
		Apoptosis in melanoma cells via the intrinsic cell death pathway and caspase 3 activation	Harmand et al. (2005)
	Sterols (daucosterol, campesterol, stigmasterol, beta-sitosterol)	Inhibition of pro-inflammatory cytokines in mice	Nashed et al. (2005)
		PC-3 apoptosis and cell cycle arrest via ROS changes and prostaglandin release	Awad and Fink (2000), Awad et al. (2005)
		Reverts impaired glutathione/oxidized glutathione ratio via estrogen/phosphatidylinositol 3-kinase pathway	Vivancos and Moreno (2005)
Juice and peels	Punicic acid	Inhibits PC-3 invasion	Lansky et al. (2005b)
		May enhance B-cell function in vivo	Yamasaki et al. (2006)
		Cytotoxic in leukemia cells via lipid peroxidation	Suzuki et al. (2001)
	Hydroxybenzoic acids (gallic and ellagic)	Induces p53/p21 expression, G_1 arrest and apoptosis in bladder cancer cells	Li et al. (2005)
		Causes growth inhibition and apoptotic death of human DU-145 prostate cancer cells	Veluri et al. (2006)
		Reduce pancreatic stellate cell inflammation	Masamune et al. (2005)
		Promote apoptosis, attenuate G_0/G_1 to the S phase, and COX in HL-60 leukemia cells	Madlener et al. (2006)
	Hydroxycinnamic acids (e.g. caffeic)	↓ Cancer cell metastasis through down-regulation of metalloproteinase expression	Hwang et al. (2005)
		Strong inhibitor of metalloproteinase-9 and tumor cell invasion	Jin et al. (2005)
	Catechins and epicatechins	Reversal of P-glycoprotein mediated multidrug resistance	Qian et al. (2005)
		Antagonize growth-factor induced proliferative diseases	Doss et al. (2005)
		Potent inhibition of protein tyrosine kinase activities	Gouni-Berthold and Sachinidis (2004)
	Procanthocyanidins and anthocyanidins	Antiangiogenic, antioxidant and anticarcinogenic activities	Bagchi et al. (2004)
		Inhibition of cyclooxygenase activity, nitric oxide production and potent inhibitor of epidermal growth factor receptor	Hou et al. (2003)
	Quercetin	Antimutagenic activity (review)	Galvano et al. (2004)
		Inhibition of carcinogensis (review)	Lambert et al. (2005)
		Antitumor effects of f lavonoids (review)	Kanadaswami et al. (2005)
		Inhibition of lung cancer cell growth via G_2/M arrest and induction of apoptosis	Yang et al. (2006)
	Ellagitannins (punicalin and punicalagin)	↓ UV-B mediated activation of NF-κB mitogen-activated protein kinases (MAPK)	Afaq et al. (2005a)
		↓ Inflammatory cell signaling in colon cancer	Adams et al. (2006)
		Antiproliferative, apoptotic and antioxidant activities	Seeram et al. (2005)
Peels	In addition to the polyphenolic compounds found in juice...		
	Flavonols (e.g., kaempferol)	↓ Expression of tumor necrosis factor-α, interleukin-1β gene expression in tumor cells	Kowalski et al. (2005)
		Acts synergistically with quercetin to inhibit breast cancer cell proliferation	Ackland et al. (2005)
		↓ Fatty acid synthase acivity in human tumor cells	Brusselmans et al. (2005)
	Flavones (e.g. luteolin)	↓ Focal adhesion kinase activity, a key regulator of tumor cell invasion	Huang et al. (2005d)
		↑ Tumor cell apoptosis through up-regulation of death receptor and activation of caspace activities	Horinaka et al. (2005)

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Table 2 (*Continued*)

Plant component	Compounds or compound classes with known anti-cancer or anti-inflammatory effects	Therapeutic activities of relevance to inflammation, cancer prevention and treatment	Recent references
Leaf	Flavanone glycosides (e.g. naringin)	Inhibition of PC-3 tumor cell invasion	Lansky et al. (2005b)
		↓ Human tumor cell growth in vitro and i growth of sarcoma S-180 implanted in mice	Kanno et al. (2005)
	Apigenin	↓ VEGF and HIF-1 expression via multiple cell signal transduction pathways	Fang et al. (2005)
		Induces apoptosis through p53 dependent pathways in human cervical carcinoma cells	Zheng et al. (2005)
		Produces degradation of HER2/neu in human breast cancer cells	Way et al. (2005)
		↓ Motility and invasiveness of human carcinoma cells	Czyz et al. (2005)
Flower	Brevifolin carboxylic acid	Strong cytotoxic activity against human tumor cell lines	Lee and Yang (1994)
	Maslinic acid	Inhibits NF-κB, NO and peroxide formation in lipopolysaccharide induced murine macrophages	Marquez Martin et al. (2006)
	Asiatic acid	Inhibits contractions in guinea pig ileum	Sadhu et al. (2006)
		Induces capsase dependent and independent cell death in PPC-1 prostate cancer cells	Gurfinkel et al. (2006)

resistance, are evident. For example, compounds like ursolic acid, γ-tocopherol, ellagic acid, quercetin, ellagitannins, luteolin and apigenin have all been associated with tumor cell apoptosis. This is achieved through a decline in activation of NF-κB, a decrease in fatty acid synthase activity and tumor necrosis factor, increased caspase activities and upregulation of p21 and p53 expression. Pomegranate component control of inflammation involves inhibition of both COX and LOX enzymes (Schubert et al., 1999) and a decline in prostaglandin release from cells (Polagruto et al., 2003). Pomegranate components decrease tumor cell invasion into normal tissue and metastasis to distant sites. Mechanisms explaining these actions include inhibition of selected metalloproteinase activity, reduced VEGF expression, and decreased focal adhesion kinase activity. Key pompegranate components (e.g. catechins) may also reduce drug resistance through interaction with p-glycoprotein expression, relevant to potential employment of pomegranate juice or extracts as helpful adjuncts to traditional cytotoxic agents, the latter often compromised by rapid development of tumor cell resistance.

3. Inflammation

Physiological or acute inflammation is a beneficial host response to tissue damage, but when timely resolution is delayed, it may lead to such immune-associated diseases as rheumatoid arthritis, inflammatory bowel disease (IBD), and cancer (Balkwill et al., 2005; Simmons and Buckley, 2005). Silica and asbestos may provoke lung cancer; schistosomiasis, bladder cancer; IBD, colon cancer; prostatitis, and prostate cancer; all directly via initiation and indirectly via introduction of inflammatory cells in the surrounding stroma. Chronic inflammation can lead to early changes associated with the development of cancer through attraction of soluble pro-inflammaotry mediators TNF-α, interleukins (e.g. IL-6 and IL-8), transcription activation factors (e.g. NF-kB), and bioactive lipids such as eicosanoids (e.g. prostaglandin E2 and lipoxygenase derived products). Elucidation of these complex inflammation-to-cancer mechanisms suggests new cancer prevention and therapeutic strategies, with pomegranate a comparably complex and intriguing potential source for the strategic agents.

3.1. Eicosanoid enzyme inhibition (Fig. 2)

Punicic acid (Nugteren and Christ-Hazelhof, 1987) and polyphenols (Landolfi et al., 1984; Welton et al., 1986; Wallace, 2002; Morikawa et al., 2003) inhibit prostaglandin biosynthesis. The ethyl acetate extract of pomegranate fermented juice (W) inhibits soybean lipoxygenase (LOX) but not sheep cyclooxygenase (COX), while, a phenolic-rich extract of pomegranate seed oil (O) strongly inhibits lipoxygenase and cyclooxygenase (Schubert et al., 1999). Applied to mouse skin, whole pomegranate aqueous extract inhibits cyclooxygenase expression (Afaq et al., 2005b), while W, pomegranate peel extract (P) and pomegranate seed oil (PSO) each inhibit human PC-3 human prostate cancer cell phospholipase A2 expression *in vitro*. These suppressive effects are supra-additively enhanced when two of W, P and PSO, but especially when all three pomegranate components are combined (Lansky et al., 2005a).

Inhibition of COX by conventional non-steroidal anti-inflammatory drugs (NSAID's) may adversely affect cardiovascular function (Grosser et al., 2006) due to suppression of PGI_2 (prostacyclin), a prostanoid required for cardiovascular homeostasis that prevents platelet aggregation, induces vasodilation and down-regulates expression of endothelial cell adhesion molecules (Noguchi et al., 2000). Interestingly, the opposite appears true for pomegranate juice (PJ). Compared to orange juice, purple grape juice (PGJ), and coffee, PJ most potently promoted PGI_2 expression in human subjects 20 min and six hours after consumption, though PGJ more strongly promoted

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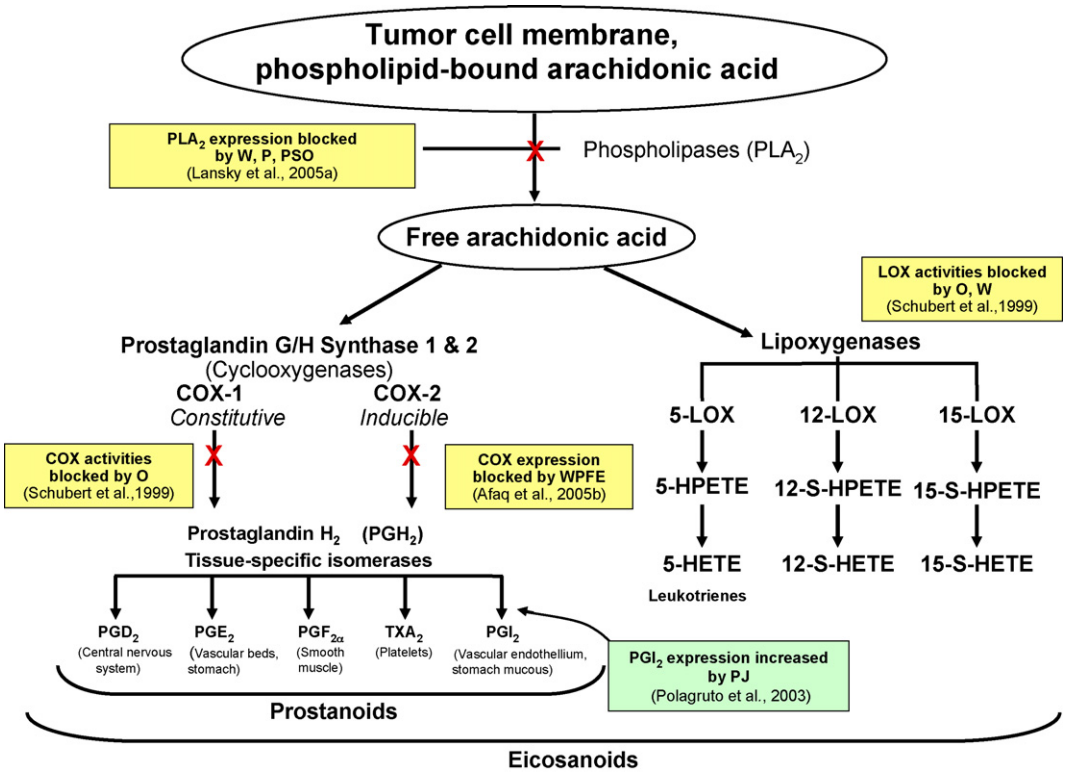

Fig. 2. Simplified diagram of eicosanoid metabolism. Phospholipase A_2 (PLA2) acts upon the cell membrane phospholipids bilayer to liberate arachidonic acid (AA) into the cell where it serves as a substrate for a variety of enzymes. Alternatively, other compounds such as linoleic acid typically derived from the diet can also serve as substrates for eicosanoid enzymes but result in different products. Prostaglandin E_2 (PGE_2) may be converted by cyclooxygenase 2 (COX-2) from AA, becoming an important stimulus for tumor cell proliferation, while AA can also be converted to lipoxygenase (LOX)-derived products, many of which as well stimulate tumor cell proliferation. These products include 12-hydroxyeicosatetraenoic acid (12-HETE) and 5-hydroxyeicosatetraenoic acid (5-HETE) derived from 12-LOX and 5-LOX, respectively. Other eicosanoid products have been shown to be involved in control of tumor cell proliferation. Such include 13-hydroxy-9,11-octadecadienoic acid (13-S-HODE) and 15-HETE although the function of these eicosanoids depends in part on the tumor cell environment in which they are generated. Punicic acid mediated inhibition of 5-LOX action has been established (unpublished data, not shown), and other points of modulation of both eicosanoid enzyme activities and expression are indicated by the red boxes. Note PGI_2 expression is promoted by PJ, though inhibited by conventional NSAID's. For more details, see text.

PGI_2 expression two hours post-drinking, but only PJ promoted PGI_2 synthesis in human aorta endothelial cells (HAEC) *in vitro* (Polagruto et al., 2003).

3.2. Cytokines

Harmful influences such as UV-b radiation may provoke DNA strand breaks, resulting in changes in phosphorylation status of proteins (Halicka et al., 2005). When such proteins are pro-inflammatory cytokines (biological response modifiers), protein modifications induce inflammatory cascades. Thus, investigation of these cascades is continuing to provide possible pharmaceutical targets, since chronic inflammation can serve as an important etiologic factor for chronic diseases including cancer (Aggarwal and Shishodia, 2004; Dominguez et al., 2005). Of interest, therefore, is the finding that acetone extracts of whole pomegranate fruits (WPFE) inhibited phosphorylation of several such cytokines in UV-B irradiated keratinocytes, including mitogen activated protein kinases (MAPK). The extracts also diminished activation of NF-κB (Afaq et al., 2005a). Inhibition of NF-κB, MAPK and related cytokines by WPFE occured *in vivo* in mouse skin exposed to 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (Afaq et al., 2005b), and in human chondrocytes induced by cytokine interleukin IL-1β (Ahmed et al., 2005) with up-regulation of MAPK-APK2 in PSO-treated human DU-145 prostate cancer cells (Albrecht et al., 2004). The beneficial effect of pomegranate extract reduction of cytokine activity has been shown to occur in patients with periodontitis. Patients experiencing this form of oral inflammation received intragingival chips impregnated with pomegranate peel extract (and extract of *Centella asiatica*), which resulted in reduced inflammatory cytokines (IL-1beta and IL-6) several months post-treatment (Sastravaha et al., 2005).

3.3. Eicosanoid/cytokine cross talk

Pure punicalagin, "total pomegranate tannin extract" (TPT) or PJ, the latter two each containing 1.74 g punicalagin/L, all significantly and dose-dependently inhibited TNF-α induced COX-2 expression (associated with cell proliferation) in HT-29 human colon cancer cells. The PJ was much more potent than the TPT which in turn was more potent than pure punicalagin, although the amount of punicalagin in PJ was only 1/300th the amount used either alone or in the TPT. Decreased phosphorylation of the p65 subunit and decreased binding to the NF-κB response element were effected as TPT > PJ > punicalagin, and

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ellagic acid (EA) was without effect. Also, PJ abolished TNFα-induced Akt (protein kinase B) activation (required for NF-κB activity), while EA and punicalagin were inactive (Adams et al., 2006). The components of PJ thus might appear to synergistically suppress inflammatory cytokine expression. Most recently, a whole pomegranate methanol extract was also shown to inhibit, in a dose-dependent manner, production and expression of TNFα in microglial cells, in which inflammation had been induced by lipopolysacchardide (Jung et al., 2006).

3.4. Matrix metalloproteinases

Matrix metalloproteinases (MMP) are enzymes important in maintenance of normal cellular architecture, assisting with creation of interstitial spaces by destroying structural proteins thereby facilitating multiple inflammatory processes (Shapiro, 1997; Leppert et al., 2001; Okamoto et al., 2004; Salvi and Lang, 2005). Human chondrocyte MMP's were inhibited by WFPE (Ahmed et al., 2005), while P, and to a lesser extent W and pomegranate seed extract (PSE), but not PSO, inhibited human dermal fibroblast MMP-1 (Aslam et al., 2005).

3.5. Antioxidant activity

Oxidative tension is a potent yet non-specific metabolic trigger for both inflammation and angiogenic processes (Hayden and Tyagi, 2004; Karageuzyan, 2005; Kapoor et al., 2005), both of which are key factors in cancer initiation and promotion (Dobrovolskaia and Kozlov, 2005; Garcea et al., 2005; Ohshima et al., 2005). Since pomegranate's antioxidative efficacy clinically may be impaired by poor bioavailability of active compounds (Cerda et al., 2004, 2006), strengths and weaknesses of pomegranate's antioxidant activity need be considered. In general, comparable juice or extracts from other common fruits show antioxidant activity *in vitro* inferior to that of the pomegranate (Halvorsen et al., 2002; Kelawala and Ananthanarayan, 2004; Xu et al., 2005).

Antioxidant activities associated with different pomegranate components are summarized in Table 3. In addition to these studies, other *in vivo* and clinical findings have been suggested as stemming from antioxidant effects. Examples of *in vivo* studies of beneficial effects of pomegranate antioxidant activity include: protection of rat gastric mucosa from ethanol or aspirin toxicity (Khennouf et al., 1999; Ajaikumar et al., 2005), protection of neonatal rat brain from hypoxia (Loren et al., 2005), prevention of male rabbit erectile tissue dysfunction (Azadzoi et al., 2005), and abrogation of ferric nitrilotriacetate (Fe-NTA) induced hepatotoxicity evidenced by miitigated hepatic lipid peroxidation, actions of glutathione (GSH), catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (GR) glutathione-*S*-transferase (GST), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP), bilirubin and albumin levels, hepatic ballooning degeneration, fatty changes, and necrosis (Kaur et al., 2006). Cardiovascular effects of PJ in man, which may or may not involve redox-linked biochemical pathways, include lowering of LDL and total cholesterol (Esmaillzadeh et al., 2004), ameliorating systolic hypertension (Aviram and Dornfeld, 2001), and reducing carotid arterial stenosis (Aviram et al., 2004).

4. Cancer prevention

4.1. Carcinogenesis

In mouse mammary organ culture (MMOC), an *ex vivo* model for pre-cancerous tumor initiation via exposure to chemical carcinogen 7,12-dimethyl-benz[*a*]anthracene (DMBA), W produced a 46% decrease in tumor occurrence (Kim et al., 2002), whereas cold-pressed PSO or an HPLC "Peak B" isolated from W resulted in up to an 87% reduction in tumor occurrence. Notably, 1 μg/ml PSO resulted in higher suppression than a 10 μg/ml dose (Mehta and Lansky, 2004) suggesting that an optimal biological dose is more important and relevant than a maximally tolerated one. In female CD-1 mice with skin tumors induced by DMBA and subsequently promoted by 12-*O*-tetradecanoylphorbol 13-acetate (TPA), external treatment with 5% PSO produced significant decreases in both tumor incidence and multiplicity ($P < 0.05$) (Hora et al., 2003). Similarly, topical pre-treatment with WPFE (2 mg/mouse) prior to TPA applications in DMBA-treated CD-1 mice decreased the tumor incidence from 100 to 30% and increased latency of tumor development from week 9 to week 14 (Afaq et al., 2005b). Pomegranate seed oil (PGO) has also been shown to reduce both the incidence and multiplicity of colon tumors in rats treated with carcinogen azoxymethane (AOM). As in MMOC, dose response is non-linear: there is an early peak, followed by a decline. The response pattern is as follows: for tumor incidence, AOM + 0.01% PGO, 44%, $P < 0.05$; AOM + 0.1% PGO, 38%, $P < 0.01$; AOM + 1% PGO, 56%) and for multiplicity: AOM + 0.01% PGO, 0.56 ± 0.73, $P < 0.01$; AOM + 0.1% PGO, 0.50 ± 0.73, $P < 0.005$; AOM + 1% PGO, 0.88 ± 0.96, $P < 0.05$ (Kohno et al., 2004). This study importantly establishes the chemopreventive activity of pomegranate seed oil against both tumor incidence and multiplicity, and also dramatically elaborates the non-linear character of these effects (i.e., a lower dose of oil may have a greater chemopreventive effect than a higher dose of oil). The study will serve as a springboard to future investigations seeking to establish optimum dosages of PSO for human cancer chemoprevention.

4.2. Cell cycle

Cell cycle changes occur following exposure of human Burkitt's lymphoma cells to pomegranate peel extract (Settheetham and Ishida, 1995) and human monocytic leukemia cells to pomegranate seed oil (Suzuki et al., 2001). Mechanisms for these effects likely involve modulation of cell signaling molecules in the cell cycle machinery (e.g., WAF1/p21) in the case of the pomegranate aqueous fractions (peel and juice) (Shukla and Gupta, 2004), and for PSO and its conjugated trienes, lipid peroxidation (Suzuki et al., 2001; Tsuzuki et al., 2004) and/or lipoxygenase inhibition (Cunningham et al., 1997). Significant increases in DU-145 androgen negative human

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Table 3
Antioxidant pomegranate studies

Assay(s)	Assay type	Effect	*Punica grantum* PART	Comment	Reference
β-Carotene	*In vitro* antioxidant	Inhibits twice as strongly as similar extract of red wine, slightly less than green tea	Fermented juice (W)	Organically grown source of W, red wine and green tea of extra fine quality	Schubert et al. (1999)
ABTS, DMPD, FRAP	*In vitro* chemical antioxidant	Three times stronger inhibition that red wine or green tea, significantly stronger than aril-pressed juice	Commercial PJ (whole fruit squeezed)	Commercial PJ is pressed from whole fruit with peels, contains considerably more punicalagin than aril-pressed PJ	Gil et al. (2000)
DPPH	*In silico* antioxidant	Three times stronger inhibition that red wine or green tea, significantly stronger than aril-pressed juice	Commercial PJ (whole fruit squeezed)	Commercial PJ is pressed from whole fruit with peels, contains considerably more punicalagin than aril-pressed PJ	Gil et al. (2000)
Low density lipoprotein (LDL)	*In vitro* biological antioxidant	Methanol extracts more potent inhibition than ethyl acetate or water extracts	Peels	Similar effects in chemical assays	Singh et al. (2002)
Low density lipoprotein (LDL)	*In vitro* biological antioxidant	Methanol extract 1/4 as potent as same from peels	Seeds	Similar effects in chemical assays	Singh et al. (2002)
TEAC, inhibition of peroxidation of phosphatidylcholine liposomes	Chemical *in vitro* antioxidant	Prodelphinidin dimers potent antioxidants in aqueous phase, only gallocatechin-(4-8)-catechin more effective than prodelphinidin monomers in lipid phase (in liposomes)	Gallocatechin and prodelphinidins from peel		Plumb et al. (2002)
H_2O_2-induced LDL oxidation	*In vitro* rat brain	Seventy percent acetone extract and principle anthocyanidins inhibit, pelargonidin 25X more potent than delphinidin or cyaniding	Whole pomegranate fruit (WPFE)	Scavenging of nitric oxide (NO) not observed	Noda et al. (2002)
Tumor necrosis factor alpha (TNF-α) in vascular endothelial cells	Biological *in vitro*	Inhibition	Fermented juice extract (W)	Suggests redox triggering of inflammation	Schubert et al. (2002)
Shear stress-mediated-NF-κB activation in vascular endothelial cells	Biological *in vitro*	Activation	Fermented juice extract (W)	Suggests redox triggering of inflammation	Schubert et al. (2002)
Shear stress in cultured human coronary artery endothelial cells	Biological *in vitro*	Oxidation sensitive responsive genes down-regulated, endothelial NO synthase (eNOS) expression increased	Fresh juice (PJ)		de Nigris et al. (2005)
Low-density liporotein (oxLDL) induced human coronary endothelial cells	Biological *in vitro*	Reverses downregulated endothelial nitric oxide synthase (NOSIII) expression; reduces NOSIII-mediated basal and bradykinin-stimulated cellular cGMP accumulation	Fresh juice (PJ)	NOSIII-mediated basal and bradykinin-stimulated cellular cGMP accumulation associated with athero-genesis and clinical vascular sequellae	de Nigris et al. (2006)
LDL oxidation and atherosclerot ic plaque formation	Mice *in vivo*	Prevents these effects, concentrating polyphenols and increasing paroxinase in macrophages	Fresh juice (PJ)		Aviram et al. (2002)

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Biochemical assessments of oxidation	Rat *in vivo*, heart, liver, kidney	Reduces malonaldehyde, hyperoxides, and conjugated dienes; enhances glutathione	Ethyl acetate and methanol/ethyl acetate WPFE's	Glutathione is an endogenous antioxidant, in response to oxidative threat	Sudheesh and Vijayalakshmi (2005)
Resistance of LDL to oxidation	Mouse *in vivo*, human serum *ex vivo*	Enhances resistance	PJ		Aviram et al. (2000)
Measurement of macrophage lipid peroxides and glutathione	Biological *in vitro* antioxidant	Three times more enhanced than treatment by PJ	Enzymatically treated, finely milled, pomegranate by-product (PBP), remains after conventional juicing		Rosenblat et al. (2006)
Paraoxonase-2 lactonase	Biological *in vitro* antioxidant	Significantly increased action	Enzymatically treated, finely milled, pomegranate by-product (PBP), remains after conventional juicing		Rosenblat et al. (2006)
Lipid and TEAC (Trolox equivalent antioxidant capacity)	Chemical *in vitro* antioxidant	Antioxidant actions as PJ > TPT > punicalagin > EA	PJ, total pomegranate tannins (TPT), punicalagin, and ellagic acid (EA)	Suggest synergistic actions among PJ compounds	Seeram et al. (2005)
DPPH	Chemical *in silico* antioxidant	Scavenges reactive species (ROS) superoxide (O_2-*), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH)	Ethanolic pomegranate flower extract (PFE)	Unlike PJ and its anthocyanins (Noda et al., 2002), also scavenges NO, also abrogates liver toxicity (see text)	Kaur et al. (2006)
DPPH	Chemical *in silico* antioxidant	*Punica granatum* leaves strongest antioxidant (93.5% enhancement) of almost 100 species tested	Leaf extract	0.5 mg/ml, incubated at 37 °C 20 min, minutes, second place *Acer buergerianum* Miq., 86.4%	Lu et al. (2003)
Endothelial nitric oxide synthase (NOSIII) induction by oxidized LDL in human coronary endothelial cells	Cellular system *in vitro*	Reversed potent down-regulation of NOSIII induced by ox-LDL	PJ	Suggests beneficial effects on vascular complications by enhancing NOSIII bioactivity	Ignarro et al. (2006)
DPPH, luminol/xanthine/xanthineoxidase	*In silico*, chemilumi-nescense *in vitro*	Good antioxidant activity, strongest from EA extract of arils	Arils, PJ, peels and their EA extracts		Ricci et al. (2006)

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prostate cancer cells in G_2/M ($P < 0.05$) were effected by PSO, W, and P, but only P and W and not PSO decreased the percentage of cells in G_1. These results, however, are not universal in all androgen negative human prostate cell lines. For example, effects of these pomegranate components are less pronounced or not seen in PC-3 human prostate cancer cells exposed to the same agents (Albrecht et al., 2004).

4.3. Differentiation

Differentiation of HL-60 promyelocytic human leukemia cells as detected by nitro blue tetrazolium reducing, non-specific esterase, specific esterase and phagocytic activities is potently promoted by P and W, whereas the ethyl acetate extract of fresh, unfermented pomegranate juice (J) has little effect. Differentiation may possibly figure into observed anticancer effects of pomegranate extracts in other cell lines, including breast and prostate (Kawaii and Lansky, 2004).

4.4. Other enzymes

Carbonic anhydrase (CA) catalyzes the reversible hydration of carbon dioxide (CO_2) to bicarbonate (HCO_3^-) (Khalifah, 2003). The presence of CA in every fluid compartment along the pathway of CO_2 transport enables dehydration of HCO_3^- to coordinate with the rapid diffusion of CO_2 across biological membranes (Henry and Swenson, 2000). At least 14 isoforms of CA are known in mammals, and though the mechanism is not known, many CA inhibitors (CAI's) strongly inhibit cancer cell growth *in vitro* and *in vivo*. Thus, CAI's may therefore provide novel anti-tumor drugs (Pastorekova et al., 2004). Since CA's also possess esterase activity, it is of interest that pomegranate peel extract and some of its active ellagitannins inhibit the de-esterification of *p*-nitrophenyl acetate catalyzed by CA's, establishing their activity and role as CAI's (Satomi et al., 1993) and raising the possibility of CA inhibition as another aspect of pomegranate's anticancer actions.

Ornithine decarboxylase (ODC) catalyzes formation of polyamines such as the naturally occurring putrescine, spermidine and spermine from the amino acid ornithine, itself a product of the breakdown of L-arginine by arginase to form urea. Polyamines regulate growth processes in both eukaryotic and prokaryotic cells, and may facilitate the growth of cancer (Bachrach, 2004). Pomegranate may also serve as a source of inhibitory components to inhibit this enzyme since epidermal ODC is inhibited by PSO (Hora et al., 2003) as well as by acetone WPFE's (Afaq et al., 2005b).

Aromatase, estrogen synthase, catalyzes the formation of estrone and estradiol from androstenedione and testosterone, respectively (Karaer et al., 2004). As the rate limiting enzyme in endogenous estrogen synthesis, aromatase can promote hormone dependent cancers, so its inhibition is an important therapeutic objective for certain malignancies, e.g., estrogen sensitive breast cancers. It is therefore significant that aromatase is potently inhibited by both W and P, although only weakly inhibited by PSO (Kim et al., 2002).

17-β-Hydroxysteroid dehydrogenase type 1 catalyzes reduction of estrone to the much more potent estrogenic 17-β-estradiol. Since this reaction also increases estrogenic stimulation of estrogen sensitive cancers, this enzyme is a valid target of importance for controlling malignant breast disease. In recognition of this, supercritical CO_2 extracted PSO (SESCO) much more potently inhibits 17-β-hydroxysteroid dehydrogenase type 1 than does either W or P (Kim et al., 2002).

A note of caution should be inserted here concerning the multiple enzyme systems shown to be influenced by specific pomegranate fractions. These findings would be more compelling against a background of negative influence of enzymes not relevant to the present discussion. Unfortunately, in many cases investigators have simply not looked at relative specificity of biochemical effects with respect to changes in normal and malignant cells or tissues. A much wider future screening of enzymes and their possible modulation (or lack of it) by pomegranate fractions is thus called for.

5. Cancer treatment

5.1. Angiogenesis

The initiation and development of new blood vessels (angiogenesis) are essential to supply oxygen and nutrients for tumor growth and metastasis. Inhibition of tumor blood vessel formation, first proposed by Judah Folkman in the early 1970s (Folkman, 1972), is still a relatively non-toxic and promising therapeutic approach for treating solid tumor afflicted patients. Interestingly, recent research indicates that pomegranates possess the ability to inhibit development of new blood vessels. Thus, angiogenesis in chicken chorioallantoic membrane (CAM) *in vivo* was significantly suppressed by W but not by P. Pro-angiogenic vascular endothelial growth factor (VEGF) was potently downregulated in MCF-7 estrogen dependent breast cancer cells, less so in estrogen negative MDA-MB-231 breast cancer cells, and most strongly in MCF-10A immortalized normal breast epithelial cells by W and SESCO, and only mildly so by P and pressed PSO. The anti-angiogenic migration inhibitory factor (MIF) was potently upregulated in MDA-MB-231 cells by W and SESCO, which also moderately suppressed human umbilical vein endothelial cell (HUVEC) proliferation and tubule formation. Conversely, P and W (SESCO and PSO only weakly so) potently inhibited human myometrial fibroblast proliferation (Toi et al., 2003) suggesting selectivity to the inhibition of cellular proliferation amongst cell types.

5.2. Apoptosis

Apoptosis, an early response cell death, is a useful marker for predicting tumor response after anticancer treatment. Aqueous pomegranate peel extract resulted in apoptotic DNA fragmentation and suppression of growth in two human Burkitt's lymphoma cell lines, Raji and P3HR-1 (Settheetham and Ishida, 1995) while 50 μg/ml PSO led to 54% greater extent of apop-

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tosis in MDA-MB-435 estrogen receptor negative, metastatic human breast cancer cells, compared to the known apoptotic compound, Δ-tocopherol (Kim et al., 2002). Pomegranate fractions have also been shown to result in apoptosis in two androgen receptor negative human prostate cancer cell lines in the highly metastatic PC-3 (P = W > PSO), and in the slower growing DU-145 (PSO > P = W). These activities were at least partially mediated by capsase enzymes (Albrecht et al., 2004), suggesting involvement of inflammatory processes in executing the suicidal apoptotic cascades (Johar et al., 2004). Capsase activation in PC-3 cells by WPFE correlates with downregulation of pro-apoptotic factors Bax and Bak and downregulation of anti-apoptotic factors Bcl-X_L and Bcl-2. Similarly, WPFE reduced expression of cyclins D1, D2, and E and cyclin-dependent kinase (cdk) 2, cdk4, and cdk6, while PJ or TPT, standardized to 100 μg punicalagin, or 100 μg EA or 100 μg punicalagin, each effected apoptosis in HT-29 human colon cancer cells, but only TPT, punicalagin and EA induced apoptosis in HCT116 colon cancer cells, suggesting PJ contains anti-apoptotic factors as well as pro-apoptotic ones (Seeram et al., 2005). In Caco-2 human colon cancer cells but not CCD-112CoN normal human colon cells, both punicalagin and its hydrolysis product EA down-regulated cyclins A and B1 and upregulated cyclin E resulting in cell-cycle arrest in S phase, and apoptosis via an intrinsic pathway (FAS-independent, caspase 8-independent) through Bcl-X_L down-regulation with mitochondrial release of cytochrome c into the cytosol and activation of initiator caspase 9 and effector caspase 3, suggesting that these effects of punicalagin are mediated mainly or entirely via EA (Larrosa et al., 2005). Thus in short, both the lipid and aqueous pomegranate fractions appear to possess selective apoptotic potential in respect to different hormone-independent cancer cell lines, suggesting chemotherapeutic potential for compounds originating from each of these pomegranate compartments.

5.3. Tumor cell invasion

Approximately 90% of all cancer deaths arise from the metastatic spread of primary tumours. Of all the processes involved in carcinogenesis, local invasion and the formation of metastases are clinically the most relevant, but they are the least well understood and have been amongst those processes most difficult to target. Nonetheless, recent research has indicated that pomegranate appears to contain components capable of suppressing tumor cell invasion. Cold-pressed PSO, for example, inhibited invasion of estrogen sensitive MCF-7 human breast cancer cells *in vitro* across an artificial Matrigel™ membrane at doses less than 10 μg/ml (Kim et al., 2002), and PSO, P, and W each resulted in 60% suppression of invasion in Matrigel™ of human PC-3 androgen negative prostate cancer cells at 3 μg/ml (Albrecht et al., 2004). When equal amounts of any two of W, P or PSO were combined as 1.5 + 1.5 = 3 μg/ml, a supra-additive, synergistic effect was obtained such that the combination resulted in a 90% suppression of invasion. When all three were equally combined as 1 + 1 + 1 = 3 μg/ml, the suppression exceeded 99% ($P < 0.01$) by Kruskal–Wallis non-parametric *H*-test (Lansky et al., 2005a). At 1 μg/ml, pure punicic acid inhibited PC-3 invasion 70%, luteolin 60%, EA 60%, and caffeic acid 50%. Any two combined effected a non-significant enhanced suppression, but punicic acid, luteolin and caffeic acid together resulted in a statistically significant 95% suppression, while addition of EA to the mix weakened the apparent synergy (Lansky et al., 2005b).

5.4. Proliferation

The ability of any chemotherapeutic agent to inhibit selectively proliferation of malignant but not normal cells is the hallmark of a promising anticancer therapeutic agent. In this regard, pomegranate peel extracts have been shown to retard proliferation of cells in several different human cancer cell lines (Settheetham and Ishida, 1995; Mavlyanov et al., 1997; Kawaii and Lansky, 2004). In human breast cancer cells, for example, the effects of W and P were most pronounced against estrogen responsive MCF-7 cells, less pronounced against estrogen negative MDA-MB-231 cells, and least pronounced against immortalized normal breast epithelial cells MCF-10A (Kim et al., 2002; Toi et al., 2003) strongly suggesting a spectrum of anticancer activity and not the presence of indiscriminate cytotoxic compounds. Also, additive inhibition of proliferation by the isoflavone genistein, common in soy, clover and other legumes, and W occured in MCF-7 cells, but further studies are required to determine if the additive effect is also supra-additive (Jeune et al., 2005). In human prostate cancer cells, DU-145 androgen independent cells were more sensitive to W and P than to cold-pressed PSO, the effect milder in PC-3 androgen independent cells or LNCaP androgen sensitive cells, but LNCaP cells were most sensitive to PSO relative to W or P. Notably, immortalized normal prostate epithelial cells hPrEC were found to be considerably less affected by either W or P than were androgen sensitive cancer cells LNCaP (Albrecht et al., 2004). When sub-lethal doses of P (6.25 μg/ml) or PSO (16.25 μg/ml) were combined with an anti-proliferative dose of W (25 μg/ml), supra-additive enhancement of the suppression of proliferation ensued ($P < 0.001$) (Lansky et al., 2005a). Similarly, the anti-proliferative actions of a TPT, punicalagin or EA were less potent against human oral (KB, CAL27), colon (HT-29, HCT116, SW480, SW620) or prostate (RWPE-1, 22Rv1) cancer cells than PJ standardized to the same dose of punicalagin used as a single agent (Seeram et al., 2005). Treatment of androgen-independent PC-3 cells with acetone WPFE dose-dependently inhibited proliferation, corresponding to changes in the cyclin kinase inhibitor-cyclin-cdk network, and WPFE treatment of nude mice implanted with androgen-sensitive CWR22Rnu1 human prostate cancer cells resulted in suppression of growth and a significant decrease in serum prostate-specific antigen (Malik et al., 2005). These studies collectively reinforce the hypothesis that whole, complex pomegranate products possess potential anti-proliferative activity against cancer cells superior to that of their key active compounds, again, suggesting therapeutic strategies that may depart from the traditional preference for pure single agents.

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5.5. Contribution of pomegranate components with estrogenic activity

We have previously shown that pomegranate components possess an ability to inhibit the estrogenic action of 17-β-estradiol, an activity best explained through competitive binding to estrogen receptors by a number of non-steroidal estrogenic flavonoids such as kaempferol, quercetin, naringenin, and luteolin (Kim et al., 2002). A methanolic eluate of pomegranate juice competed with 17-β-estradiol for estrogen receptors, stimulated estrogen receptor positive (ER+), MCF-7 breast cancer cells and increased uterine weight in ovariectomized mice (Maru et al., 2001), though elsewhere, pomegranate fermented juice inhibited MCF-7 growth through a range of concentrations (Kim et al., 2002). Further, an estrogen-agonist protective effect of pomegranate juice and seed extract was shown in ovariectomized mice, evidenced by improved bone density and attenuation of experimental depression (Mori-Okamoto et al., 2004), and both oral and intramuscularly injected pomegranate seed oil increased uterine weight and vaginal cornification in ovariectomized mice and immature female rabbits, respectively (Sharaf and Nigm, 1964; Sharaf, 1969). Estrogenic agonism may exert cancer therapeutic potential by inhibiting androgenic activity, especially in prostate cancer (Zhu et al., 2005), but also by anti-inflammatory mechanisms (Harris et al., 2003; Harris, 2006) or by promoting apoptosis in cancer cells via Fas/FasL pathways (Song and Santen, 2003).

5.6. Phase 2 clinical trial

Despite the impressive amount of preclinical work indicating cancer preventive or therapeutic efficacy with limited toxicity, there still remain few well designed clinical trials investigating the relative anticancer health benefits of pomegranate. Against this paucity of clinical work, in a recent open-label, single-arm, 2-year, phase-2, Simon two-stage clinical trial of 48 men (46 men actually completed the trial) with increasing prostate-specific antigen (PSA), an important surrogate biomarker for prostate cancer mortality after surgery or radiotherapy, 8 oz daily of pomegranate juice (wonderful variety, 570 mg, total polyphenol gallic acid equivalents) *per orum* resulted in a significant increase in PSA doubling time from a mean of 15–37 months ($P < 0.048$). Furthermore, *ex vivo* application of the post-treatment patient serum to LNCaP androgen-sensitive cancer cells in culture resulted in a 12% decrease in cell proliferation and a 17% increase in apoptosis ($P = 0.0048$ and 0.0004, respectively), 23% increase in serum nitric oxide ($P = 0.0085$), and significant ($P < 0.02$) reductions in oxidative state and sensitivity to oxidation of serum lipids after versus before pomegranate juice consumption. Eligible patients had a detectable PSA > 0.2 and < 5 ng/mL that was documented as rising, enough pretreatment PSA time points to calculate a baseline PSA doubling time (PSADT), no hormonal therapy before entering the study, no evidence of metastatic disease, and Gleason score ≤7. Markers for compliance included serum and urinary polyphenol/ellagic acid levels. Though the careful study design exacted significance, it suffered from a lack of placebo groups. No serious adverse effects were reported in any of the participants (Pantuck et al., 2006a,b).

6. Toxicology

Pomegranate has been widely consumed by persons in many different cultures for thousands of years, largely without untoward incident, and thus is considered generally safe. However, some toxicity is known, and undoubtedly, more remains to be discovered. Consumption of decoction of the tree bark, and to a lesser extent, pericarps of the fruit, may cause severe acute gastric inflammation and even death due to the presence of both tannins and alkaloids (Squillaci and Di Maggio, 1946). Whole fruit extracts have been shown to cause congestion of internal organs and elevated creatinine *in vivo* (Vidal et al., 2003). Pomegranate seed oil was not toxic to brine shrimp larvae (Fatope et al., 2002), however both severe allergic reactions (Igea et al., 1991; Gaig et al., 1999; Hegde et al., 2002) from eating the fruit and esophageal cancer from chronic consumption of roughly ground pomegranate seeds (Ghadirian, 1987; Ghadirian et al., 1992) have been reported.

7. Conclusion

Pomegranate is an ancient fruit with an illustrious medical history and has been the subject of classical reviews for over 100 years (Lloyd, 1897; Li et al., 2002). However, until only very recently, the importance of the oily phase of the seed has been largely overlooked. Recent studies have also begun to suggest possible synergistic interactions between aqueous and lipid phases of the fruit, and between different chemicals in each phase. Though, undoubtedly, much more is still unknown than known about the pomegranate's chemistry and medicinal potential, the beginnings of a possible use for the fruit in cancer chemoprevention (Malik and Mukhtar, 2006) and chemotherapy, largely deriving from the anti-inflammatory properties of both the aqueous and lipid phases, is in the earliest stages of being appreciated (Longtin, 2003). Clinical trials with pomegranate materials, though, particularly with regard to inflammation and cancer, are still sorely lacking.

Much of the work completed on pomegranate over the past 7 years has focused on antioxidant activity of the tree's various components. The relationship of this activity to health and disease has not been established, so direct extrapolation of such findings to medical recommendations is premature.

In short, the studies reported in this survey while possibly provocative, leave many gaps. Though inconclusive, however, they do suggest further study, including clinical trials of properly designed pharmaceutical products. Toward such an end, it is hoped that the present review will provide some valuable clues for ongoing explorations of this most fascinating botanical species. *Note*: At the time of resubmission of this manuscript, the authors have learned of a new medical monograph on the subject of *Punica granatum* (Seeram et al., 2006), and also an editorial on the subject of pomegranate–pharmaceutical interactions (Summers, 2006). It is likely that much more will follow, as the medical community and public continue to

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exhibit renewed interest in the pomegranate as a therapeutic article.

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Interest statement: The authors are collaborating on the development of an anticancer pharmaceutical product derived from pomegranate. One of the authors (E.P.L.) is a founder and owner of Rimonest Ltd., a company which also markets and sells pomegranate derived functional products.

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