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Review Paper

Bioactive Chemical Constituents from Pomegranate (*Punica granatum*) Juice, Seed and Peel-A Review

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Abstract **-** The pomegranate tree, *Punica granatum* possesses a vast ethnomedical history and represents a phytochemical reservoir of heuristic medicinal value. The pomegranate tree can be divided into several anatomical compartments like seed, peel, juice, flower, leaf, bark, roots, etc. each of which has interesting pharmacologic activities. The chemical composition of fruits differs depending on the cultivar, growing region, climate, maturity, cultural practice and storage. Significant variations in organic acids, phenolic compounds, sugars, water-soluble vitamins and minerals composition of pomegranates have been reported over the years. Pomegranates contain high levels of a diverse range of phytochemicals including polyphenols, sugars, fatty acids (conjugated and non-conjugated), aromatic compounds, amino acids, tocopherols, sterols, terpenoids, alkaloids, etc. The synergistic action of the pomegranate constituents appears to be superior to that of single constituents. In the past decade, numerous studies on the antioxidant, anti-carcinogenic, and anti-inflammatory properties of pomegranate constituents have been published, focusing on treatment and prevention of cancer, cardiovascular disease, dental conditions, bacterial infections and antibiotic resistance, and ultraviolet radiation-induced skin damage. This article provides a critical review of various phytochemical constituents isolated from pomegranate juice, seeds and peels; and their associated medicinal properties dealing with antioxidant, anticancer, anti-inflammatory, antibacterial/antimicrobial properties, as well as a brief summary on other activities.

Key words: Pomegranate, *Punica granatum*, Juice, Seed, Peel, Chemical Constituents, Biological activity, Toxicity etc.

Introduction

Punica is a small genus of fruit-bearing deciduous shrub or small trees. Its better-known species is the Pomegranate (*Punica granatum* L.). *P. granatum* is a member of the Punicaceae family which shares its botanical family only with *Punica protopunica*, the latter restricted in occurrence to Socotra, an island of the Yemeni coast. *P. protopunica* differs in having pink unlike the red flowers of *P. granatum* and smaller, less sweet fruit. Over 1000 cultivars of *P. granatum* exist [1], originating from the Middle East, extending throughout the Mediterranean, east ward to China and India, and on to the American Southwest, California and Mexico. 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. The fruit itself gives rise to three parts: the seeds, about 3% of the weight of the fruit, and themselves contain 20% oil; the juice, about 30% of the fruit weight; and the peels which also include the interior network membranes. The fruits are globally consumed fresh, in processed forms as juice, jam, wine and oil and in extract supplements.

The pomegranate is a symbol of life, longevity, health, femininity, fecundity, knowledge, morality, immortality and spirituality, if not Divinity [2]. In the ancient Egyptian culture the pomegranate fruit was regarded as a symbol of prosperity and ambition, making it common practice to decorate sarcophagi with depictions of the plant. In Ayurvedic medicine the pomegranate is considered "a pharmacy unto itself," the bark and roots believed to have anthelmintic and vermifuge properties [3], the peels a powerful astringent and cure for diarrhea and oral aphthae, and the juice a "refrigerant" [4] and "blood tonic" [5]. Authors from India [6], Tunisia [7], and

Guatemala [8], reported that the 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 [9] but also conception [10-12]. In Unani medicine, a Middle Eastern traditional medical system that later took root in India [13] pomegranate flowers serve as a remedy for diabetes mellitus [14]. Modern uses of pomegranate derived products now include treatment of acquired immune deficiency syndrome(AIDS) [15] in addition to use for cosmetic beautification[16-17] and enhancement [18], hormone replacement therapy [19], resolution of allergic symptoms [20], cardiovascular protection [21-22], oral hygiene [23], ophthalmic ointment [24], weight loss soap [25], and as an adjunct therapy to increase bioavailability of radioactive dyes during diagnostic imaging [26-27].

The current explosion of interest in pomegranate as a medicinal and nutritional product is evidenced by a MedLine search from 2000 to present, revealing over 150 new scientific papers pertaining to its health effects. Between 1950 and 1999 only 25 such publications appear on MedLine. Over the past few decades scientific investigations have laid a credible basis for some of the traditional ethnomedical uses of the pomegranate [28]. These studies, most completed in the past 7 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. The other potential therapeutic properties of pomegranate are wide-ranging and include treatment and prevention cardiovascular disease, diabetes, dental conditions, erectile dysfunction, protection from ultraviolet (UV) radiation, infant brain ischemia, Alzheimer's disease, male infertility, arthritis, obesity, etc.

Chemical Constituents

A compilation of the major chemical constituents from pomegranate juice, seed and peel found from various reports in literature are in this review article, along with chemical structures for selected compounds. Some of the listed chemical compounds from each individual part were obtained from the other parts of Pomegranate in varying degree of occurrence.

Compounds isolated from pomegranate juice: Juice was reported to be comprised of 85.4% water, 10.6% total sugars, 1.4% pectin, 0.2-1.0% polyphenols. Other reported minor compounds include fatty acids, amino and organic acids, indoleamines, sterols, triterpenoids and α tocopherol. Anthocyanins, potent antioxidant flavonoids, provide pomegranate juice with its brilliant color, which increases in intensity during ripening [29], and declines after pressing [30-31]. 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 [32].

The diverse classes of chemical constituents reported from Pomegranate Juice include:

Sugars: Glucose, Fructose, Sucrose (Figure 1).

Organic Acids: Citric acid, Malic acid, Tartaric acid, Fumaric acid, Succinic acid, Ascorbic acid (Figure 2)

Cyclitol carboxylic/Hydroxybenzoic acids: Quinic acid, Gallic acid, Ellagic acid (Figure 3)

Hydroxycinnamic acids: Caffeic acid, Chlorogenic acid, *p*-Coumaric acid (Figure 4)

Flavan-3-ols/Flavonoids and their glycosides: Catechin, Epicatechin, Epigallocatechin-3-gallate, Quercetin, Rutin (Figure 5)

Anthocyanins: Cyanidin-3-O-glucoside, Cyanidine-3,5-di-O-glucoside, Delphinidin-3-O-glucoside, Delphinidin-3,5-di-O-glucoside, Pelargonidin-3-O-glucoside, Pelargonidin-3,5-di-O-glucoside (Figure 6).

Amino acids: Proline, Valine, Methionine, Glutamic and Aspartic Acid (Figure 7).

Indoleamines: Tryptamine, Serotonin, Melatonin (Figure 8).

Tocopherols: α-tocopherol (Figure 9).

Ellagitannins: Punicallin, Punicalagin, Corilagin, Casuarinin, Gallagyldilacton

Compounds isolated from pomegranate seeds: Pomegranate seed oil comprises 12–20% of total seed weight. The oil consists of approximately 80% conjugate doctadecatrienoic fatty acids, with a high content of cis 9, trans 11, cis 13 acid (i.e. punicic acid), synthesized in situ from nonconjugated octadecadienoic fatty acid, linoleic acid [33-34], itself about 7% of Pomegranate seed oil. The fatty acid component of Pomegranate seed oil comprises over 95% of the oil, of which 99% is triacylglycerols. Minor components of the oil include sterols, steroids, tocopherols, and a key component of mammalian myelin sheaths, cerebroside [35]. Seed matrix includes lignins [36], fusion products of cell wall components and hydroxybenzoic/cinnamic acids, isoflavones, and potently antioxidant lignin derivatives [37].

The major chemical components identified from Pomegranate Seeds are:

Hydroxybenzoic acids: Ellagic acid, 3,3'-Di-O-methylellagic acid, 3,3'.4'-Tri-O-methylellagic acid

Conjugated fatty acids: Punicic acid (cis-9, trans-11, cis-13 octadecatrienoic acid) (Figure 10).

Non-Conjugated fatty acids: Linoleic acid, Oleic acid, Palmitic acid, Stearic acid (Figure 10).

Sterols: Stigmasterol, β-Sitosterol, Daucosterol, Camesterol, Cholesterol, 17-α-Estradiol, Estrone, Testosterone, Estriol (Figure 11).

Tocopherols: γ-tocopherol (Figure 9).

Triterpenes: Ursolic acid, Oleanolic acid (Figure 12).

Isoflavones: Genistein, Daidzein (Figure 13).

Phenyl aliphatic glycosides/Lignins: Coniferyl-9-O-[β-D-apiofuranosyl(1→6)-O-β-D-glucopyranoside, Sinapyl-9-O-[β-D-apiofuranosyl(1→6)-O-β-D-glucopyranoside, Phenylethyl rutinoside, Icariside D1

Compounds isolated from pomegranate peel

Both flavonoids and tannins are more abundant in the peels of wild-crafted compared to cultivated fruits [38]. Complex polysaccharides from the peels have been studied and partially characterized [39]. The presence of alkaloids (e.g., pelletierine) in the peel is equivocal, positive by Dragendorff assay, but negative by Mayer assay [40].

The main chemical constituents isolated from Pomegranate Skin/Pericarp/Peel are:
Hydroxybenzoic acids: Gallic acid, Ellagic acid (Figure 3).
Hydroxycinnamic acids: Caffeic acid, Chlorogenic acid, p-Coumaric acid
Cyclitol carboxylic acids: Qunic acid (Figure 3).
Flavon-3-ols/Flavonoids and their glycosides: Catechin, Epicatechin, Epigallocatechin-3-gallate, Quercetin, Kaempferol, Luteolin, Rutin, Kaempferol-3-O-glycoside, Kaempferol-3-O-rhamnoglycoside, Naringin (Figure 14).
Anthocyanins: Cyanidin, Pelarginidin, Delphinidin (Figure 6).
Ellagitannins: Punicallin, Punicalagin, Corilagin, Casuarinin, Gallagyldilacton, Pedunculagin, Tellimagrandin, Granatin A, Granatin B.
Alkaloids: Pelleteriene (Figure 15).

Biological Activity of the Chemical Constituents from Pomegranate

While detailed knowledge of relationships of the chemical contents of pomegranates and their pharmacologic endpoints has yet to be obtained, a very significant progress has been made over the past 10 years toward a much more comprehensive understanding of some of the important pharmacologic components of pomegranate. Pomegranate, juice, seeds and peels are a source of many nutrients but the pomegranate whole fruit can also be used for various medicinal purposes. The sweet types of pomegranates are said to be mildly laxative, while the less sweet types are believed to be good in inflammation of stomach and in heart pain. The fruit's medical significance dates back to ancient times and is even noted in Egyptian mythology and art [41]. Extracts of the juice, bark, leaves, immature fruit, and fruit rinds have all been noted to have some medical significance, most notably antioxidant activity, antibacterial properties, uses in diabetes, heart disease and cancer. Although pomegranate's wide-ranging therapeutic benefits may be attributable to several mechanisms, most research has focused on its antioxidant, anticarcinogenic, antibacterial/antimicrobial and anti-inflammatory properties.

Antioxidant activity

The primary bioactive constituents of pomegranate juice are the polyphenols and their potent antioxidant characteristics were described in detail by Aviram, et.al [42]. Punicalagin is a major antioxidant polyphenol from pomegranate juice [43] and is widely reported for its potential activity. Antioxidant activities were tested *in vitro* with pomegranate juice, punicalagin, ellagic acid and total pomegranate tannin (polyphenol extracts from whole pomegranate juice). Results of several experiments identified that whole pomegranate juice is having more antioxidant activity than any of its individual constituents. The superiority of pomegranate juice compared to its individual polyphenols provides evidence of the synergy of multiple compounds in comparison to its individual polyphenols. Borges et al [44] compared the antioxidant activity of thirty six common European fruit juices to ascertain their antioxidant capacity and polyphenolic composition. Three of the "pure" pomegranate juices had the highest ellagitannin content and reported to have the highest antioxidant capacity. Statistical analysis of both the antioxidant assay and the HPLC online antioxidant data demonstrated that the ellagitannins were the major antioxidants in the pomegranate juices. Recently, Liu et al [45] reported the presence of 33 flavonoids that have been detected from pomegranate fruit juice, pericarp and foliage, which are widely used in the health food and medicinal industries. They summarize the recent progress in the constitution, content, detection methods and pharmacological studies of flavonoids in the fruit, leaf and petal of *P. granatum*. Fazeli et al [46] reported in their study that the antioxidant capacities of probioticated and nonprobioticated aril juices of sweet (SWV) and sour (SV) pomegranate cultivars were determined by ferric reducing antioxidant power (FRAP) and 1,1-di-phenyl 2-picrylhydrazyl assay. Experimental results indicated that the total counts of *Lactobacillus casei* GG increased by about 3 log in SWV and 2 log in SV juices after incubation for 48 h. Probiotication improved the antioxidant activity of SWV juice from 74.4% to 91.82% and SV juice from 82.64% to 97.8%. Also it was found that the reducing power of the probioticated pomegranate juices was also much stronger than the nonprobioticated juices. Gil et al [47] reported that pomegranate juice possessed a 3-fold higher antioxidant activity than that of red wine or green tea and 2-, 6-, and 8-fold higher levels than those detected in grape/cranberry, grapefruit, and orange juices, respectively. The determination of the antioxidant capacity of pomegranate components and their derivatives is being given greater importance by researchers and those involved in the agro-food industry for use as natural additives to replace synthetic antioxidants, whose use is increasingly restricted due to the secondary effects they may produce. The antioxidant activity of pomegranate components has been the subject to many studies [48], most conducted *in vitro* and *in vivo*. All these activities may be related to the diverse phenolic compounds present in pomegranate, including the isomers of punicalagin, tannin derivatives, and anthocyanins (delphinidin, cyanidin and pelargonidin 3- glucosides and 3,5-diglucosides). These compounds are known for their properties to scavenge free radicals and to inhibit lipid oxidation in vitro [47]. However, Tzulker et al [49] suggested that punicalagin originating from the peels is one of the major phytochemicals contributing to the total antioxidant capacity of pomegranate juice, whilst anthocyanins play only a minor role in this activity. The effect of variety of pomegranate cultivars from Iran, Georgia, Turkey and Israeli on antioxidant activity also target of study of some authors [50-52]. All authors reported considerable variation in some of the chemical composition profile (lipids, phenols, organic acids, vitamins, sugars) and antioxidant properties of pomegranate samples, independent on the antioxidant method performed. Borochov-Neori et al. [50] also described the importance of harvesting season on the phenolic content as well as on the antioxidant activity. Different samples of pomegranates harvested in

different orchards presented drastic differences in the content of anthocyanins and total phenols as well. The antioxidant activity measured by two methods (BPPH and ABTS) was better correlated with the total phenolic compounds present in the samples than with the content of anthocyanins. Such results revealed that other phenolic compounds may be responsible for the important antioxidant activity of pomegranate samples that differed significantly from orchard to orchard [53].

To study the antioxidant effects of extracts from the peel, leaf, seed and flower (petal, stamen and receptacle) of pomegranate, their ethanolic extracts were added to soybean oil determining the peroxide value (POV) and malondialdehyde (MDA) with the schall heating oven method; the ability of scavenging free-radicals was measured by 1,1-diphenyl-2-picrylhydrazyl free-radical (DPPH) elimination method. Experimental results indicated that the peel was the strongest one, and the petal, the stamen and the receptacle were of about a same level, but the leaf was weaker than them. The polyphenol content was significantly correlative to the antioxidant effect and antibacterial activity, which indicated that polyphenols were the main active compounds of pomegranate [54]. The *in vitro* antioxidant activities of the whole fruits and leaves of pomegranate was studied by Zhang et al [55], which presented the radical scavenging activities of water soluble extracts of leaves, fruit peel, seeds and juice of pomegranate were measured by the 1, 1-diphenyl-2-picrylhydrazyl (DPPH) and 2, 2'-azinobis 3-ethyl-benzothiazoline-6-Sulfonate (ABTS) methods. In both methods, both leaf and peel exhibited very strong antioxidant activity and high polyphenol content when compared to seeds and juice and they had the same IC_{50} values of 0.14 mg/mL in the DPPH method, juice of pomegranate had higher radical scavenging activity than seeds but lower polyphenol content. The antioxidative capacities among three juices of pomegranate, apple and orange were also compared by the authors. The pomegranate juice is obviously higher than the apple juice and the orange juice in two kinds of free radical elimination activity, and apple juice showed the lowest in both DPPH and ABTS radical scavenging activities.

Antimicrobial/antibacterial activity

The antibacterial and antimicrobial properties of *P. granatum* have been studied extensively by various scientists all over the World. Extracts from the plant have been found to work against methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant (MRSA) *Staphylococcus aureus*, *Escherichia coli* O157:H7, *Salmonella typhi*, and some *streptococci* strains [56-61]. Thus, alternative medications that incorporate *P. granatum* have potential usefulness against bacterial infections. An important potential application for the anti-microbial properties of *P. granatum* is in its use as a topical microbicide for HIV prevention. *In vitro* research indicates that an anti-HIV1 microbicide could potentially be made from *P. granatum* [58]. The antibacterial and antimicrobial attributes of *P. granatum* may have applicability to the dental field. *P. granatum* phytotherapeuticals was tested against the streptococci strains *Staphylococcus mutans*, *Streptococcus mitis* and *Candida albicans*. It was effective against the isolated bacteria species, and when tested against an assembly of different microorganisms, the *P. granatum* phytotherapeutic gel had greater efficiency in inhibiting microbial adherence to glass than the miconazole (Daktarin oral gel). This suggests that this phytotherapeutic agent might be used to control the adherence of different microorganisms in the oral cavity [60]. The hydroalcoholic extract from *P. granatum* was found to be very effective against dental plaque microorganisms in an *in vivo* study, decreasing the number of colony forming units per milliliter by 84% versus the control group's 11% decrease (distilled water), which indicates that this may be a possible alternative for the treatment of dental plaque bacteria [62]. It was reported that both fermented and nonfermented pomegranate juices exhibited a potent and wide-spectrum antibacterial effect, with the highest activity against *Pseudomonas aeruginosa* [46]. Work focused on the kinetic evaluation of physicochemical changes during the fungal fermentation of the peel portion of the tannin rich plant materials like *P. granatum* has been reported which indicated a major decrease in the chemical composition of reducing sugars (about 88%) after 96 hours cultivation [63]. Su et al [64] reported that a combination of pomegranate juice and pomegranate polyphenols appear to be promising natural remedies for preventing or reducing human norovirus infections. They also reported that these polyphenols are effective against food-borne viral infectivity. In the absence of culturable human noroviruses, feline calicivirus (FCV/F9), murine norovirus (MNV/1), and MS2 (ssRNA) bacteriophage were used as foodborne viral surrogates. Such a combination was capable of causing reduction of foodborne viral surrogates FCV-F9, MNV-1 and MS2. Endo et al [65] suggested that punicalagin isolated from pomegranate peels possessed strong activity against *Candida albicans* and *Candida parapsilosis* as well as the combination of punicalagin and fluconazole showed a synergistic interaction in a very effective way. Haidari et al., 2009 [66] reported that the punicalagin present in the pomegranate extract had virucidal capability and inhibited influenza virus RNA proliferation independent on the virucidal effect. It was also reported that pomegranate purified polyphenol extract inhibited influenza virus which causes epidemics and pandemics in human population. Bialonska et al., 2009 [67] reported that the commercial extract of pomegranate byproduct provided by POM Wonderful (Los Angeles, CA) and punicalagins inhibited the growth of pathogenic clostridia and *Staphylococcus aureus*. Duman et al [68] indicated the importance of the physicochemical properties of pomegranate on the antimicrobial activity was related to their phenolic and anthocyanin content of fruits.

Kannat et al [69] reported that the pomegranate peel extract (PE) showed excellent antioxidant activity while the seed extract (PS) did not have any significant activity. The IC_{50} value of PE for 2,2-diphenyl-1-picrylhydrazyl radical scavenging was 4.9 µg/ mL while that of butylated hydroxy toluene was 21.2 µg/ mL, indicating that it was a stronger antioxidant. PE showed good antimicrobial activity against *Staphylococcus aureus* and *Bacillus cereus* having minimum inhibitory concentration of 0.01%. They also reported that addition of PE to popular chicken meat products enhanced its shelf life by 2-3 week during storage at chilled conditions. PE was also effective in controlling oxidative rancidity in these chicken products. Machado et al [52] reported that the ethyl acetate extract of *P. granatum* fruits which afforded the

ellagitannin punicalagin was found to be active against methicillin-resistant *Staphylococcus aureus* strains. An *in vivo* study was done to test the effects of the combined extracts from *Centella asiatica*, commonly known as Asiatic Pennywort, and *P. granatum* on periodontal healing following scaling and root planning in adult periodontitis patients. The results indicated that the local delivery with *C. asiatica* and *P. granatum* extracts, plus scaling and root planning, significantly reduced the clinical signs of chronic periodontitis [70]. Sagdic et al [71] reported that the ethanol extract was more effective as an antimicrobial agent than other solvent extracts of pomegranate seed samples. In their study, pomegranate seeds were extracted by methanol, ethanol and water were tested for antioxidant and antiradical potential and antimicrobial activities against total fifteen microorganisms including thirteen bacteria and two yeasts. The highest phenolic content was found in the methanol extracts and the lowest in aqueous extracts of pomegranate seeds and hulls. The values of IC_{50} in methanol extracts of the pomegranate seeds and hulls were founded as 39.40 and 7.02, respectively. Their results further indicated that the potential use of the extracts of the pomegranate seeds and hulls which are waste of pomegranate juice industry as an alternative to food preservative agents due to antioxidant and antimicrobial activities.

Anti-inflammatory and Anti-cancer activity

Various parts of the pomegranate plant have been shown to exert antiproliferative effects on a number of tumor cells [72]. The polyphenols from the fermented juice of pomegranate have shown their anticancer effects on human breast cells *in vitro*. Mehta et al [73] indicated that the pomegranate seed oil is more active compared to the polyphenols from juice. Amin et al [74] reported in their review article that pomegranate fruit, pomegranate juice, pomegranate seed and seed oil act in prostate, breast, skin, colon, lung, oral and leukaemia cancers, through antioxidant, antiproliferation (growth inhibition, cell cycle disruption and apoptosis), antiangiogenisis and anti-inflammatory mechanisms of action. Ellagic acid, one of the constituents of pomegranate juice and seed oils are reported as acting against cancer of skin, pancreas, breast, prostate, colon, intestine, oesophagus, bladder, oral, leukaemia, liver and neuroblastoma, the mechanisms of action are similar to those described for pomegranate. Ellagic acid acts synergistically with cisplatin, vinorelbine, quercetin, resveratrol, cyclosporine A, 6-gingerol and selenomethionine. The same authors gave information about ongoing clinical trials with natural compounds, including pomegranate, in several parts of the World. Sturgeon et al [75] described the *in vitro* cell culture studies, animal studies and provided the available data about the property of pomegranate and its constituents to prevent breast cancer and the possible mechanisms involved. Lee et al [76] demonstrated that the usage of pomegranate extracts for inhibiting NO production by RAW 264.7 macrophage cells. In addition, it was also found that pomegranate significantly decreased carrageenan induced mice paw oedema for several hours (5 h at the maximum). Further, the authors separated punicalagin, punicalin, strictinin A, and granatin B using a column chromatography combined with in vitro bioassay-guided fractionation found that these compounds were able to inhibit NO production as well as iNOS expression in RAW 264.7 cells. Granatin B showed the strongest iNOS and COX-2 inhibitory effects, and exhibited these effects in the inhibition of paw swelling and PGE2 level in carrageenan-induced mice. Based on these results, it was proposed that granatin B could be used as a standard marker for the anti-inflammatory effect of pomegranate. Rasheed et al [77] reported the effect of polyphenol rich pomegranate fruit extract on the activation of mitogen-activated protein kinases (MAPKs) and the NFkB in PMACl stimulated KU8I2 cells. From their results, it was found that the polyphenol-rich pomegranate fruit extract decreased PMACl stimulated inflammatory gene expression and production of IL-6 and IL-8 in KU8I2 cells. The inhibitory effect of the extract on the pro-inflammatory cytokines was MAPK subgroups c-junction N-terminal kinase (JNK- and extracellular-regulated kinase (ERK) dependent. The crude extract also inhibited NF-kB by inhibiting IkB-degradation in human basophil cells. Based on their results obtained, the authors suggested that polyphenol-rich pomegranate fruit extract exerts its inhibitory effect on IL-6 and IL-8 expression via modulation of the activation and DNA binding activity of NF-kB.

Albrecht et al [78] studied the effects of pomegranate oil, seed oil, fermented juice polyphenols and pericarp polyphenols on human prostate cancer cell growth in vivo and found that it demonstrated significant antitumor activity against human prostate cancer. Lansky et al [79] reported that utilizing pomegranate fruit extract the cell growth was inhibited and followed by apoptosis of extremely aggressive human prostate carcinoma PC-3 cells. Several animal studies have elucidated pomegranate's potential anticancer mechanisms. Two studies in mice implanted with the prostate cancer PC-3 cell line demonstrated pomegranate fruit extract (PFE; edible parts of the fruit, excluding the peel) inhibits cell growth and induces apoptosis via modulation of proteins regulating apoptosis [80]. These studies provide evidence suggesting that consuming pomegranate may delay prostate cancer progression [80]. Also, fermented pomegranate juice polyphenols were tested in combination with pericarp polyphenols on the proliferation of DU 145 human prostate cancer cell lines *in vitro*. Toi et al [81] has found that pomegranate seed oil and fermented juice polyphenols tend to inhibit breast cancer cell proliferation, invasion, and promotes apoptosis of breast cancer cells. Kim et al [74] reports that fermented pomegranate juice polyphenols consistently showed twice the anti-proliferative effect as fresh pomegranate juice polyphenols. Research on lung cancer looked at the effect of pomegranate fruit extract as a source of treatment [82]. The results suggested that pomegranate fruit extract can be a chemo preventative agent against lung cancer. Flavonoid-rich polyphenols can be extracted from fresh and fermented juice.

These polyphenols were tested for their ability to induce differentiation in human HL-60 promyelocytic leukemia cells. Extracts from the fermented juice and pericarps promoted differentiation the best when compared to fresh juice and had similar inhibitory effects on proliferation of the cell line [83]. Pomegranate tannin extract and punicalagin were found to suppress the COX-2 protein expression and inhibited phosphorylation and binding of the p65 subunit in HT-29

colon cancer cells indicating that these chemicals could play a major role in modifying the inflammatory cell signaling in colon cancer cells [84].

Clinical research into the effects of the antioxidant polyphenol-rich pomegranate juice on chronic obstructive pulmonary disease (COPD) found no differences between the control group and that receiving pomegranate juice. The conclusion of this study was that pomegranate juice supplementation (400ml pomegranate juice daily) added no benefit to the current therapy standards in patients with COPD [85].

The selected chemical constituents isolated from juice, peel, and seeds that have been found to have anti-inflammatory/anti-cancer properties and their activity results from the reported literature of Lansky et al [86] and many other authors [87-128] were shown in Table 1.

Other biological activities

Research findings indicated that apart from the potential benefits for antioxidant, anti-inflammatory, anticancer, etc., pomegranate may confer a multitude of other health promoting effects in the body. However, more conclusive studies are needed to confirm these effects, because, there are very few references present in the scientific literature to substantiate these findings.

Pomegranate fruit extract, has been found to be a source of a protection for skin. A study by Syed et al [129] suggests that pomegranate fruit extract (PFE) is effective for ameliorating UVA-mediated damages by modulating cellular pathways and preventing potential skin cancers. Studies have been performed to see if pomegranate can treat or prevent diabetes and heart disease. Esmaillzadeh et al [130] found that pomegranate juice significantly reduced total cholesterol, low-density lipoproteins (LDL), the ratio of LDL/ high-density lipoproteins (HDL), and the ratio of total cholesterol to HDL. These findings show that consumption of pomegranate juice may modify heart disease risk factors in patients with hyperlipidemia. Sumner et al [131] tested the effects of pomegranate juice in its efforts to help patients with coronary heart disease concluded that daily consumption of pomegranate juice may improve stress-induced myocardial ischemia in patients who have coronary heart disease (CHD). When ingested, pomegranate juice could help patients with carotid artery stenosis, decrease carotid intima-media thickness, and their systolic blood pressure [132]. A small clinical trial demonstrated PJ inhibits serum ACE and reduces systolic blood pressure in hypertensive patients. Ten hypertensive subjects (seven men and three women, ages 62-77) were administered 50 mL/ day pomegranate juice containing 1.5 mmol total polyphenols for about two weeks. Results indicated that two of seven patients were also diabetic and two were hyperlipidemic. About 70% experienced a 36-percent average decrease in serum ACE activity and a small, but significant, five-percent decrease in systolic blood pressure. Consuming PJ for three months did not significantly affect triglyceride, HDL cholesterol, HbA1C, glucose, or insulin values, but did lower serum C-peptide values by 23 percent compared to baseline in diabetic patients, a sign of improved insulin sensitivity. Consumption of PJ significantly reduced oxidative stress in the diabetic patients was evident by a 56-percent reduction in lipid peroxides and a 28-percent reduction in TBARS compared to baseline serum levels. In addition, a 39-percent decrease in uptake of oxidized LDL by human monocyte-derived macrophages (an early development in foam cell formation and atherogenesis) was observed in diabetic patients after PJ consumption [28].

Researchers confirmed that despite the sugars naturally present in pomegranate juice, consumption did not adversely affect diabetic parameters but had a significant effect on atherogenesis via reduced oxidative stress [133]. The neuroprotective properties of pomegranate polyphenols were evaluated in an animal model of Alzheimer's disease. Transgenic mice with Alzheimer's like pathology treated with PJ had 50-percent less accumulation of soluble amyloid-beta and less hippocampal amyloid deposition than mice consuming sugar water, suggesting PJ may be neuroprotective. Animals also exhibited improved learning of water maze tasks and swam faster than control animals [134]. Research in rats demonstrates that pomegranate juice consumption improves epididymal sperm concentration, spermatogenic cell density, diameter of seminiferous tubules, and sperm motility, and decreases the number of abnormal sperm compared to control animals. An improvement in antioxidant enzyme activity in both rat plasma and sperm was also noted [135]. A recent well-controlled trial of pomegranate juice for the treatment of mild-to-moderate erectile dysfunction in men was made by Forest et al [136]. Pomegranate juice's therapeutic effect on erectile dysfunction (ED) was studied in a randomized, double-blind, placebo-controlled, 10-week crossover trial in 53 men. All the subjects with other medical conditions that might contribute to ED were excluded and subjects were asked to refrain from taking ED medication for the duration of the study. The trial consisted of two four-week treatment periods separated by a two-week washout. First four weeks each subject was given pomegranate juice containing 1.5 mmol polyphenols daily or placebo beverage, followed by washout and crossover to the other group. Results indicated a trend toward improvements in ED, but statistical significance was not achieved. Pillai [137] investigated the antidiarrheal activity of aqueous and alcohol extracts of the pomegranate fruit rind in 3 experimental models using albino rats. The extracts exhibited significant activity in rats when compared to loperamide hydrochloride, a standard antidiarrheal drug. Cerd´a et al [138] investigated the effects of pomegranate extract (6% punicalagin) in female rats following exposure to a diet containing 20% of the extract for 37 d. The exposure to pomegranate extract resulted in an intake of 4800 mg punicalagin/kg/d. A significant decrease in feed consumption and body weight of the animals during the early part of the study was noted. Kaur et al [139] evaluated antioxidant and hepatoprotective activity of pomegranate flowers. The efficacy of extract was tested *in vivo* and it was found to exhibit a potent protective activity in acute oxidative tissue injury animal model: ferric nitrilotriacetate (Fe-NTA) induced hepatotoxicity in mice. These results indicate pomegranate flowers to possess potent antioxidant and hepatoprotective property, the former being probably responsible for the latter

Toxicology Studies of Pomegranate

For thousands of years, Pomegranate has been widely consumed in many different cultures, by considering this fruit is generally safe. Studies of pomegranate constituents in animals at concentrations and levels commonly used in folk and traditional medicine did not indicate any toxic effects. Squillaci et al [140] indicated that the consumption of the decoction made from the tree bark and to a lesser extent, pericarps of the fruit, may cause acute gastric inflammation and even death due to the presence of both tannins and alkaloids. Vidal et al [141] indicated that consumption of whole fruit extracts have been shown to cause congestion of internal organs and elevated creatinine *in vivo*. Pomegranate juice is known to inhibit intestinal cytochrome P450 3A4. During rosuvastatin treatment for myopathy, juice may increase the risk of rhabdomyolysis, the breakdown of muscle fibers resulting in the release of muscle fiber contents into the circulation [142]. Some of these are toxic to the kidney and frequently result in kidney damage. However, rosuvastatin is not known to be metabolized by hepatic P450 3A4 [143]. Some people are allergic to *Punica granatum*. Several adverse reactions to pomegranate, including severe symptoms such as anaphylactic shock or laryngeal edema, have been described in recent years. Patients with pomegranate allergy are often sensitized to other allergens. Pomegranate should be considered a potential allergen in patients suffering anaphylaxis in autumn and living in countries where this fruit is consumed [144]. Fatope et al [145] reported that pomegranate seed oil was not toxic to brine shrimp larvae, but was reported to have severe allergic reactions from eating the fruit [144, 146], and esophageal problems from chronic consumption of roughly ground pomegranate seeds [147-148]. Toxicity of the polyphenol antioxidant punicalagin, abundant in pomegranate juice, was evaluated in rats and experimental results indicated that no toxic effects or significant differences were observed in the treatment group compared to controls, which was confirmed via histopathological analysis of rat organs.

Conclusion

After extensive literature reports on the medicinal properties of pomegranate it is easy to understand why researchers, such as Robert Longtin [149], have referred to the pomegranate as "nature's power fruit". It is rich in antioxidants, has antibacterial properties, has been found useful in treating dental and dermatological conditions, and improves cardiovascular health apart from various other medical applications. These benefits along with its anticancer capabilities have compelled researchers to fully investigate the therapeutic uses of pomegranate.

Pomegranate is an ancient fruit with an illustrious medical history and has been the subject of classical reviews for over 100 years [150-151]. An explosion of interest in the numerous therapeutic properties of *P. granatum* over the last decade has led to numerous *in vitro*, animal, and clinical trials. Pomegranate is a potent antioxidant, superior to red wine and equal to or better than green tea. In addition, anticarcinogenic and anti-inflammatory properties suggest its possible use as a therapy or adjunct for prevention and treatment of several types of cancer and cardiovascular disease. Because of pomegranate's antimicrobial properties, it may aid in preventing infection by dental pathogens, pathogenic *E. coli* O157:H7, and antibiotic-resistant organisms such as MRSA. Pomegranate's effect on bacterial pathogens has only been tested *in vitro*, however, necessitating human trials to refute or substantiate any clinical effect. The possibility that pomegranate extracts may also have an effect on several other disease processes, such as Alzheimer's disease, osteoarthritis, neonatal brain injury, male infertility, and obesity, underscores the need for more clinical research. Currently, numerous clinical trials are in progress exploring the therapeutic potential of pomegranate extracts. 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 [152] and chemotherapy, largely deriving from the anti-inflammatory properties of both the aqueous and lipid phases, is in the earliest stages of being appreciated [149]. 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 so far 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 literature reported till date will provide some valuable clues for ongoing explorations of this most fascinating botanical species. A new medical monograph on the subject of *P. granatum* [153], and also an editorial on the subject of pomegranate–pharmaceutical interactions [154] are published recently with more information. It is likely that much more will follow, as the medical community and public continue to exhibit renewed interest in the pomegranate as a therapeutic source.

Based on the literature precedence, most of the important research about Pomegranate and its biological activity have been performed during the past decade. It may be worth looking deep into chemical constituents of different parts of Pomegranate and their activity profiles either individually or in combination.

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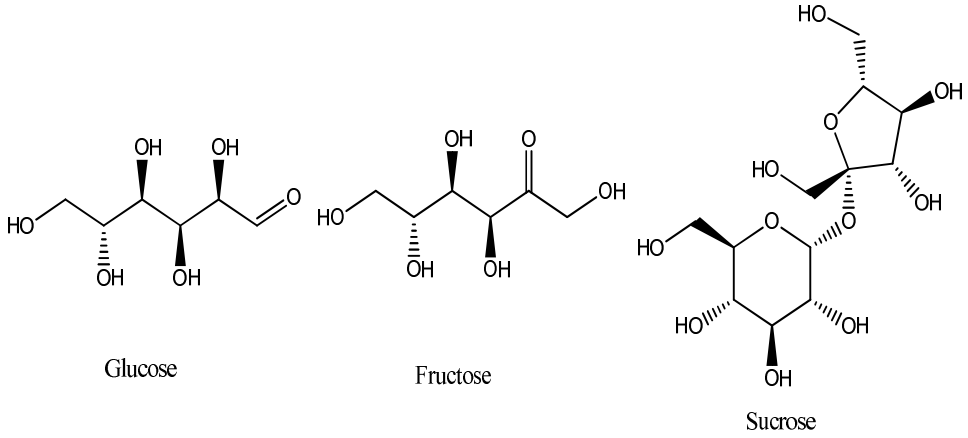


Figure 1: Sugars from Pomegranate juice

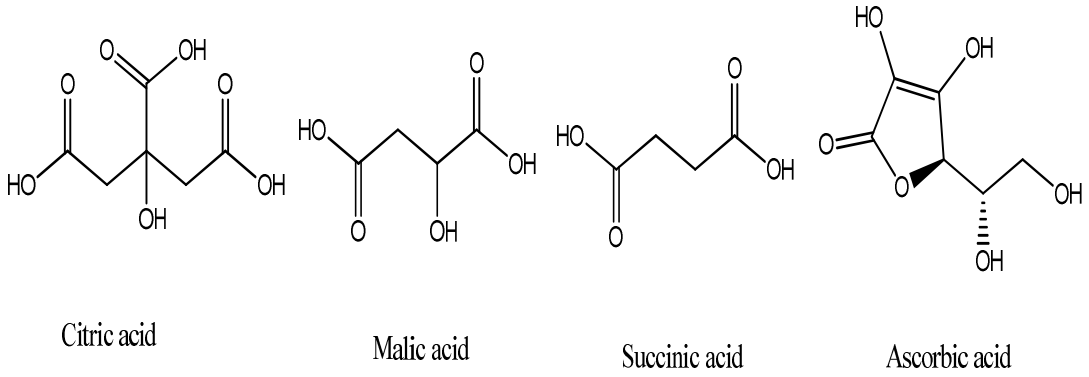


Figure 2: Organic acids from Pomegranate juice

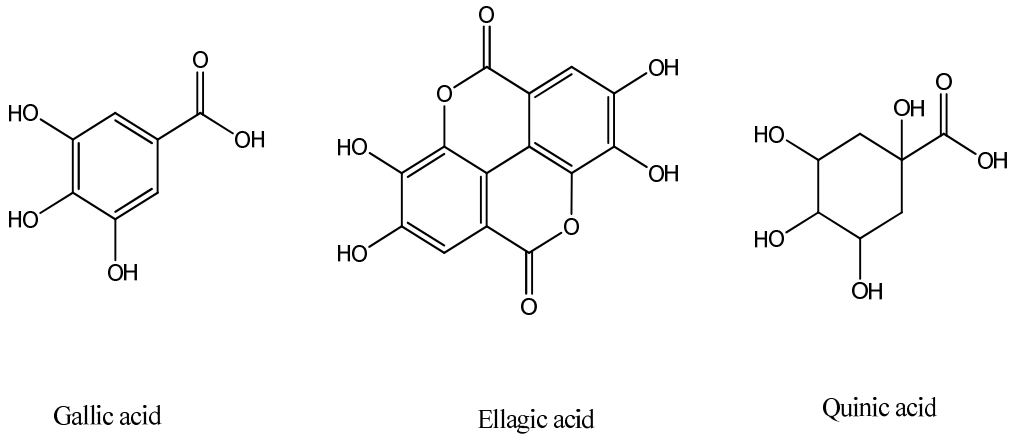


Figure 3: Cyclitolcarboxylic/Hydroxybenzoic acids from Pomegranate juice

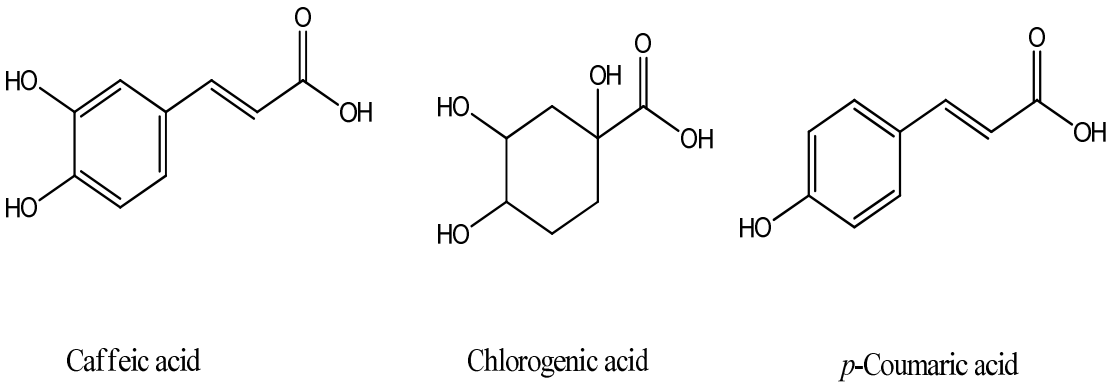


Figure 4: Hydroxycinnamic acids from Pomegranate juice

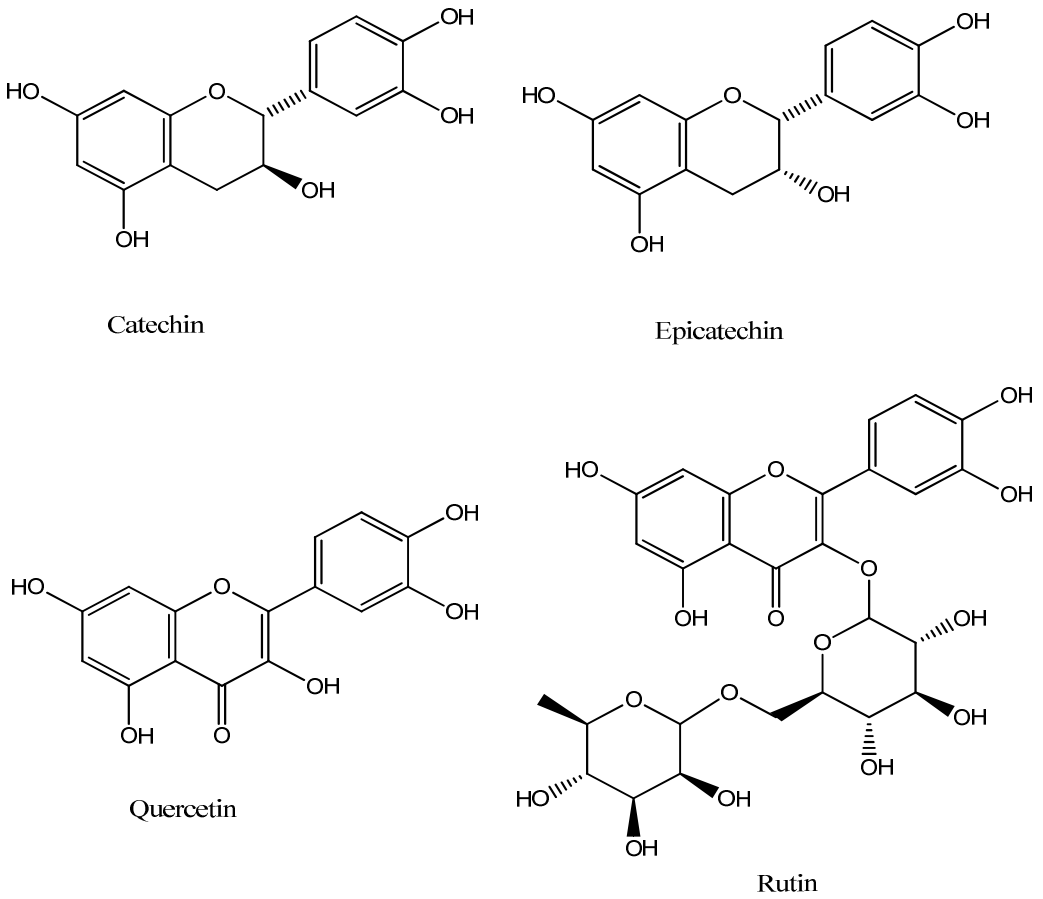


Figure 5: Flavan-3-ols/Flavonoids and their glycosidesfrom Pomegranate juice

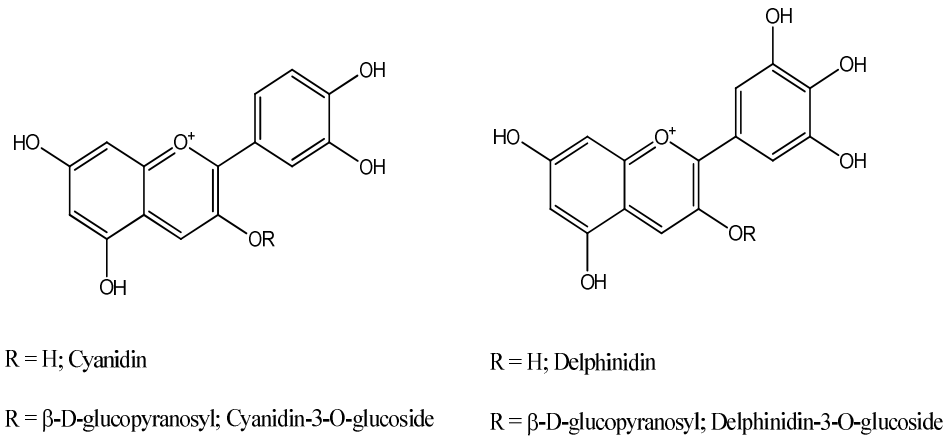


Figure 6: Anthocyaninsfrom Pomegranate juice and peel

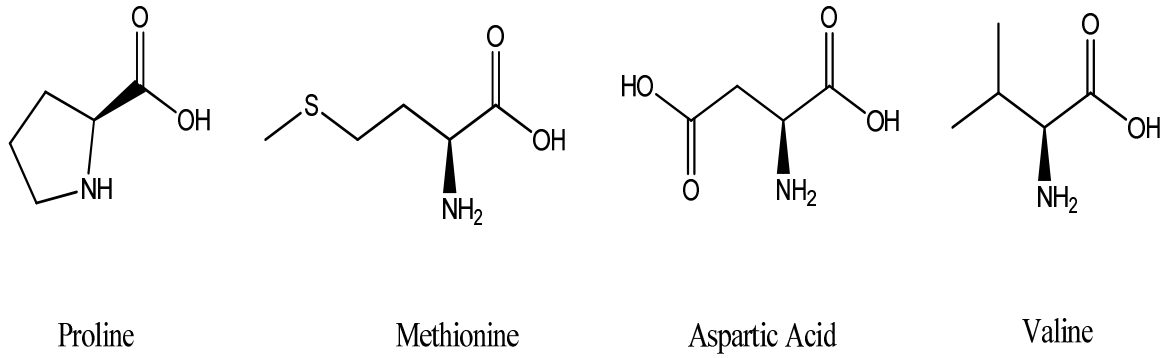


Figure 7: Amino acids from Pomegranate Juice

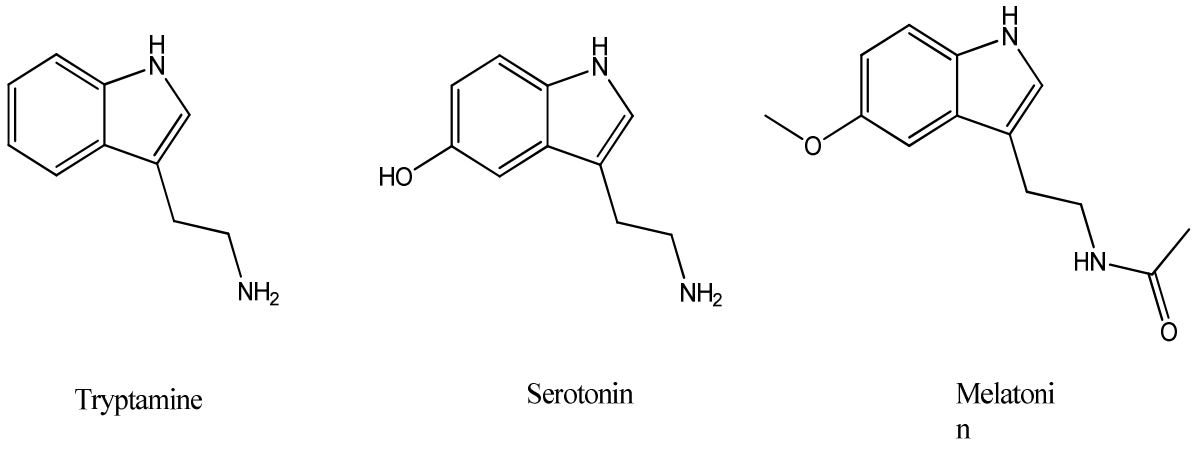
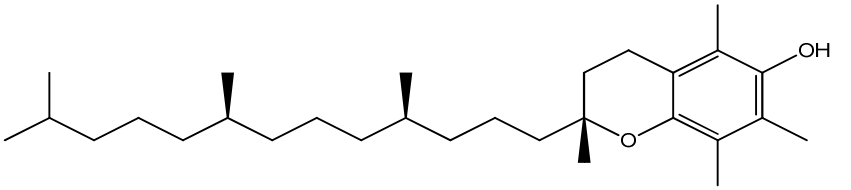
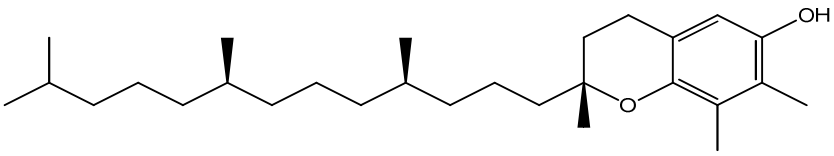


Figure 8: Indoleamines from Pomegranate juice

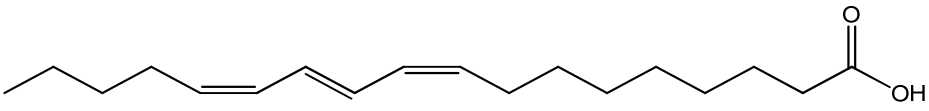


α-Tocopherol

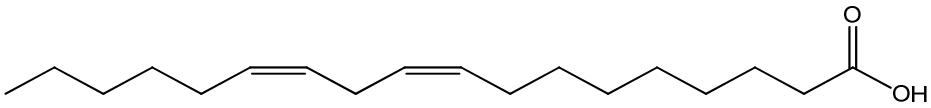


γ-Tocopherol

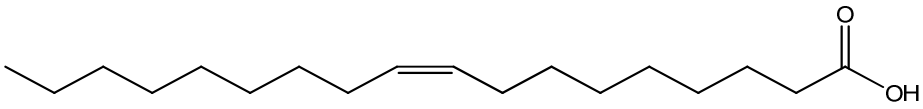
Figure 9: Tocopherols from Pomegranate juice and seeds



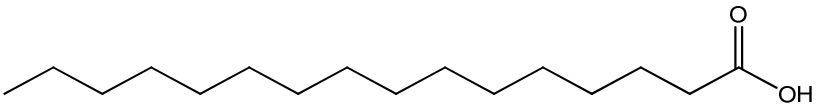
Punicic acid (cis-9, trans-11, cis-13 octadecatrienoic acid)



Linoleic acid

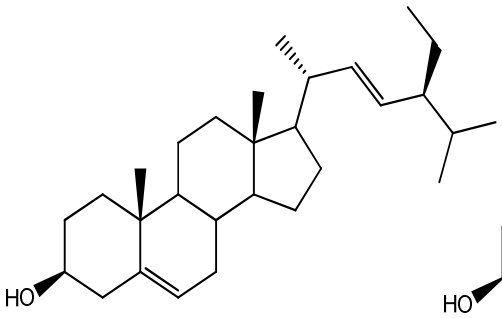


Oleic acid

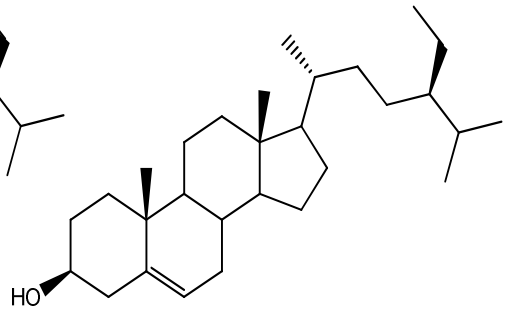


Palmitic acid

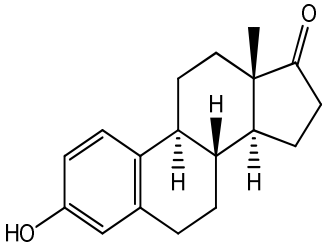
Figure 10: Conjugated and non-conjugated fatty acids from Pomegranate seeds



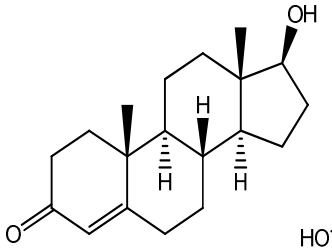
Stigmasterol



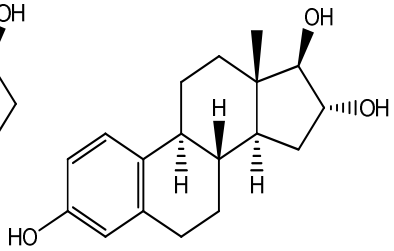
β-Sitosterol



Estrone

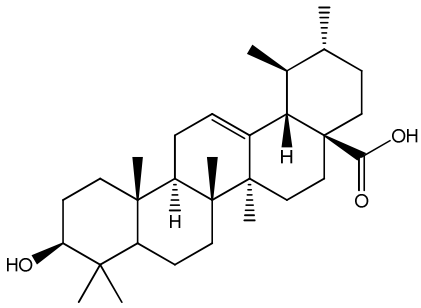


Testosterone

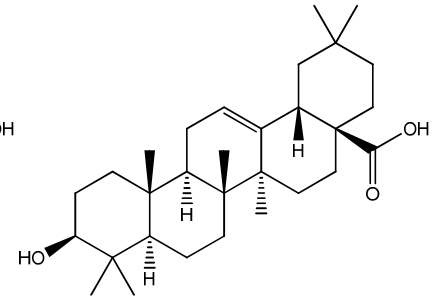


Estriol

Figure 11: Sterols from Pomegranate seeds

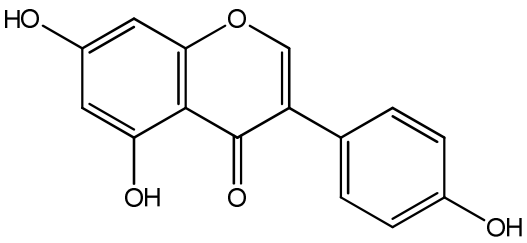


Ursolic acid

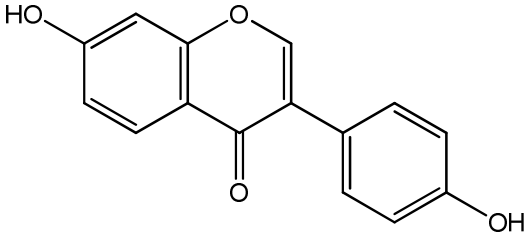


Oleanolic acid

Figure 12: Terpenesfrom Pomegranate seeds

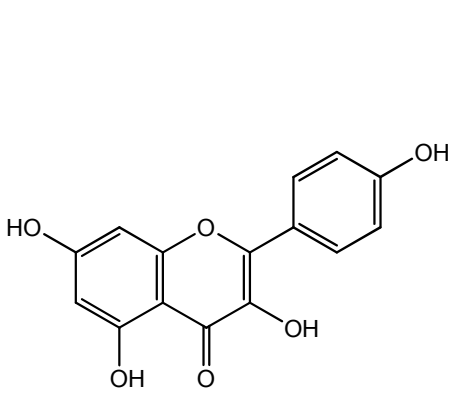


Genistein

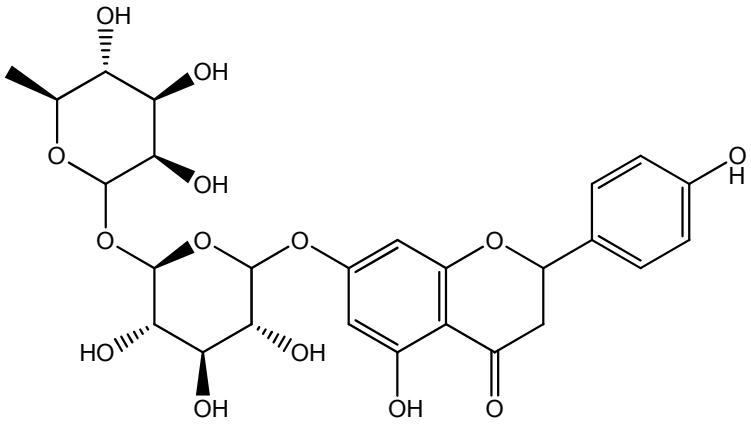


Daidzein

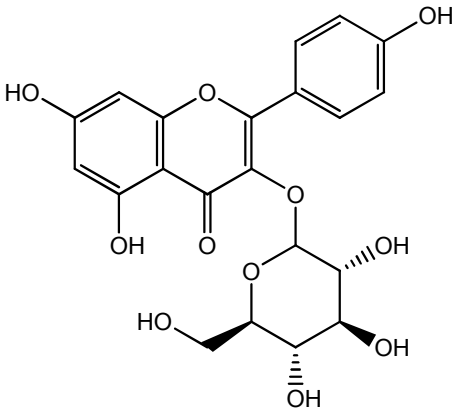
Figure 13: Isolflavonesfrom Pomegranate seeds



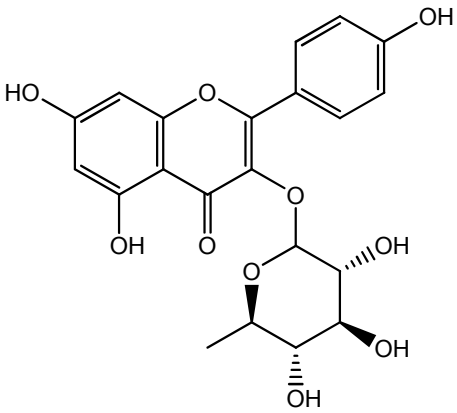
Kaempferol



Naringin

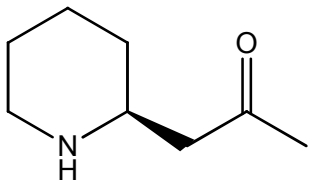


Kaempferol-3-O-glycoside



Kaempferol-3-O-rhamnoglycoside

Figure 14: Flavonoids and their glycosides from Pomegranate peels



Pelletierine

Figure 15: Alkaloids from Pomegranate peels