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Pomegranate an ancient seed for modern cure – A review of potential applications

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Abstract

Pomegranate (*Punica granatum*) is a delicious fruity shrub or a smaller tree that gains maximum height of about 5 to 8 m and usually harvested from March to May in Southern Hemisphere and September to February in Northern Hemisphere. The arils or juices of its fruit are used in wines, cocktails, alcoholic beverages, cooking food, meal garnishes, juice blends and baking industry. Pomegranate (*Punica granatum*) is found native to India and Iran but has also been evident to be adapted from Mediterranean regions along with tropical Africa, East Indies, India and some arid regions of Southeast Asia. The fruit of pomegranate (*Punica granatum*) is drought tolerant thus can be cultivated in relatively dry areas having minimum rainfall and maximum temperature. Some important chemical constituents of this plant include steroid hormone, 17β-estradiol (E2), pectin, sugars, ascorbic acid, citric acid, amino nitrogen, proteins, lipids and crude fibers along with some minerals such as sodium, magnesium, iron, zinc and copper. The essential oil of fruit peel of pomegranate (*Punica granatum*) is known to contain punicalin, punicalagins, ellagic acid, gallotannins and gallic acid. Some important fatty acids of different parts of pomegranate (*Punica granatum*) include lauric acid, myristic acid, palmitic acid, palmetoleic acid, stearic acid, oleic acid, linolenic acid and arachidic acid. Pomegranate (*Punica granatum*) is famous as medicinal plant owing to its excellent pharmacological applications because of anti-parasitic, anti-inflammatory, anti-oxidant, anti-microbial, anti-carcinogenic and anti-athrogenic effects.

Key words: Fruity shrub, 17β-estradiol (E2), citric acid, pectin, magnesium, anti-inflammatory, anti-carcinogenic effects

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1. Introduction

The botanical name of pomegranate is *Punica granatum*. It is a fruit-having deciduous shrub and small tree of lythraceae family that propagates between 5 to 8 m (16 and 26 ft) in length. The fruit is generally harvested in season from September to February in Northern Hemisphere and from March to May in the Southern Hemisphere. The genus "Punica" was the Roman name for "Carthage" where best pomegranates were known to grow. As intact juice or arils, pomegranates are helpful in baking, juice blends, meal garnishes, cooking and alcoholic beverages such as cocktails and wines [1]. The word pomegranate comes from Latin word "*pōmum*" means "apple" and "*grānātum*" means "seeded". It has great effect on the common name of pomegranate in various languages (e.g. *Granada* in Spanish, *Granatapfel* or *Grenadine* in German, *grenade* in French, *granatäpple* in Swedish, *pomogranà* in Venetian). *Mālum grānātus*, using the classical Latin word for apple, gives rise to the Italian name *melograno* or less commonly *melagrana*. Perhaps stemming from the old French word for the fruit, *pomme-grenade*, the pomegranate was known in early English as "Apple of Grenada", a term which today survives only in heraldic blazons. This is a folk etymology, confusing Latin *granatus* with the name of the Spanish city of Granada, which derives from Arabic language.

The pomegranate trees have various types of fruits having a rind of yellowish pink to a burgundy color spectrum. Different kinds of pomegranate have not only different outer hues but they also bear soft to hard arils. The choice of type of plant usually depends upon on the nature of use and final application. For instant, if you want to make juice of the fruit, either it is hard or soft it doesn't matter, but if you are going to eat it fresh, softer will be preferred. Although shrub is the natural habit of pomegranates, they also grow as small trees. Among the different types of pomegranate tree, there are many of them that mature earlier. Areas where there is long, hot dry summers they can grow probably any kind of fruit tree of pomegranate. The leaves of the pomegranate are glossy and as the tree become

older, the bark of the tree changed into gray. The flowers of the pomegranate are large, white, red or partly colored and bear a calyx that eventually changes into the fruit. The ripened fruit of pomegranate will be more than five inches in width with a red colored, leathery skin and grenade-shaped that is covered by pointed calyx.

In the area of modern Iran, pomegranate was believed to be cultivated by the ancient Persians. Now-a-days, the fruit of pomegranate that is grown in Iran and those countries that are around the Caucasus Mountains and Mediterranean Sea are yet among the finest. China is one of the biggest producers of pomegranate fruits. In Europe, pomegranate was produced in fifteen century when Islam was at its renaissance. The Spanish pioneers bring the fruit to other parts of the continents as Spanish ships sailed to the America [2]. The trees and fruits of pomegranate are usually called "red flowers" in the gardens and nurseries in Singapore. Pomegranate is important in various religious paintings by the like Leonardo da Vinci and Sandro Botticelli, often in the hands of infant Jesus or Virgin Mary. The breaking and brusting of fruit, is a symbol of the fullness of his sorrow and relieve. Actually, pomegranate was symbolized as a most wanted food and a symbol of beauty in the Bible. Prophet Mohammed is said to have admired pomegranate due to its spiritual and nutritional values and have asked his supporters to eat the fruit as a source of purifying their body of greed and hate.

2. History/Origin

The pomegranate is native to Himalayas in northern India to Iran but has been produced and adapted since earlier times around the whole Mediterranean region. Similarly it was also found in tropical Africa, India, the East Indies and more arid regions of Southeast Asia. The tree is also produced in the drier regions of California and Arizona for its fruit [3]. The word pomegranate originates from Medieval Latin word that means "seeded apple". It was named in different earlier texts from the Book of Exodus in the Torah, Homeric Hymns and Mesopotamian records, to name a few. The pomegranate actually comes from Persia or in modern age from Western Himalayas and Iran. It was produced for many times in countries such as Iran, Pakistan, Russia, Iraq, India, Afghanistan, and the Mediterranean region. It roamed from east as Southeast Asia and China and has been present around the Silk Road as a sign of richness and prosperous future. It was cultivated abundantly in Latin America, in Japan and Korea and it has been introduced there by pioneers or dealers. The history of the pomegranate contains the pillars of the Solomon's temple in Jerusalem, on the robes of Jewish priests and in mosaics from ancient Rome (including Pompeii) where it has been named as the "Phoenician Apple". Its branches have been worn on head dresses of Roman women's to indicate marital status. In temples of Zoroastrian, pomegranates indicate the sign of eternal life and were related with fertility. Pomegranates were extremely valuable in Ancient Egypt and are supplied as part of fruits required in a pharaoh's residence (1600 BC). It has been valuable enough to paint on tombs and walls as a sign of life after death. The pomegranate has various benefits, such as the fruit as food, the juice used as a stimulant to kill parasites, the blossom has been used to manufacture a red dye and the peel has been applied for dyeing leather.

3. Demography/Location

Fruits of pomegranates are drought-tolerant and can be cultivated in those areas that are dry and may have a Mediterranean winter or summer rainfall climates. In wet areas, they are vulnerable to root damage from diseases caused by fungus. They can bear temperate frost of about 12°C**.** Pomegranate can be grown for its fruit crop and also in parks and gardens as ornamental shrubs and trees. Pomegranate is produced in following countries: USA, Turkey, Tunisia, Italy, India, Iraq, Saudia Arabia and Israel [4]. Juice of pomegranate is better in taste due to its dietary components and nutritional value. Pomegranate juice is very appropriate method of taking the useful and healthy constituents that are found in its fruit. There are different amounts of juice, anti-oxidant contents and color of pomegranate produced by different cultivars. The factors that affect the quality aspects may differ and it depends upon the cultivars.

4. Botany, Morphology and Ecology

Pomegranate is a shrub that has bushy appearance and natural tendency to develop different trunks. It can grow up as a small tree that grows upto 5m when it is domesticated. It often grows upto more than 7m under natural conditions. However, under extreme weather conditions, we can find sliding bush varieties [5]. Nevertheless, there are dwarf cultivars that do not exceed 1.5 m [5-6]. Mostly, on short branches and on spurs, flowering can occurs about 1 month after bud breakage on newly developed branches on the same year. Flowers can grow in pairs, clusters and may be solitary. In different conditions, clusters grow on terminals however the solitary flowers will appear on spurs all along the branches. Flowering appears in April in the northern hemisphere. Although in young trees, flowering will continue till the end of summer. The fruit is a fleshy berry and it develops from the ovary. The visible calyx rounded the nearly round fruit. Depending on the variety and on the stage of ripening, the apex of this crown almost closed to widely open. With short stalk, the fruit is connected to the tree. Most pomegranates can survive temperature down upto 12°F and other kinds tolerate without damage down to 7°F. Most of the pomegranate plants do not need winter chill hours, except few that require cold-hardy cultivars. On deep loamy soils, pomegranates grow well however they also grow quite good in clay and sandy soils. Short periods of standing water can be tolerated by pomegranates. Pomegranates will prefer well-drained soils. But excessive moisture will harm the

trees. Pomegranates can tolerate irrigation with water containing 2,000 to 2,500 ppm salt.

5. Chemistry

Pomegranate is a nutrient rich fruit containing phytochemical compound. Pomegranate produces phytochemicals that are lower in molecular weight. These compounds which are usually called phytochemicals perform a mechanism of defense. Different plants have various families of phytocompounds, that are similar in structure to steroid hormone such as 17β-estradiol (E2) compete for binding to estrogen receptor with endogenous hormone for binding to estrogen receptor (ER). It thus minimizes the hormonal effect of endogenous estrogens. Such compounds are called as "phytoestrogens". Most of the phytoestrogens found in food are inactive constituents that pass through series of enzymatic reactions in the gastrointestinal tract as a result of this many compounds are formed that have similar to that of estrogens. Phytoestrogens are clinically very important because of its efficiency in the curation and treatment of menopausal and premenopausal signs, over hormone replacement therapy (HRT). They can perform the function of both agonists and/or antagonists as a site-specific way that is same to the hormonal action of selective estrogen receptor modulators (SERMs). It may also perform the function of anti-oxidants and also defend DNA from the damage caused by oxidants [7].

5.1 Chemical Composition

The total weight of edible parts of pomegranate fruit is about 52% comprising of 78% juice and 22% seeds. The fresh juice of pomegranate has 85.4% moisture, 1.4% pectin, 10.6% total sugars, 0.7 mg/100 ml ascorbic acid, 0.1 g/100 ml total acidity (as citric acid), 19.6 mg/100 ml free amino nitrogen and 0.05 g/100 ml ash. However, the seeds are main source of total proteins, lipids, crude fibers and ash representing 27.2, 13.2, 35.3 and 2.0%, respectively. It also has 4.7% total sugars and 6.0% pectin contents. The sodium, iron, magnesium, copper and zinc constituents of the juice are lower than that of seeds, but potassium has 49.2 ppm concentration in the juice. However, chemical and physical properties of seed's lipids showed that the refractive index was 1.518, iodine value 74.2, saponification value 188.9, melting point 13.0°C, glycerol contents 10.3%, iodine value 74.2, acid number 1.1, unsaponifiable matters 0.7% and ester value 187.8. However, the studied lipids have 11 fatty acids, among them caprylic acid is the main acid constituting 36.3% along with stearic acid upto 22.5%. Furthermore, linoleic and oleic acids constitutes 5.1% and 10.3% respectively. However the total fatty acids content of the saturated fatty acids of seed's lipids of pomegranate form 83.6% [7].

5.2 Phytochemistry

Pomegranate fruit contains many polyphenolic compounds. Peels of this fruit have various phytochemical compounds like gallic acid, gallotannins, ellagic acid, punicalagins and punicalin [8]. Phytochemicals are produced by plants to protect them against danger such as herbivorous predators, ultraviolet radiation and pathogens. They are often referred to non-nutritive compounds. Pomegranate will be taken fresh and is passed through different stages to form as flavors, extracts, juices and wines. Commercial pomegranate is a high value product in agriculture market. As compared to other fruit juices, green tea and red wine, this juice has the highest anti-oxidant activity. The main groups of anti-oxidant phytochemicals are phenolic compounds including tennis, flavonoids and anthocyanin. Phytochemicals are more valued to their biological and free radical scavenging activities with interesting properties [8].

6. Post-Harvest Management

Post harvesting technology of pomegranate is same to that of apple. The fruits are transported to a cauterizing facility in a timely manner after harvesting. It is not needed to cool the fruit when it is harvested but it is useful to place fruit into cold storage after harvesting. Fruit that is fated for fresh market must be washed with water, rinsed with chlorine and categorized by defects, size, weight, culls, color and size. If the fruit is to be stored for relatively long period of time in cold storage, it must also be treated with a postharvest fungicide like Scholar (Syngenta). A storage wax can reduce the moisture loss that increases its storage time. It is also being applied to promote the visual quality of the fruit. For the appropriate use of fruit it must be packaged into cartons and should be kept in storage bins (for later packaging). Pomegranates are categorized into two grades, grade-1 or grade-2 [9]. Fruit must be kept in open-air upto six weeks and for five months using controlled atmospheric storage (CA). Controlled atmosphere is also beneficial for regulating the incidence of the browning of red pigments in the rind of the fruit. For less-time storage and high quality fruit, lowest temperature used will be 41°F and for longer-time storage 45°F is very suitable. It is worthwhile for fruit with known disease pressures to store for less than three weeks at a less temperature of 32-34°F [10]. Chilling injury shows the browning of white interlocular membrane and arils. Arils will necessarily lose their wanted pigment and will also unstiffen the matter that result in higher levels of pathogenicity.

7. Potential Uses and Industrial Applications

Pomegranate is a fruit famous in the middle ages and most usual in the symbolism, both Christian and Pagan of ancient times and mediaeval, adds a specifically cheerful touch, with its color bright red against evergreen twigs. Various legends said that the pomegranate is a symbol of fertility. In Turkey, after the marriage, a fruit is thrown on the ground by the Mercy when they pray for children. Good bride and the number of seeds that fall out indicate how many children she will have. Chinese women offer pomegranates to the Goddess of Mercy when they pray for children. Good fortune and riches come to persons dreaming of pomegranates. In the case of married people, this also

means children. To a young man in love, it implies that his sweetheart is de-voted and loyal to him. In Christian art the pomegranate, often split and showing the seeds, was interpreted as a symbol of fertility, hope of immortality and the resurrection [11].

Pomegranate can be used as fresh, fermented fruit, fruit juice, frozen aril, dried aril, aril, jam, minimally-processed aril, canned, wine, vinegar, jelly, paste, leather, fruit juice and in flavoring products. Pomegranate arils can be used as processed or fresh fruit (frozen, canned, dried and minimally processed). Traditional uses of wild pomegranate fruit is in the dehydrated seeds beside with pulp which formed a traditional product called as "*Anardana*" [12]. The dehydrated arils are acidic, aids in improving digestion and mouth feel and are mostly useful as acidulate in gastronomic preparations. The dry anardana has sugars, acids and crude fiber in contrast to fresh fruit [2].

In earliest Ayurvedic system of medicines, the pomegranate has widely been used as a source of traditional remedies for many years. The bark of the pomegranate tree and the rind of the fruit are used as a conventional curative agent against intestinal parasites causing diarrhea and dysentery. The juice and seeds are regarded as a tonic for the throat, eyes, heart and various purposes like as treating hemorrhoids and gum bleeds, firming up sagging breasts, stopping nose bleeds and toning skin [13]. Pomegranates have been consumed as conventional medicine for osteoarthritis, anemia, heart diseases, dental care, cancer, diabetes and stomach disorders [14].

7.1 Pharmacological Applications

Now-a-days demand of pomegranate is merely because of its pleasant taste. Nevertheless, scientific proofs suggested various therapeutic activities of this plant including anti-parasitic, anti-inflammatory, anti-oxidant, anti-microbial and anti-carcinogenic and anti-athrogenic effects. The pomegranate phenolic compounds, tannins, anthocyanin's and phytochemicals have useful effects owing to their qualified anti-oxidant properties. So, medical efforts proved the therapeutic power of pomegranate products, furthermore, pomegranate extracts are now used to detect the cancer, inflammation, diabetes, U.V radiation induced skin damage and cardiovascular diseases. Peels of pomegranate have unique phytochemical compounds like gallotannins, ellagic acid, gallic acid, punicalins and punicalagins [8]. Phytochemicals provide protection against harmful UV radiations, pathogens and are often referred to as non-nutritive compounds thought to be produced by plants as means of protection against some dangers such as harmful ultraviolet radiations, pathogens and herbivorous predators. Pomegranate is consumed fresh and in processed form as juices, wines, flavors and extracts. Commercial pomegranate juice has the highest anti-oxidant activity compared to other fruit juices, red wine and green tea and currently is a highly valued product in the agricultural market. Phenolic compounds including flavonoids, anthocyanin's and tannins are the main group of anti-oxidant phytochemicals with interesting properties and have high value because of their biological potentials and free radical scavenging activities [8].

7.1.1 Anti-Microbial Activity

Methanolic extracts of the peels of pomegranate showed strong anti-microbial potentials against various bacterial strains such as *Yersinia enterocolitica*, *Escherichia coli*, *Staphylococcus aureus* and *Listeria monocytogenes* using in-vivo and in-vitro approaches due to the presence of phenolic compounds [15]. Combination of polyphenols of pomegranate juice and fruit was found effective against various food borne viral infections. In absence of culturable human noroviruses, MS2 (ssRNA) bacteriophage, murine norovirus (MNV/1) and feline calicivirus (FCV/F9) were preferably used as food borne viral surrogates. This effective combination was found to be able of significantly reducing food borne viral surrogates such as MS2, MNV-1 and FCV-F9 [16]. Some further evidences collected from recent scientific investigations showed that punicalagin possesses strong anti-virucidal potentials and anti-influenzal activities. Furthermore, synergistic effects of polyphenolic extracts were also assessed with oseltamivir. These combinations were found to be very effective owing to low cost, negligible side effects, less toxicity and better clinical efficiencies [17]. Hexane fractions obtained by the stems of this plant exhibited strong anti-fungal effects [18].

7.1.2 Anti-Oxidant Activity

Various extracts of different parts of pomegranate such as fruit peel and fruit juice are known to exhibit strong anti-oxidant potentials owing to the high concentration of phenolic and flavanoids contents that were tested against standard ABTS and DPPH methods. Even the by-products of cooked pomegranate showed excellent anti-oxidant activities. Raw rind powder of pomegranate is a rich source of anti-oxidants that is more preferably used for refrigerated storage of goat meat that is known to promote lipid oxidation [19]. Arils of the ripened fruits constitute soluble phenolics that showed anti-oxidant properties as measured by ferric reducing ability assay. Nevertheless, anti-oxidant potentials depends on the nature of extract of this plant [20]. Some recent scientific researches demonstrated that juice, seeds and peel of pomegranate have strong anti-oxidant potentials due to the presence of tannins like ellagic acid and punicalagins that readily enters the systemic circulation of body. Some scientists also studied the anti-oxidant effects of different urolithins derivatives in a cell-based assay and found that urolithins are correlated with number of hydroxyl groups as well as lipophilicity of molecules.

7.1.3 Glucose and Lipid Metabolism

Extract of the flowers of pomegranate was tested for pancreatic lipid peroxidation, serum lipid profile and on both enzymatic and non-enzymatic anti-oxidant assay in streptozotocin induced diabatic rats. These researchers reported that there was increase in cholesterol level, blood

glucose level, triglyceride contents, low-density-lipoprotein-cholesterol, low-density-lipoproteins and lipid peroxidation level with slight decrease in glutathione contents including catalases, superoxide dismutase, glutathione-S-transferase, glutathione reductase and glutathione peroxidase [21]. Leaf extract of pomegranate is known to contain appreciable concentration of ellagitannins that proves to be a potential source for lowering the action of fat deposition in mice and decreasing the triglyceride accumulation at cellular level through oral administration of lipid emulsions along with noticeable activity of modulating lipid metabolites of high lipid contents and inhibiting HMG2CoA reductase in vitro. Some recent investigations have shown that leaves of pomegranate are rich source of tannins that modulate the lipid metabolism and acts on the liver cells. Number of scientific investigations has shown that ellagic acid of pomegranate can be transported into cells that was in correlation with total cholesterol alterations in cells [22].

7.1.4 Anti-Cancer Effects

In traditional system of medicines, powder of the pomegranate is used with powder of *Vernonia cinerea* L. and leaves of *Crataeva nurvala* that was heated with coconut and castor oil for treatment of breast cancer [23]. Seed oil, seed powder and fruit juice of pomegranate proves to be fruitful in leukemia, oral carcinoma, lung, colon, skin and breast cancer through anti-inflammatory, anti-oxidant, anti-angiogenesis and anti-proliferating effects. Ellagic acid of seed oil and fruit juice has reported to be acting against skin cancer, pancreatic cancer, breast cancer, prostate cancer, colon cancer, intestinal cancer, esophagus cancer, bladder cancer, mouth cancer, liver cancer, leukemia and neuroblastoma. Ellagic acid synergistically acts with cyclosporine A, selenomethionine, cisplatin, 6-gingerol, vinorelbine, resveratrol and quercetin. After ingestion, polyphenols of pomegranate are metabolized while ellagitannins are transformed to urolithins from human colon. In mouse model, these chemical metabolites were accumulated in the tissues of intestine, colon and prostate. These compounds exhibiting cytochrome P450 seems to exert beneficial effects at different stages of prostate cancer development. In a recombinant CYP1B1-mediated ethoxyresorufin-O-deethylase (EROD) assay, pomegranate ellagitannins/microbial metabolites were examined for their CYP1B1 inhibitory activity. Punicalins, urolithins and punicalagins were also tested for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)-induced CYP1B1 inhibitory activity in the 22Rv1 prostate cancer cell line. Urolithins were also studied for their cellular uptake and inhibition of TCDD-induced CYP1B1 expression [24].

7.1.5 Anti-Inflammatory Activity

The pomegranate aqueous extracts controlled the production of nitrous oxide caused by lipopolysaccrides macrophage cells. Cytotoxicity could not be found in the extracts and the concentration tests [25]. Mediators are the precursors of mast cells that cause oedema and destroy connective tissues so they participated in pathological fibrosis in rheumatoid arthritis joints, infiltration and in lymphocyte chemotaxis. The production of chemical mediators such as histamine, proteases, metabolites of arachidonic acid and several inflammatory and chemotactic cytokines including IL-6 and IL-8 show the degranulation activation of the myeloid precursor cell line KU8I2 by the such cells are suitable models for studying the activation of degranulation of human mast cells [26].

Table 1 Fatty acid composition in pomegranate varieties

Lipids and Fatty Acids	VA	ME	AD	PTA	AA	AB
Lipids	107.7	97.8	65.8	50.9	152.2	134.5
Lauric Acid	0.19	ND	ND	3.08	0.02	0.37
Myristic Acid	ND	ND	ND	ND	0.04	0.03
Palmitic Acid	22.63	20.79	18.16	20.10	22.38	18.50
Palmetoleic Acid	1.40	0.90	0.22	2.70	1.01	0.74
Stearic Acid	8.35	8.77	9.72	8.10	10.14	10.42
Oleic Acid	29.77	26.44	30.03	31.26	26.59	24.76
Linolenic Acid	35.47	38.61	36.30	31.73	33.52	31.49
Arachidic Acid	0.61	2.39	2.96	1.59	5.00	9.94

8. Summary

Pomegranate is a fruit having deciduous shrub and small tree of lythraceae family. It is cultivated in different countries. Pomegranate can be used as fresh, fermented fruit, fruit juice, frozen aril, dried aril, aril, jam, minimally-processed aril, canned, wine, vinegar, jelly, paste, leather, fruit juice and in flavoring products. Pomegranate arils can be used as processed or fresh (frozen, canned, dried, and minimally processed). Pomegranate (Punicaceae) is a nutrient rich fruit containing phytochemical compound. Pomegranate produces phytochemicals that are lower in molecular weight. Pomegranate fruit contains many

polyphenolic compounds. Peels of this fruit have various phytochemicals like gallic acid, gallotannins, ellagic acid, punicalagins and punicalin. Pomegranate has various uses in food and in medical field.

References

[1] R. Adsule, P. Kotecha, S. Kadam. (1992). Preparation of wine from pomegranate. Beverage and food world. 19(4): 13-14.

[2] A. Akpinar-Bayizit, L. Yilmaz-Ersan, T. Ozcan. (2012). The therapeutic potential of pomegranate and its products for prevention of cancer. INTECH Open Access Publisher: pp.

[3] J. Jurenka. (2008). Therapeutic applications of pomegranate (Punica granatum L.): a review. Alternative medicine review. 13(2): 128.

[4] V. Gallo, H.B. Bueno-De-Mesquita, R. Vermeulen, P.M. Andersen, A. Kyrozis, J. Linseisen, R. Kaaks, N.E. Allen, A.W. Roddam, H.C. Boshuizen. (2009). Smoking and risk for amyotrophic lateral sclerosis: analysis of the EPIC cohort. Annals of neurology. 65(4): 378-385.

[5] G.M. Levin. (2006). Pomegranate roads: a Soviet botanist's exile from Eden. Pomegranate Roads: pp.

[6] Q. Huang, Y. Zhu, H. Chen, Y. Wang, Y. Liu, W. Lu, X. Ruan. (2003). First report of pomegranate wilt caused by Ceratocystis fimbriata in Yunnan, China. Plant disease. 87(9): 1150-1150.

[7] M. Abbas, F. D'Amico, L. Morresi, N. Pinto, M. Ficcadenti, R. Natali, L. Ottaviano, M. Passacantando, M. Cuccioloni, M. Angeletti. (2009). Structural, electrical, electronic and optical properties of melanin films. The European Physical Journal E. 28(3): 285-291.

[8] A.J. Ullmann, J.H. Lipton, D.H. Vesole, P. Chandrasekar, A. Langston, S.R. Tarantolo, H. Greinix, W. Morais de Azevedo, V. Reddy, N. Boparai. (2007). Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. New England Journal of Medicine. 356(4): 335-347.

[9] A. Valli, G. Carey, A. Coutinho. (2002). Control strategies for timestep selection in simulation of coupled viscous flow and heat transfer. Communications in Numerical Methods in Engineering. 18(2): 131-139.

[10] J.-Y. Lee, Y. Nagano, J.P. Taylor, K.L. Lim, T.-P. Yao. (2010). Disease-causing mutations in parkin impair mitochondrial ubiquitination, aggregation, and HDAC6-dependent mitophagy. The Journal of cell biology. jcb. 201001039.

[11] H. Schneider. (1945). On the Pomegranate. small. 3: 1il.

[12] J. Pruthi, A. Saxena. (1984). Studies on Anardana (dried pomegranate seeds). Journal of food science and technology. 21: 296-299.

[13] A.P. Kulkarni, H. Mahal, S. Kapoor, S. Aradhya. (2007). In vitro studies on the binding, antioxidant, and cytotoxic actions of punicalagin. Journal of Agricultural and Food Chemistry. 55(4): 1491-1500.

[14] D. Heber. (2008). Multitargeted therapy of cancer by ellagitannins. Cancer letters. 269(2): 262-268.

[15] N. Al-Zoreky. (2009). Antimicrobial activity of pomegranate (Punica granatum L.) fruit peels. International journal of food microbiology. 134(3): 244-248.

[16] G. Aad, B. Abbott, J. Abdallah, A. Abdelalim, A. Abdesselam, O. Abdinov, B. Abi, M. Abolins, H. Abramowicz, H. Abreu. (2010). The ATLAS simulation infrastructure. The European Physical Journal C. 70(3): 823-874.

[17] M. Haidari, M. Ali, S.W. Casscells, M. Madjid. (2009). Pomegranate (Punica granatum) purified polyphenol extract inhibits influenza virus and has a synergistic effect with oseltamivir. Phytomedicine. 16(12): 1127-1136.

[18] J.G. March, J.P. Olsen. (2010). Rediscovering institutions. Simon and Schuster: pp.

[19] S.K. Devatkal, K. Narsaiah, A. Borah. (2010). Anti-oxidant effect of extracts of kinnow rind, pomegranate rind and seed powders in cooked goat meat patties. Meat Science. 85(1): 155-159.

[20] S. Johnston, J. Pippen Jr, X. Pivot, M. Lichinitser, S. Sadeghi, V. Dieras, H.L. Gomez, G. Romieu, A. Manikhas, M.J. Kennedy. (2009). Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor–positive metastatic breast cancer. Journal of Clinical Oncology. 27(33): 5538-5546.

[21] P. Bagri, M. Ali, V. Aeri, M. Bhowmik, S. Sultana. (2009). Antidiabetic effect of Punica granatum flowers: effect on hyperlipidemia, pancreatic cells lipid peroxidation and antioxidant enzymes in experimental diabetes. Food and Chemical Toxicology. 47(1): 50-54.

[22] R. Wang, Y. Ding, R. Liu, L. Xiang, L. Du. (2010). Pomegranate: constituents, bioactivities and pharmacokinetics. Fruit, vegetable and cereal science and biotechnology. 4(2): 77-87.

[23] A.R. Amin, O. Kucuk, F.R. Khuri, D.M. Shin. (2009). Perspectives for cancer prevention with natural compounds. Journal of Clinical Oncology. 27(16): 2712-2725.

[24] M.G. Miguel, M.A. Neves, M.D. Antunes. (2010). Pomegranate (Punica granatum L.): A medicinal plant with myriad biological properties-A short review. Journal of Medicinal Plants Research. 4(25): 2836-2847.

[25] M. Matsui, S. Kumar-Roine, H.T. Darius, M. Chinain, D. Laurent, S. Pauillac. (2009). Characterisation of the anti-inflammatory potential of Vitex trifolia L.(Labiatae), a multipurpose plant of the Pacific traditional medicine. Journal of ethnopharmacology. 126(3): 427-433.s

[26] H. Yan, D.W. Parsons, G. Jin, R. McLendon, B.A. Rasheed, W. Yuan, I. Kos, I. Batinic-Haberle, S. Jones, G.J. Riggins. (2009). IDH1 and IDH2 mutations in gliomas. New England Journal of Medicine. 360(8): 765-773.