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Review Article

THE PHARMACOLOGICAL, PHYSIOLOGICAL AND TOXICOLOGICAL EFFECTS OF POMEGRANATE FRUIT EXTRACT AND ITS CONSTITUENTS

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ABSTRACT

The utilization of plants for the development of new drugs and alternate therapies is mainly due to the wide spread confidence that medicines obtained from plants are secure, economical, and quite effective when compared with synthetically prepared medicines based on cost, efficacy, unwanted and harmful effects. This global trend for the use of medicines derived from natural sources particularly from plants has created an emergent need for accurate, detailed, and thorough information about the usefulness, particular constituent's properties, effectiveness, and safety of plant and its products of medicinal interest. Pomegranate (*Punica granatum;* Latin name) is a fruit having deciduous shrub or little trees of 5-8 meters height. Pomegranate has become of great interest for researchers for the development of lots of new drugs because of its different nutritional components and their miraculous properties as improving skin health, anti-inflammatory agent, obesity reducer, antioxidant, antiviral, antimicrobial, anticancer, antidiabetic, antidiarrheal, its effects on different enzymes, effect on cellular differentiation. Previous researches have indicated that metabolites of Pomegranate fruit extract ellagitannins are particularly localized in colon, prostate gland, and mice intestinal tissues and show their effects. The objective of this review is to study all the constituents of pomegranate fruit, its dietary importance and physical, chemical as well as toxicological properties of this fruit. Thorough analysis of all these properties strongly suggests a wide range use of Pomegranate for clinical applications.

***Keywords*:** Pomegranate, Properties, Constituents, Toxicological properties, obesity, antioxidant, antiviral, antimicrobial, anticancer, antidiabetic, antidiarrheal, cellular differentiation.

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INTRODUCTION

Plants are used as the most important remedy in many of diseased conditions and also as food stuff for human and they remain persistent to give the new beneficial remedies to mankind till day. Since the previous four decades, there have been astonishingly sound revivals of concern in medicinal plants study (Basu and Chaudhuri 1991). In the study of medicinal plants, this new world wide interest has led to the categorization of new molecules and segregation of active chemical compounds from the plants of curative nature (Faizi, Khan et al. 2008). The resurgence in drugs derived from plants is mainly due to the wide spread confidence that medicines obtained from plants are secure and more reliable than artificially prepared medicines which are costly and also have many effects which are toxic (Shikov, Pozharitskaya et

al. 2008). This recent global tendency for the use of drugs derived from plants, therefore, produced an emergent need for precise and timely information about the uses, properties, effectiveness, safety and worth of plant products of medicinal interest(Sucher and Carles 2008)

Pomegranate fruit

Punica granatum is a fruit of deciduous shrub or little trees of 5-8 meters length. It is indigenous to Iran (Kumar *et al.,* 1990) and from there it extends to Asian areas such as Caucasus, the Himalayas, and North India and in Kerala (Janic *et al.,* 2008). This fruit is grown in the regions of Northern Hemisphere from September to February (LaRue & James, 1980) and in the Southern regions it is cultivated during months of March to May. It is commonly known as Anaar in native language and belongs to family Lythraceae. The benefits of Pomegranate fruit are also explained in many religious books like "The book of Exudos", "Homeric Hymn" and the "Holy Quran" (Surah Al Inam and Al Rehman).

History of pomegranate tree

Along with olives, figs and grapes, pomegranates are among the first plants to have been cultivated by man. Pomegranate (*Punica granatum* L.) is considered one of the oldest known edible fruit about which the Holy Quran, the Bible, the Jewish Torah, and the Babylonian Talmud has told as 'Food of Gods' that is symbolic of plentyness, fertility and prosperity(Aviram, Dornfeld et al. 2000; Seeram, Henning et al. 2006). This distinctive fruit pomegranate is the important member of two species belonging to family Punicaceae. The genus name Punica, was given with name of the Roman Carthage, the place where the best pomegranate fruits were grown. In French this fruit is named as grenade, in Spanish as Granada (derived from the ancient city of Granada), and literally translates to seeded ("granatus") apple ("ponium") (Jurenka 2008). The name of the edible part of pomegranate, in ancient Greek mythology, is the "fruit of the dead" which consists of significant amounts of saccharides, polyphenols, and available in Hades for its residents. The Babylonians named the kernels as an agent of renewal, the Persians as conferring strength on the battle field and for ancient Chinese alchemical adepts; the bright red liquid was mythopoetically regarded as a "soul concentrate", a substitute to human blood, consulting to permanency and immortality (Dahham, Ali et al. 2010). Since ancient times, the pomegranate has been used extensively in the folk medicine of many cultures as a "healing food" in order to eliminate parasites, as an anthelmintic and antipyretic, vermifuge and to treat aphtae, acidosis, ulcers, diarrhea, dysentery, microbial infections, hemorrhage, and respiratory pathologies. It also features prominently in the ceremonies, art, and mythology of the Egyptians and Greeks, and was the personal emblem of Maximilian, the Holy Roman Emperor (Larrosa, Gonzalez-Sarrias et al. 2010).

Scientific classification

Punicaceae is monogenic family with two species in world. One is endemic to Socotra (*Punica protopunica)* with pink flowers and having smaller less sweetened fruits. Other species, *Punica granatum* is distributed throughout Tropical and Sub tropical region of the world.

Methods of extraction

For the preparation of pomegranate fruit extract, pomegranates are selected, washed, frozen and stored in reservoir containers. The fruits are then crushed, squeezed, grounded and blended with electronic blender and finally dried in an oven adjusted at 40°C for time of 24 hours, then the fine powder is sieved with the help of 24-mesh and stored at room temperature for further extraction(Qu, Pan et al. 2010) then these fruits were further extracted by standard analytical methods. 100ml of the total extract of the fruit gives about 16% vitamin C of an adult's daily need. Also it consists of potassium, Vitamin B5 and polyphenols which are tannins and flavonoids (Schubert, Lansky et al. 1999).

Ethno medicinal uses

For thousands of years, many cultures have believed that pomegranate have beneficiary effects on health and fertility. The recent interest for this fruit is not only because of the pleasant taste, but also due to the scientific evidences that suggest therapeutic activity such as anti-atherogenic, antiparasitic, antimicrobial, and antioxidant, anticarcinogenic and anti-inflammatory effects. Pomegranate has high anti oxidative (Ismail *et al*., 2012) and anticancer activities (Khan *et al*., 2013). Metabolites of Pomegranate fruit extract ellagitannins are particularly localized in colon, prostate gland and mice intestinal tissues (Seeram, Aronson et al. 2007). In 2011, 32 clinical trials were suggested to be conduct with National health institute to observe the effects of pomegranate extract or juice against prevention of various diseases. The various uses of pomegranate fruit as an antiparasitic agent, ulcers and in healing of aphtae and blood tonic, diarrhea are also enlisted in Ayurvedic medicines(Jurenka 2008).

Different diseases against which pomegranate extract is useful for prevention are prostate cancer, lymphoma, prostatic hyperplasia, oxidative rhinovirus infection and common cold, Acquired immune deficiency syndrome (AIDs)(Lee and Watson 1998), cardiovascular protection and atherosclerosis. It is also used as an ophthalmic ointment, oral hygiene and weight loss soap. Pomegranate *(Punica granatum)* and its fruit extract which is most commonly consumed is specially associated with decreased risk of various proliferative diseases such as prostate cancer, prostatic hyperplasia and atherosclerosis in humans (Aviram, Dornfeld et al. 2000). It is also used in infant brain ischemia, male infertility, stress in diabetic hemodialysis, diabetes(Saxena and Vikram 2004), Alzheimer's disease and arthritis.

Claim

In this review, we thoroughly reviewed and discussed different constituents of Pomegranate fruit and their effects (Pharmacological, physiological and toxicological). All the claimed effects are based on previous researches, experimental data, and reports collected from different sources.

Constituents of pomegranate fruit and its effects

Table 1: Phytochemicals present in pomegranate plant (Jurenka, 2008)

Plant component	Constituent
Pomegranate juice	Anthocyanins; catechin, glucose; ascorbic acid; phenolics such as ellagic acid, gallic acid, caffeic acid,), quercetin, epigallocatechin gallate (EGCGrutin; mineral elements; aminoacids.
Pomegranate seed oil	Punicic acid; ellagic acid; fatty acids; sterols
Pomegranate pericarp (Rind, peel)	Phenolic compounds like punicalagins, gallic acid, catechin, EGCG, quercetin, rutin, anthocyanidins, other flavonoids
Pomegranate leaves	Tannins (Punicalagins and punicafolins) and flavones glycosides including apigenin and luteolin
Pomegranate roots and bark	Ellagitannins including Punicalagins and punicalin, numerous piperidine alkaloids
Pomegranate flower	urosolic acid, gallic acid, triterpenoids including Asiatic and maslinic acid and other unidentified constituents.

The pomegranate fruit is round, with stringy covering or rind, classically yellow, coated with light or deep pink or rich red. The eatable part of the fruit, the arils can be conserved as molasses or used for liquor, queue, jelly, plum, jam, juice, vinegar, and can be an alternative to flavoring and coloring agent used in beverages (Ozgen, Durgaç et al. 2008; Al-Said, Opara et al. 2009; Akbarpour, Hemmati et al. 2010). During the last few years, many attempts have been made to evaluate the different constituents of pomegranate fruit, their isolation and their physiological, pharmacological and toxicological properties. The pomegranate tree can be divided into several anatomical compartments: seed, juice, peel, leaf, flower and root bark, each of which is widely used in therapeutic and food formulas, and cosmetics. Pomegranate is a good source of tannins, dyes, and alkaloids(Khan 2009; Wang, Ding et al. 2010). Different constituents of pomegranate fruit are as follows:

The edible fruit weighs about 5-1/2 ounces, 104 calories, 1.5g protein, 26.4g carbohydrate, 9mg vitamin C and 399mg potassium. Unlike the red pomegranates, white pomegranate seeds are high with sugar content and have low acidity levels. The chemical composition of the pomegranate and its products depends on the cultivar, growing region, and climate, the fruit's stage of maturity, cultural practices and manufacturing systems (Borochov-Neori, Judeinstein et al. 2009; Zarei, Azizi et al. 2011). Table shows the chemical composition of pomegranate fruit and phytochemicals in pomegranate and its parts.

Table 2: Values per 100 g of edible portions (Yilmaz, 2007).

Constituent	Composition
Moisture	72.6-86.4%
Protein	Protein 0.05-1.6%
Fat	0.01-0.9%
Mineral elements	0.36-0.73%
Fibre	3.4-5.0%
Carbohydrates	15.4-19.6%
Calcium	3.0-12.0 mg
Phosphorus	8.0-37.0 mg
Iron	0.3-1.2 mg
Sodium	3.0 mg
Magnesium	9.0 mg
Ascorbic acid (Vitamin C)	4.0-14.0 mg
Thiamine (Vitamin B1)	0.01 mg
Riboflavine (Vitamin B2)	0.012-0.03 mg
Niacine	0.18-0.3 mg

Pomegranate fruit extracts/constituents possesses huge biological activities such as antidiarrhoeal (Das, Mandal et al. 1999), anticarcinogenic(Malik, Afaq et al. 2005), antibacterial(Duman, Ozgen et al. 2009), antifungal(Dutta, Rahman et al. 1998), antiulcer (Gharzouli, Khennouf et al. 1999), antioxidant activity and free radical scavenging capability (Festa, Aglitti et al. 2000), strengthening of the immune system(Lee, Kim et al. 2008), prevention of heart disease(Johanningsmeier and Harris 2011) and liver fibrosis(Thresiamma and Kuttan 1996), and inhibition of lipid peroxidation even at lower concentrations than vitamin E (Rosenblat, Draganov et al. 2003). Most of these therapeutic activities are because of the *'phenolic compounds'* which include the acids like gallic, protocatechinunic, chlorogenic, caffeic, ferulic and coumaric, as well as some other compounds including *'hydrolysable tannins'* (such as punicalin, pedunculagin, punicalagin, corilagin, casuarinin, punicacortein, granatin and ellagic acid),*'anthocyanins'*

(delphinidin, cyanidin and pelargonidin3-glucosides and 3,5- diglucosides) and catechins (a phenolic compound by chemical nature) (Noda, Kaneyuki et al. 2002; Viuda-Martos, Fernández-López et al. 2010).

Polyphenols

Polyphenols are one of the most abundant groups in plant which have a high antioxidant activity. Phenolic compounds are biologically active group of phytochemicals. They are classified according to their chemical structure into flavonoids, phenolic acids, coumarins, and tannins(Tapiero, Tew et al. 2002; Mennen, Walker et al. 2005). Because of its potent antioxidant activity, pomegranate is considered one of the commonly used natural antioxidants.

Tannins:

Pomegranate fruit extract is rich in hydrolysable tannins called ellagitannins(Singh, Chidambara Murthy et al. 2002; Passamonti, Vrhovsek et al. 2003). These ellagitannins are produced from binding of ellagic acid with carbohydrates. Punicalagins are tannins with free radicals in experiments conducted in laboratory premises(Kulkarni, Mahal et al. 2007).

Flavonoids

Anthocyanins are the major and utmost key group of flavonoids existing in pomegranate arils, which acquired from the juice. These colorants provide the fruit and juice its characteristic red color (Afaq, Saleem et al. 2005). There is a huge variety of anthocyanins found in pomegranate juice, particularly pelargonidin-3,5-diO-glucoside,5-diO-glucoside, pelargonidin-3-O-glucoside, delphinidin-3-O-glucoside, cyanidin-3-O-glucoside and delphinidin-3,5-di- glucoside(Jaiswal, DerMarderosian et al. 2010). The presence of hydroxylated groups in number, the nature and the number of bonded sugars, aliphatic or aromatic carboxylates bonded to these sugars in the structure and the position of these bonded molecules, are the major differentiating elements for different anthocyanins (Kong, Chia et al. 2003).

Organic Acids

The seeds of pomegranate are rich in poly unsaturated fatty acids including linoleic acid, Oleic acid, palmitic acid and other lipids punicic acids, stearic acid and linolenic acid (Schubert, Lansky et al. 1999). The citric acid and malic acid are major components of juice while tartaric acid, succinic acid and oxalic acid are also present in juice (Poyrazoğlu, Gökmen et al. 2002). Phenolic acids are also present in juice which consists of Caffeic acid, Chloroenic acid and fumalic acid (Amakura, Okada et al. 2000).

Other constituents

Other ingredients such as water-soluble vitamins, minerals and sugars of pomegranates have been stated many times by various researchers in past (Aviram, Dornfeld et al. 2000; Davidson, Maki et al. 2009; Tezcan, Gültekin-Özgüven et al. 2009). Peel bears almost half of the total weight of the fruit and it is a major source of bioactive compounds for example minerals like potassium, nitrogen, calcium, phosphorus, magnesium, and sodium some proanthocyanidin compounds, flavonoids, ellagitannins (ETs) and different phenolic compounds (Li, Guo et al. 2006; Mirdehghan and Rahemi 2007), as well as polysaccharides which are stated by(Jahfar, Vijayan et al. 2003). Fruit seeds are good source of lipids; pomegranate seed oil consists of 12% to 20% of its total weight. The seeds also have the phytoestrogen coumestrol, and the sex steroid, estrone , pectin, crude fibers, vitamins, minerals ,proteins, sugars ,isoflavones (mainly genistein) and polyphenols(Syed, Afaq et al. 2007).

PHYSIOLOGICAL PROPERTIES

1. Anti-inflammation

Physiological or acute inflammation is a useful host response to tissue damage but it may also cause immune-associated diseases such as inflammatory bowel disease, rheumatoid arthritis, and cancers(Simmons and Buckley 2005). Pomegranate has been shown to inhibit inflammation by different mechanisms. Cyclooxygenase (COX) and lipooxygenase (LOX), which are key enzymes in the conversion of arachidonic acid to prostaglandins and leukotrienes (important inflammatory mediators), respectively, are inhibited by Pomegranate(SHAMS ARDEKANI MOHAMMAD, HAJIMAHMOODI et al. 2011). Non-steroidal anti-inflammatory drugs (NSAIDs) have more side effects on cardiovascular function by inhibiting COX and suppressing (prostacyclin) in comparison to Pomegranate (Grosser, Fries et al. 2006).

2. Improving Skin Health

Destruction to the skin arises from the consequence of the regular aging process and damage is aggravated in excessive exposure of skin to sun (photo aging)(Lavker 1995). The major reason of serious adverse effects to human skin is extended exposure to ultraviolet (UV) radiations causing skin cancer, premature skin aging, sunburn, oxidative stress and immune-suppression(Widmer, Ziaja et al. 2006). Some of the scientists stated that pomegranate peel extract (and to a lesser extent, both the fermented juice and seed cake extracts) stimulates the type I procollagen synthesis and inhibits matrix metalloproteinase-1 (MMP-1; interstitial collagenase) production by dermal fibroblasts, and has no effect on growth of keratinocytes. Whereas pomegranate seed oil has a stimulatory effect on keratinocytes proliferation in monolayer culture. These results indicate that pomegranate aqueous extract (especially of pomegranate peel) enhances the regeneration of dermis, and seed oil of pomegranate enhances the regeneration of epidermis(Aslam, Lansky et al. 2006).

3. Obesity

As per WHO statistics, there are more than 300 million out of 1000 million overweight adults which are obese (Mensah, Mendis et al. 2004). Cerda & others(Cerdá, Cerón et al. 2003; Cerdá, Llorach et al. 2003) studied the effects of pomegranate extract (6% Punicalagins) in female rats feeding them to a diet containing 20% of the extract for 37 days. The extract intake was about 4800 mg punicalagin/kg/d. A sufficient decline in body weight of the animals was observed in the rats.

PHARMACOLOGICAL PROPERTIES

1. Cardiovascular effects

It is assumed that antioxidants possess valuable effects on cardiovascular and neurodegenerative diseases by counteracting the reactive oxygen species (ROS) which is majorly produced because of heavy work out and increased metabolic processes. Pomegranate pure juice consumption before and after a moderate exercise have significant effect on lipid per oxidation, blood pressure, and urinary gluco-corticoid levels.

2. Antioxidant properties

Destruction because of oxidation is one of the major reasons in the deterioration of quality in food products. This oxidative deterioration starts with an exposure of heat, ionizing radiation, light, metal ions, and metallo-protein catalysts to a particular enzyme lypoxygenase, (Daker, Abdullah et al. 2008). This oxidative deterioration leads to a huge loss of nutritional value of food because of the damage to vitamins and essential fatty acids in food. The apparent qualities of the food are also widely changed including taste, texture and color of food which decreases its shelf life and ultimately rejection by consumers(Fernández-

López, Viuda-Martos et al. 2007). Polyphenolic antioxidants are found richly in pomegranate(Çam, Hışıl et al. 2009). The Phenolic compounds present in pomegranate, including punicalagin isomers, EA derivatives, and anthocyanins (delphinidin, cyanidin and pelargonidin 3- glucosides, and 3, 5-diglucosides) are well known for their properties to reduce free radicals and to prevent lipid oxidation in vitro(Noda, Kaneyuki et al. 2002). However, some scientists recommended that punicalagin originating from the peels is an important phytochemical subsidizing to the total antioxidant ability of pomegranate juice, whereas anthocyanins has only a minor role in this measure(Tzulker, Glazer et al. 2007).

3. Antiviral properties

Pomegranate has been used in phage amplification assays as a viricidal agent(De Siqueira, Dodd et al. 2006). Four different types of polyphenols in pomegranate extracts Ellagic Acid, caffeic acid, luteolin, and punicalagin have been evaluated by many researchers and they found punicalagin as an anti-influenza component(Haidari, Ali et al. 2009), it inhibits the replication of the viral RNA, reduces agglutination of chicken RBC's by the virus, and had viricidal effects in chicken. Further investigations showed that replication of human influenza A/ Hong Kong (H3N2) in vitro is also inhibited. This effect has also been associated with other flavonoid compounds found in pomegranate (Kwak, Jeon et al. 2005).

4. Antimicrobial Properties

One of the most practiced schemes to control the growth of microorganisms is by means of use of the substances that have antimicrobial activity for example, growth reducers, inhibitors, or even inactivators. To maintain the safety and quality of food, preservatives are used as first choice(Viuda-Martos, Ruiz-Navajas et al. 2008). Health-related problems caused by deteriorated food, foul smell, disagreeable tastes, textural problems, or changes in color, which are basically caused by the enzymatic or metabolic systems of the principal microorganisms in food lead to the variation in its quality and beneficiary effect. Natural antimicrobials having microbicidal or static effect sufficiently increase the useful life of foods and its prevention form deterioration (Feng and Zheng 2007).

Pomegranate has significant inhibitory effect on various pathogenic bacteria especially gram positive bacteria which are methicillin resistant and methicillin susceptible *Staphylococcus aureus(Braga, Leite et al. 2005)*, *Streptococcus haemolyticus, Vibrio cholera, Proteus bacillus, Proteus vulgaris, Pseudomonas aeruginosa, Mycobacterium tuberculosis, Listeria monocytogenes, Candida albicans, Yersinia enterolytica(Al-Zoreky 2009)*. Tannins, ellagitannins and flavonoids are responsible for antibacterial activities of pomegranate extracts (Al-Zoreky 2009).

5. Anticancer properties

Pomegranate possesses inhibitory effects on different type of cancers such as prostate (Rettig, Heber et al. 2008), breast (Sturgeon and Ronnenberg 2010), colon (Kasimsetty, Bialonska et al. 2010), and lung cancers(Khan, Afaq et al. 2007). The components of many fruits which do not have nutritional value are known to have potential as anticancer by means of having chemoprotective agents. Some of the general mechanism of action proposed for such compounds are (Tanaka and Sugie 2007); (1) Induction of phase II (detoxification) enzymes; (2) inhibition of phenotypic expressions of pre neoplastic and neoplastic cells; (3) Blockage of carcinogen formation or inhibition of the phase I enzymes; (4) Intonation of homeostatic hormones; (5) Apoptosis induction; (6) Destruction of DNA-reactive agents; (7) Suppression of hyper-cell proliferation induced by carcinogens; and (8) tumor angiogenesis depression. For finding the effectiveness of pomegranate fruit and its constituents many studies have been conducted endowed with a very high antioxidant activity as an anti-invasive, antiproliferative, and pro-apoptotic agent in various cancer cell lines and animal models (Afaq, Saleem et al. 2005; Lansky and Newman 2007; Hamad and Al-Momene 2009).

6. Antidiabetic Properties

Most common metabolic disease in the world is diabetes. According to the World Health Org., it is the 3rd-most prevalent disease after cardiovascular and oncological disorders. The Intl. Diabetes Federation stated that 194 million people had diabetes in 2003, which will increase to 333 million by 2025(Sicree, Shaw et al. 2003). One of the strategies to control diabetes mellitus is through diet. Numerous studies have described that pomegranate fruits and derivatives of its constituents can play an essential part in dietotherapy as antidiabetic agent(Katz, Newman et al. 2007; Bagri, Ali et al. 2009).

7. Antidiarrheal properties

The antidiarrheal effect of pomegranate fruit peel extract in rats was assessed by administering an oral dose of 400 mg/kg and concluded from their experiments that extract decreases the number of defecations and the weight of feces in comparison with the control (Olapour, Mousavi et al. 2009). A similar type of study by Qnais and his colleagues in 2007 demonstrated the antidiarrheal effects of the aqueous extract of pomegranate peels in rats. The results showed that this extract possess a concentration-dependent inhibition of the spontaneous movement of the ileum and attenuated acetylcholine-induced contractions.

TOXICOLOGICAL PROPERTIES

1. Apoptosis

To predict tumor response after anti-cancer treatment apoptosis is a useful marker which is basically a process of programmed cell death. Pomegranate extracts gives punic acid (an omega-5 long chain poly unsaturated fatty acid derived from Pomegranate), has shown to induce apoptosis in both an estrogen sensitive cell line developed from MDA-MB-231 cells (MDA-ERalpha7) and an estrogen non sensitive breast cancer cell line (MDA-MB-231) through PKC (Protein kinase C) signaling pathway and lipid peroxidation (Grossmann, Mizuno et al. 2010). Destruction in cellular mitochondrial membrane has also been observed(Grossmann, Mizuno et al. 2010). The relationship between pomegranate-induced apoptosis in human prostate cancer cells (LAPC4) and the IGF/IGFBP system has also been studied (Koyama, Cobb et al. 2010). Pomegranate (a highly potent Pomegranate extract prepared from skin and arils, minus the seeds) and IGFBP-3 have been shown to synergistically excite the apoptosis.

2. Cell cycle arrest

The cell cycle is a series of events, which consists of four distinct phases; G1 phase, S phase (synthesis), G2 phase (collectively known as interphase), and M phase (mitosis) and because of this cycle cell duplicates. For the verification of processes of each phase multiple checkpoints have been identified which confirms whether the phase has been accurately completed before progression into the next phase or not. Certain types of alterations may result in the cease of cell duplication. Ellagitannins, derived from Pomegranate juice, and their metabolites, urolithins exhibit dose and time-dependent decreases in cell proliferation and clonogenic efficiency of HT- 29 cells through cell cycle arrest in the G0/G1 and G2/M stages of the cell cycle followed by induction of apoptosis(Khan 2009). Previous studies have suggested several mechanisms of cell cycle arrest by pomegranate juice, such as modulation of cell signaling molecules in the cell cycle machinery. Pomegranate treatment induced a dose-dependent arrest in the G0/G1 phase of the cell cycle which was assessed by DNA cell cycle analysis in the lung cancer cell line (A549)(Khan, Afaq et al. 2007). Another study showed that pre-treatment of normal human epidermal keratinocytes (NHEK) with pomegranate increases the cell cycle arrest induced by UVA in the G1 phase of the cell cycle(Syed, Malik et al. 2006).

3. Effects on important enzymes

Enzymes are proteins that catalyze biochemical/chemical reactions. Pomegranate has been shown to inhibit different enzymes including phospholipase A2 (PLA2) (that catalytically hydrolyzes the bond releasing arachidonic acid and lysophospholipids) (Lansky *et al.,* 2005), cyclooxygenase (COX), lipooxygenase (LOX), cytochrome P450(Kimura, Ito et al. 2010) (Kimura *et al.,* 2010) and ornithine decarboxylase (ODC)(Bachrach 2004) (Bachrach *et al.,* 2004) which plays a role in the urea cycle and catalyzes the decarboxylation of ornithine to polyamines such as putrescine. Polyamines standardize the growth processes and enhance the growth of cancer cells (Hora, Maydew et al. 2003). Meanwhile Carbonic anhydrase (CA) that catalyzes the hydration of carbon dioxide to form bicarbonate (HCO3-) is also inhibited(Khalifah 2003). Carbonic Anhydrase inhibitors such as Pomegranate have been shown to inhibit cancer cell growth *in vitro* and *in vivo(Pastorekova, Parkkila et al. 2004)*. Aromatase is an enzyme responsible for a key step in the biosynthesis of estrogens and catalyzes the formation of estrone and estradiol, which is inhibited by Pomegranate (Rahimi *et al.,* 2012). One of the possible mechanisms in which Pomegranate can inhibit breast cancer is its inhibitory effect on aromatase and 17 beta-hydroxysteroid dehydrogenase enzymes (17*β*-HSDs), as well as its antiestrogenic activity. Furthermore, ellagitannins (ET) and urolithin B (UB), which are found in relatively high quantities in Pomegranate, have been shown to most effectively inhibit aromatase activity in a live cell assay(Adams, Zhang et al. 2010). Serine protease is another enzyme which is inhibited by Pomegranate. Serine proteases (SP) are enzymes in which one of the amino acids in the active site is serine. Protease plays an essential role in modulating the turnover of extracellular matrix (EC), which provides morphological support for cell growth and differentiation(Vu and Werb 2000). Punicalagin and ellagic acid, from Pomegranate, have presented lesser inhibitory effects on alpha-secretase (TACE) and further serine proteases such as trypsin, chymotrypsin, and elastase, which indicates that they are relatively particular inhibitors of beta-secretase (BACE1)(Kwak, Jeon et al. 2005). Other studies have shown that catechin and epicatechin (epigallocatechin-3-gallate) (Iwasaki, Ito et al. 2009), which are present in Pomegranate can inhibit SP.

4. Cellular differentiation

In developmental biology, cellular differentiation is a process by which a less specialized cell becomes a more specialized cell type. Studies have shown that Pomegranate stimulates the differentiation of osteoblastic MC3T3-E1 cells and also alters the role of these cells(Kim and Choi 2009). Pomegranate seed oil has been found to stimulate keratinocytes proliferation in monolayer culture and has no effect on the function of fibroblasts thus results as a facilitator for skin repair and promoting regeneration of dermis as well as epidermis (Aslam, Lansky et al. 2006).

DISCUSSION

In this review, we gathered most of the published studies on Pomegranate without date elimination. However, attempts were made to explain the new data. Iran is considered to be the primary origin of Pomegranate. Pomegranate juice, fruit, and extracts have been used widely in the folk medicine of ancient cultures for various medicinal properties. Pomegranate has proven to possess phytochemicals that hold pharmacological and toxicological properties. The information presented in this review article which was obtained from *in vitro*, *in vivo* and clinical trial investigations has shown some of the pharmacological and toxicological mechanisms and properties of Pomegranate. Existence of these pharmacological and toxicological mechanisms and properties and interference of several signaling pathways suggest that Pomegranate can be widely consumed as a potential therapy for prevention and management of several types of diseases including hypertension, leukemia, hyperlipidemia, colon cancer, prostate cancer, breast cancer, lung cancer, skin cancer, and anti-atherosclerosis, myocardial ischemia, myocardial perfusion,

diabetes, oral inflammation, infection, anti-erectile dysfunction, male infertility, neonatal hypoxia, ischemic brain injury, Alzheimer's disease and obesity reducer.

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