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A REVIEW OF BIOACTIVE CHEMICAL CONSTITUENT, FROM POMEGRANATE JUICE, SEEDS, PEELS] IN PROCESS CHEMISTRY

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ABSTRACT

Being an ancient, unique fruit, pomegranate, Punica granatum L, borne on a small, long-living tree. Originated in central Asia, it is cultivated throughout the Mediterranean region, like Himalayas, in Southeast Asia, and in California and Arizona in the United States. The broad range action of the pomegranate indicates the presence of variety of constituents instead of single constituents. Last previous decade studies on the antioxidant, anticarcinogenic, and anti-inflammatory properties of pomegranate constituents have been published, focusing ontreatment and prevention of cancer, cardiovascular disease, diabetes, dental conditions, erectile dysfunction, bacterial infections and antibiotic resistance, and ultraviolet radiation-induced skin damage. Other potential applications include infant brain ischemia, male infertility, Alzheimer's disease, arthritis, and obesity.

Abbreviations: Pop, Pomegranate peel; PoPx, Paraoxonase 1; MMP-9, Metalloprotease-9; TNF, TumorNecrosis.

INTRODUCTION

Punica is a compact genus of deciduous shrubs or small trees that bear fruit. The pomegranate (Punica granatum), originating from the Middle East, is most commonly recognized. It spreads from the Mediterranean to China and India, and from there reaches the American

Southwest, including California and Mexico. The fruit is surrounded by a tough outer layer, inside of which are many arils, with each one enclosing a seed and a sac filled with clear juice.

Thin membranes with a sharp taste spread into the fruit's interior from the pericarp, creating a framework for holding the arils. The fruit is divided into three parts: the seeds, making up 3% of the fruit's weight with 20% oil content; the juice, accounting for 30% of the fruit's weight; and the peels, which contain the inner network membranes. Fruits are consumed worldwide in fresh form, as well as processed into juice, jam, wine, oil, and extract supplements.[1]

In ancient Egyptian society, the pomegranate fruit symbolized success and drive, leading to the tradition of adorning sarcophagi with images of the plant. In Ayurvedic medicine, the pomegranate is seen as a complete pharmacy, with the bark and roots thought to possess properties for expelling worms. The rind is a strong astringent and remedy for diarrhea and oral ulcers, while the juice is described as a cooling agent and blood purifier. Researchers from India and Tunisia[2-7] suggest that dried pomegranate peels can be boiled in water and used internally and externally for various issues that require astringent or germicidal treatments, particularly for conditions like aphthae, diarrhea, and ulcers.

Combining pomegranate seed, juice, and peel products has been shown to have contradictory effects, with reports of both preventing abortion and affecting conception.[8-12] In the Unani medical system, which originated in the Middle East and expanded to India, pomegranate flowers are used to treat diabetes mellitus.[13-14] Contemporary applications of products derived from pomegranates.

Treatment of AIDS is now included with cosmetic beautification and enhancement, hormone replacement therapy, resolution of allergic symptoms, cardiovascular protection, oral hygiene, ophthalmic ointment, weight loss soap, and as an adjunct therapy for diagnostic imaging. Pomegranate is also recognized for its anti-inflammatory and anti-atherosclerotic effects against various health conditions, including osteoarthritis, prostate cancer, heart disease, and HIV-1. The edible part of pomegranate is a rich source of organic acids, soluble solids, polysaccharides, vitamins, fatty acids, and minerals.[15-28]

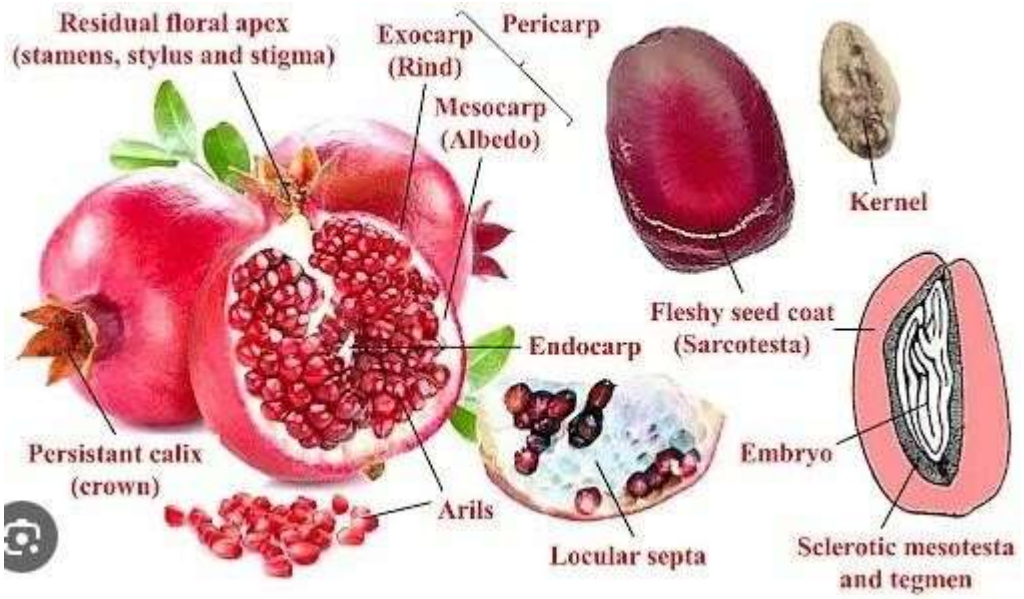

Figure 1: Pomegranate Fruit.

Pomegranate fruits have an irregular rounded shape with coriaceous rinds that vary from yellow, green or pink to bright deep red, depending on the variety and stage of ripening.[29] However, there are some exceptional cultivars such as the black pomegranate. These cultivars acquire black colour very early and remain black until ripening time[30] Internally, pomegranates have a multi-ovule chamber separated by membranous walls (septum) and a fleshy mesocarp. The chambers are filled with seeds called arils. The arils are the succulent and edible portion, which develops from the outer epidermal cells of the seed and elongates to a very large extent in a radial direction.[31] Arils vary in size and in hardness depending on the varieties, while some varieties are referred to as seedless but contain soft seeds. The colour of the arils equally varies from white to deep red depending on the variety. And occasionally, a state of metaxenia does occur wherein there are several seeds of different colour within a pomegranate fruit (Levin 2006). The physicochemical properties of pomegranate fruit cultivars grown in different regions have been reported by several researchers.[32] The physical properties reported include the fruit weight, whole fruit and aril colour, juice content and juice dry matter content. These and other researchers have also shown that the physicchemical properties of pomegranate cultivars vary among agroclimatic regions.[33]

Furthermore, several chemical properties and phytonutrients such as the vitamin C, total phenolics, total tannins and condensed tannins, total soluble solids and anthocyanins in the peel and arils of various pomegranate cultivar have been reported.[33] Deterioration in

Pomegranate Fruit Quality Pomegranate is classified as a non-climacteric fruit.observed that pomegranate fruits had a relatively low respiration rate, which declined with post-harvest to a steady rate of 8 ml^{-1} kg^{-1} h^{-1} for about 3 months and ethylene production was in trace quantity less than 0.2 μl^{-1} kg^{-1} h^{-1}, when stored at 20 °C for 2 weeks. These observed metabolic processes confirms pomegranate as a non-climacteric fruit, being that it exhibits no drastic changes in postharvest physiology and composition.

Additionally, maturation and ripening occur on the plant prior to harvest, fruits harvested before ripening do not continue ripening in storage and are of inferior eating quality.

In spite of the non-climacteric nature of the fruit, quantitative and qualitative loss still occur due to postharvest handling processes, resulting in chilling injuries, husk scalding, weight loss and decay of pomegranate.[34]

Deterioration in Pomegranate Fruit Quality

Pomegranate is categorized as a non-climacteric fruit. It was noted that the respiration rate of pomegranate fruits was relatively low, decreasing to a stable rate of 8 ml−1 kg−1 h−1 over a period of 3 months postharvest. Ethylene production remained at trace levels, less than 0.2 µl−1 kg−1 h−1, after being stored at 20 °C for 2 weeks. The observed metabolic processes provide evidence that pomegranate is a non-climacteric fruit since it does not show significant changes in postharvest physiology and composition. Furthermore, the process of maturation and ripening takes place on the plant before harvest, and fruits that are picked before ripening will not ripen further during storage, resulting in poo eating quality.[29] Despite not being climacteric, pomegranates still experience quantitative and qualitative losses during postharvest handling, leading to issues such as chilling injuries, husk scalding, weight loss, and decay.

Chilling Injury

According to experimental data from the 'Wonderful' cultivar, pomegranate fruit quality is optimal when stored at 5 °C with over 95% humidity for 8 weeks.[29]

Yet, different varieties of pomegranates can be kept for 2 to 7 months at temperatures of 0 to 10 °C. It has been noted that storing pomegranates for over a month at temperatures lower than 5 °C can lead to chilling injury, resulting in various negative symptoms like skin rotting, etiolation, cracking, browning of the rind, necrotic pitting, and discolouration of seeds. A

study has shown that subjecting food to a hot water bath at 45 °C can lowerthe risk of chilling damage and boost the levels of specific fatty acids in the membrane, along with increasing the presence of spermidine and putrescine.[35] Additionally, it has been demonstrated that intermittent exposure of fruits to high temperatures before storage can help to prevent symptoms of chilling injury and fruit decay.[32]

Husk Scald

Husk scald is another postharvest physiological disorder common to pomegranate fruits. It is a superficial browning which is restricted to the husk, with no observable internal changes on the arils or on the white astringent membrane as observed with chilling injury (Ben-Arie and Or 1986). This physiological disorder is suggested to be due to the oxidation of phenolic compounds on the husk when stored at temperatures above 5 °C. Ben-Arie and or (1986) observed a correlation between husk scald incidence and the amount of extractable o-dihydroxy phenols obtained from the affected husk. In line with Ben-Arie and or (1986) they observed that, the most effective control of husk scald in 'Wonderful' pomegranates was the storage of late harvest fruits in 2% oxygen at 2°C. However, the treatment resulted in accumulation of ethanol which led to offflavours in the fruits.

Weight Loss

Beside chilling injury another major storage challenge is the effect of weight loss on the pomegranate fruit, which leads to hardening and browning of the rind and arils[32] Weight loss is regarded as a major cause of loss of visual quality for horticultural products, as excessive transpiration can lead to desiccation, shrivelling, wilting, reduced firmness and crispness and promotes senescence by lowering the endogenous enzymatic processes or regulators and ageing reported weight losses of 1.2–1.3% in shrinkwrapped 'Ganesh' pomegranates stored at 8 °C for 12 weeks and weight losses of 2.2–3.7% for those stored at 15 °C for 10 weeks, in comparison to non-wrapped fruits with weight loss of 20.4 and 30.7% at 8 and 15 °C, respectively. In a similar study, by D' Aquino et al. (2010) they observed that after 6 weeks of storage at 8 °C unwrapped and untreated control 'Primosole' pomegranate hada weight loss of 5.1%, while polyolephinic film-wrapped fruits lost only 0.6%, and weight loss increased up to 12.7% in control as against 3.1% for wrapped fruits after 12 weeks of cold storage.[32] observed weight losses of 1.15% or 1.34% in unpackaged control 'Mollar de Elche' cultivars exposed to thermal treatment prior to storage at 5 or 2 °C for 12 weeks, compared with weight loss of 0.07% in thermal treated fruits packaged in standard polypropylene films at both 5 and

2 °C for 12 weeks.

Chemical Constituent

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.

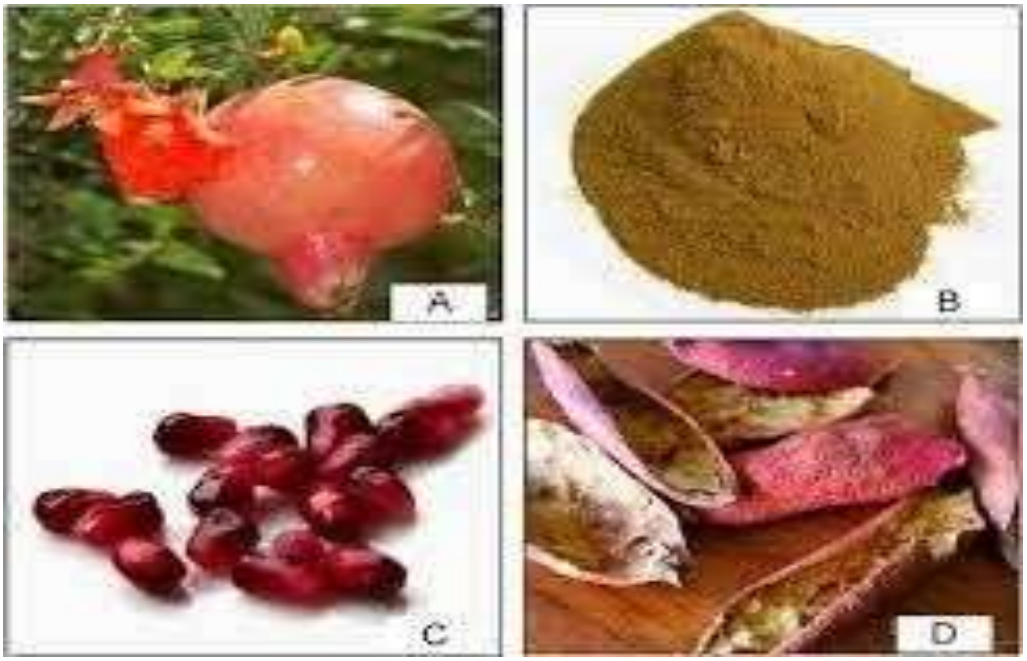

Figure 2: A: Fruit, B: Powder, C: Seeds, D: Peels.

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[38] and declines after pressing.[39-40] 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.[41] The diverse classes of chemical constituents reported from Pomegranate Juice include: Sugars: Glucose, Fructose, Sucrose. Organic Acids: Citric acid, Malic acid, Tartaric acid, Fumaric acid, Succinic acid, Ascorbic acid Cyclitol carboxylic/Hydroxybenzoic acids: Quinic acid, Gallic acid, Ellagic acid Hydroxycinnamic acids: Caffeic acid, Chlorogenic acid, pCoumaric acid Flavan-3-

ols/Flavonoids and their glycosides: Catechin, Epicatechin, Epigallocatechin-3-gallate, Quercetin, Rutin, Anthocyanins: Cyanidin-3-O-glucoside, Cyanidine-3,5-di-Oglucoside, Delphinidin-3-O-glucoside, Delphinidin- 3,5-di-Oglucoside, Pelargonidin-3-O-glucoside, Pelargonidin-3,5-di-Oglucoside.Amino acids: Proline, Valine, Methionine, Glutamic and Aspartic Acid.Indoleamines: Tryptamine, Serotonin, Melatonin . Tocopherols: α- tocopherol. 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[42-43] 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.[44] Seed matrix includes lignins[45] fusion products of cell wall components and hydroxybenzoic/cinnamic acids, isoflavones, and potently antioxidant lignin derivatives.[46] 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). Non-Conjugated fatty acids: Linoleic acid, Oleic acid, Palmitic acid, Stearic acid. Sterols: Stigmasterol, β-Sitosterol, Daucosterol, Camesterol, Cholesterol, 17-α-Estradiol, Estrone, Testosterone, Estriol. Tocopherols: γ-tocopherol (Figure 9). Triterpenes: Ursolic acid, Oleanolic acid. Isoflavones: Genistein, Daidzein. Phenyl aliphatic glycosides/Lignins: Coniferyl-9-O-[β-Dapiofuranosyl(1→6)-O-β-D-glucopyranoside, Sinapyl-9-O-[βD-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.[47] Complex polysaccharides from the peels have been studied and partially characterized.[48] The presence of alkaloids (e.g., pelletierine) in the peel is equivocal, positive by Dragendorff assay, but negative by Mayer assay.[49] The main chemical constituents

isolated from Pomegranate Skin/Pericarp/Peel are: Hydroxybenzoic acids: Gallic acid, Ellagic acid. Hydroxycinnamic acids: Caffeic acid, Chlorogenic acid, pCoumaric acid Cyclitol carboxylic acids: Qunic acid. 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. Anthocyanins: Cyanidin, Pelarginidin, Delphinidin. Ellagitannins: Punicallin, Punicalagin, Corilagin, Casuarinin, Gallagyldilacton, Pedunculagin, Tellimagrandin, Granatin A, Granatin B. Alkaloids: Pelleteriene.

Peel phenolics extraction modelling

Large-scale extraction of phenolic compounds from PoP is conducted using solvents like methanol, ethanol, acetone, chloroform, and ethyl acetate. Polar solvents extract antioxidants better than non-polar solvents. Using solvents other than water for extracting phenolics from peels can result in varying levels of phenolic content and antioxidant activity. Phenolics extracted from dried PoP using ethyl acetate, acetone, methanol and water show increased antioxidant activity, while aqueous extracts display higher anti-mutagenic activity compared to methanolic extracts. Because of methanol's suitable polarity, pomegranate peel methanolic extracts show greater antioxidant properties compared to extracts obtained using different solvents. The solvent type, solid-liquid ratio,extraction temperature, and size of peel particles all play a significant role in determining the efficiency of antioxidant extraction. Tiny peel fragments enhance powder surface area, causing faster solvent transfer among particles, leading to higher antioxidant extraction efficiency. Likewise, the phenolic content and antioxidant activity of PoPx rise as the peel particle size decreases. Separating water in methanol extracts of PoP between 2% acetic acid and ethyl acetate boosts ellagic acid production (7.06–13.63%) and enhances diphenyl-1- picrylhydrazyl (DPPH) radical scavenging ability (38.21–14.91 mg/mL).

Biological Activity of the Chemical Constituents from Pomegranate

Although a complete understanding of how the chemical components of pomegranates relate to their pharmacological effects has not been achieved, there has been substantial progress in the last decade towards a more thorough grasp of some key pharmacological aspects of pomegranates. The whole pomegranate fruit, including its juice, seeds, and peels, is rich in nutrients and is commonly utilized for medicinal reasons. It is suggested that the sweet varieties of pomegranates have a mild laxative effect, while the less sweet varieties are

thought to be beneficial for stomach inflammation and heart pain. The importance of the fruit in medicine can be traced back to ancient times, and it is mentioned in both Egyptian mythology and art. The juice, bark, leaves, immature fruit, and fruit rinds have been found to possess medical benefits such as antioxidant activity, antibacterial properties, and applications in diabetes, heart disease, and cancer. While there are many potential reasons for the wide variety of health benefits of pomegranate, most studies have concentrated on its antioxidant, anticarcinogenic, antibacterial/antimicrobial, and anti-inflammatory properties.

Antioxidant activity

Aviram provided a detailed description of the powerful antioxidant properties of polyphenols, which are the main bioactive components in pomegranate juice. Punicalagin, a primary antioxidant polyphenol found in pomegranate juice, is well-known for its possible effects. In vitro experiments were conducted to assess the antioxidant properties of 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 compared the antioxidant activity of thirty-six common European fruit juices to ascertain their antioxidant capacity and polyphenolic composition.

Antimicrobial/antibacterial activity

Scientists from all around the world have investigated P. granatum's antibacterial and antimicrobial qualities in great detail. It has been discovered that plant extracts are effective against Salmonella typhi, Escherichia coli O157:H7, methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) strains of Staphylococcus aureus, as well as certain strains of streptococci.Therefore, P. granatum-containing alternative medicines may be effective in treating bacterial infections. Using P. granatum as a topical microbicide to prevent HIV is a significant potential usage for its anti-microbial characteristics. Based on in vitro study, P. granatum may be used to make an anti- HIV1 microbicide. The dentistry industry may benefit from P. granatum's antibacterial and antimicrobial properties. The phytotherapeutical P. granatum was evaluated against the streptococci strains of Candida, Staphylococcus mutans, and Streptococcus mitis.

Anti-inflammatory and Anti-cancer activity

It has been demonstrated that some pomegranate plant sections have antiproliferative effects on a variety of tumor cells. In vitro tests on human breast cells have demonstrated the anticancer effects of the polyphenols found in fermented pomegranate juice. Mehta suggested that the polyphenols in juice are not as active as the oil from pomegranates. In their review article, Amin stated that pomegranate fruit, juice, seed, and oil have anti- inflammatory, antioxidant, antiproliferation (growth inhibition, disruption of the cell cycle, and apoptosis) and anti-tumor effects on cancers of the prostate, breast, skin, colon, lung, and oral regions.

The chemical ellagic acid, which is present in pomegranate juice and seed oils, has been shown to have anti-cancer properties against skin, pancreatic, breast, prostate, colon, intestine, oesophagus, bladder, oral, leukemia, liver, and neuroblastoma cancers. The mechanisms of action of ellagic acid are comparable to those of pomegranates. Ellagic acid exhibits synergistic effects when combined with cyclosporine A, 6-gingerol, quercetin, resveratrol, vinorelbine, and selenomethionine.

Wound healing potential

The common elements of the wound healing process that prevail in wounded tissues are epithelialization, antioxidant immunity, and distinctive biochemical characteristics. It is indicated to apply PoPx topically to woundmodels with dead tissue, incisional, and excisional wounds. The healing process of wounds treated with PoPx is characterized by enhanced contraction, breaking strength, and epithelialization of incised wounds, as well as higher hydroxyproline content, dry weight, and breaking strength of granulated tissues.

In tests, topical treatment of PoPx formulated with hydrophilic gel and oral administration of a 100 mg/kg aqueous extract of PoPx to Wistar rats led to considerable improvement in all wound models. PoP extracts including methanol have a strong inhibitory effect on stomach mucosal damage. When 70% methanolic PoMx was given orally to rats with aspirin-induced stomach ulcers at 250 and 500 mg/kg, it prevented the ulcers from progressingby 22.37% and 74.21%, respectively, and by 21.95% and 63.41%, respectively, in rats with ethanol-induced gastric ulcers.

Toxicology Studies of Pomegranate

Since pomegranates have been consumed in many different civilizations for thousands of years, it is generally believed that this fruit is safe. Research on the components of

pomegranates at levels and concentrations frequently used in folk and traditional medicine on animals did not show any harmful effects. Due to the presence of both tannins and alkaloids, Squillaci suggested that consuming the decoction made from the tree bark and, to a lesser extent, the fruit's pericarps, may result in acute gastrointestinal inflammation and possibly death. Vidal stated that it has been demonstrated that consuming whole fruit extracts can result in increased creatinine in vivo and internal organ congestion. It is well known that pomegranate juice inhibits intestine cytochrome P450 3A4. Juice may raise the risk of rhabdomyolysis while taking, Punica granatum allergies exist in certain persons. In recent years, a number of negative pomegranate reactions have been reported, including serious symptoms including anaphylactic shock or laryngeal edema. People who have pomegranate allergies frequently develop sensitivities to other allergens. Patients who have anaphylaxis in the fall and who reside in nations where pomegranates are consumed should be advised that this fruit may be allergenic. Pomegranate seed oil was found to be non-toxic to brine shrimp larvae by Fatope; nevertheless, prolonged ingestion of roughly powdered pomegranate seeds was linked to esophageal issues and severe allergic reactions to the fruit. Punicalagin, a polyphenol antioxidant that is prevalent in pomegranate juice, was tested for toxicity in rats, and the outcomes of the experiment

CONCLUSION

Our knowledge of the relationship between nutrition and human health has changed since it was discovered that plants produce phytochemicals that are hormonally active. Fruit and plant extracts are known to be complex mixtures of several ingredients; in most cases, it is unclear which chemical, or combination of compounds, is responsible for the claimed effects. In addition to addressing several targets, the idea of a whole herb or multiherb preparation may also lessen the toxicity and adverse effects of a single, isolated plant ingredient. Numerous investigations conducted in vitro and in vivo have demonstrated the high nutritional content and possible tissue- specific effect of Punica granatum extract. Evidence is mounting that some chemicals found in fruit or herb extracts.

For instance, it has been shown that the combination of quercetin and ellagic acid, which are both found in pomegranates, has a stronger inhibitory effect on the proliferation of cancer cells than either substance does working alone. We discovered that PME lacked estrogenicity in the uterus and had an antiestrogenic effect on the mammary gland while maintaining the positive effects of estrogen on the skeletal and cardiovascular systems. PME may be the best

SERM, and more research may show that it is appropriate and may be used in estrogen-dependent breast tumors, with positive outcomes in other hormone-dependent tissues. To further prove PME's applicability in HRT, it would be beneficial to look into the long-term effects of the drug in in vivo models of estrogen deficiency. This is because human clinical trials are few, and animal testing and in vitro assays yield a large amount of scientific conclusions. The metabolism, bioavailability, toxicity, and dose/response of these dietary bioactive chemicals, or nutraceuticals themselves, are some important aspects that are still poorly understood. Many clinical trials investigating the possible therapeutic benefits of pomegranate extracts are now underway. It is necessary to look into its possible application as a nutraceutical. Therefore, it is reasonable to assume that many of the unresolved questions regarding the biological effects of Punica granatum extract will soon be resolved.

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