

Role Of Pomegranate Phenolic Antioxidants In Disease Management

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Abstract

Pomegranate (*Punica granatum* L.), a member of the Lythraceae family and a fruit often regarded as a superfood, with a wide range of therapeutic benefits. Its study interest is heightened by the presence of a range of bioactive substances, including ellagic acid, punicalagins, quercetin, rutin, tannic acids, anthocyanins, pedunculagins, catechins, and polyphenols. Anti-inflammatory, Antioxidant, cytoprotective, neuroprotective, anti-angiogenic, anticancerous, anti-diabetic, anti-mutagenic, cardiovascular protective, antibacterial, hepatoprotective anti-ulcerogenic and antifungal potentials are all present in these pomegranate constituents. Natural polyphenol compounds (PCs) from plants have recently attracted the attention of many academics, businesses, and the general public due to their special benefits as pharmaceuticals and preservatives for the physiological system. They can fend against fatal and debilitating conditions including cancer, heart disease, and Alzheimer's. Polyphenols are vital components and play a key part in *Punica granatum*'s anti-oxidant capability. The current chapter focuses on *Punica granatum*'s polyphenolic components and their supporting role in the treatment of various illnesses.

Keywords: Pomegranate, Antioxidant, *Punica granatum*, Polyphenols, Antiinflammatory.

Introduction

The pomegranate, scientifically known as *Punica granatum* L., is a member of the family Punicaceae, which also contains the species *Punica protopunica* (which is native to the Socotra islands) and *Punica granatum* (which is native to the Mediterranean regions and Iran). It is commonly cultivated in the regions of Central Asia, the Middle East, the American Southwest, the Himalayas, and the Mediterranean. [1, 2]. It is believed to have originated in Iran and Afghanistan. Pomegranate trees have a lifespan of more than 200 years and normally grow to heights of between 12 and 16 feet. leaves that have a glossy sheen and blooms that can be red, white, large, or a mix of colours; these blooms have tubular calyxes that eventually develop into the fruit. The pomegranate fruit resembles a grenade and has a skin that is a deep crimson colour and leathery in texture. The calyx of this plant has a structure that resembles a crown. The seeds are contained within a thin layer of a crimson and acidic liquid, which is separated from them by a thin layer of a white membrane called the pericarp [3, 4].

Plant polyphenols are employed extensively as natural antioxidants because they have properties that are anti-carcinogenic, anti-microbial, antioxidant, antiviral, anticancer, anti-inflammatory, antipyretic, and analgesic [5]. Plant polyphenols component (natural antioxidant) has recently attained exceptional significance for its ability to prevent food spoilage, scavenge free radicals, and provide health advantages for a number of disorders [6]. Due to consumer demand, health benefits, and increased public awareness, the global market for polyphenol compounds is expected to grow significantly between 2015 and 2021, from an estimated \$757 million to \$1,121 million. The increased consumption of plants high in polyphenol compounds by elderly and ill people also played a significant impact in the expansion of the global market. The use of preservatives to preserve food has become widespread and is essential to the food industry. Consumer demands for natural food preservatives are still rising despite the fact that numerous types of preservatives have been used to protect food. Meat is very sensitive to microbial deterioration since it has a high-water content and a lot of nutrients on its surface. Meat deterioration typically results from microbial activity and the oxidation of meat lipid and protein. Meat can be preserved in a number of ways, including by using various chemicals and natural ingredients to inhibit microbial and oxidative

processes. Additionally, consumers have recently increased their demand for healthy food free of chemical ingredients and preservatives. It has been suggested to integrate new, risk-free processing techniques with organic antioxidants and antimicrobials [7, 8]. There are two types of preservatives: artificial and natural. Toxicology and carcinogens are caused by artificial preservatives. Therefore, natural antioxidants are preferred by businesses and consumers for food preservation. Fruit and various plants with high levels of phenolic chemicals can be employed as antioxidants or preservatives. All portions of the pomegranate contain a high concentration of antioxidants, making it one of the fruits with the strongest antioxidant capabilities. The peel of the pomegranate is a respectable source of flavonoids, anthocyanins, and tannins [9]. Pomegranate is one of many common fruits that possesses significant antioxidant qualities, according to a study by am et al. Polyphenol compounds have been extracted from many different kinds of plants using a variety of techniques. A common technique is to extract using a Soxhlet device and a separate polar solvent such water, methanol, ethanol, or ethyl acetate. Other advanced extraction methods such as ASE (accelerated solvent extraction), UAE (ultrasound-assisted extraction), SFE (supercritical fluid extraction), HHPE (high hydrostatic pressure extraction), and MAE (microwave-assisted extraction), have all produced a wide range of quantitative and qualitative findings. However, creating a special standard process for extracting many plant species remains difficult. Researchers are looking for an effective, economical, and environmentally friendly way to extract polyphenols [10, 11].

Applications of Pomegranate

As a result of the fact that traditional Persian medicine places a significant emphasis on modifying one's diet in addition to other parts of one's lifestyle, eating should always come first before taking any kind of medication [12]. There has been a lot of research done on the nutritional value of pomegranates, and these studies have shown that they have properties that make them an excellent candidate for use in food additives and preservatives. These properties include antioxidant and antibacterial properties, as well as a high pectin and fibre content. Waste materials (peels), in addition to having a unique hue, would be an excellent alternative for food packaging due to the activity of plasticizing, strengthening, and elongating [13]. Pomegranate is believed to be a cardiac tonic and has been used in traditional medicine to treat a variety of conditions, including dysentery, diarrhoea, haemorrhoids, sore throats, intestinal parasites, epistaxis, diabetes, and vaginal itching [14]. In addition to this, it is currently being utilised in the treatment of a broad variety of diseases. Many of the traditional qualities of medicinal plants have been proven by contemporary research, which makes these plants a source for producing novel pharmaceutical formulations [15]. The pandemic caused by COVID-19 is currently being regarded as a hazard to public health all around the world. There is currently no cure or treatment that is unique to COVID19. There are currently a great deal of clinical and preclinical studies being carried out in order to investigate a gold-standard medication that has a high potential for efficacy but only a small number of potential negative effects [16]. Pomegranates are generally acknowledged to be the primary supplier of important components including flavonoids, magnesium, potassium, and iron. Pomegranates are also a rich source of antioxidants [17]. In vitro studies showed that an aqueous extract of pomegranate peel was effective at inhibiting COVID19 viral replication. Consumption of pomegranate juice (PJ) has been suggested as a potential prophylactic as well as treatment method for COVID-19 [18]. More clinical study needs to be carried out in order to evaluate the effect that pomegranate may be having on the ongoing COVID 19 epidemic. In the current research, we investigated the clinical applications of pomegranates, specifically how they are used to treat and prevent a variety of diseases [19, 20].

Chemical Constituents of *P. granatum* Fruit

Polyphenols: Hydrolysable tannins, such as ellagitannins, gallotannins, hydroxycinnamic acids, gallagyl esters and hydroxybenzoic acids, are the principal types of polyphenols found in pomegranates. Punicalagin, the primary component of ellagitannins, is mostly present in the pericarp, bark, flowers, and seeds that have been separated by preparative HPLC. Pomegranate also contains pedunculagin isomers that have been discovered by MS and/or NMR, as well as punicalin A and B. By using HPLC and NMR techniques, several acids from pomegranates have been identified [21, 22].

Anthocyanosides

Another essential substance found in the flower and fruit is anthocyanoside, which gives arils their red colour. The major anthocyanins identified by nuclear magnetic resonance and high-performance liquid chromatography

are cyanidin 3-rutinoside, cyanidin-3-glucoside, cyanidinpentoside, cyanidin-3, 5-diglucoside, delphinidin-3-glucoside, pelargonidin-3, 5-diglucoside, and pelargonidin-3-glucoside. Moreover, cyaniding [23, 24].

Other Chemical constituents

Pomegranate leaves and pericarp have been discovered to contain flavonols and flavones by NMR and IR, including catechin, gallic acid, epicatechin, quercetin, apigenin, and kaempferol. Alkaloids were discovered by GLC-MS and organic acids were explained by UHPLC-MS and NMR. Additionally, lignans, minerals, ursane and oleanane triterpenes as well as steroids, were isolated from pomegranates and identified by LC-MS, GC-MS and HPLC-DAD [25, 26].

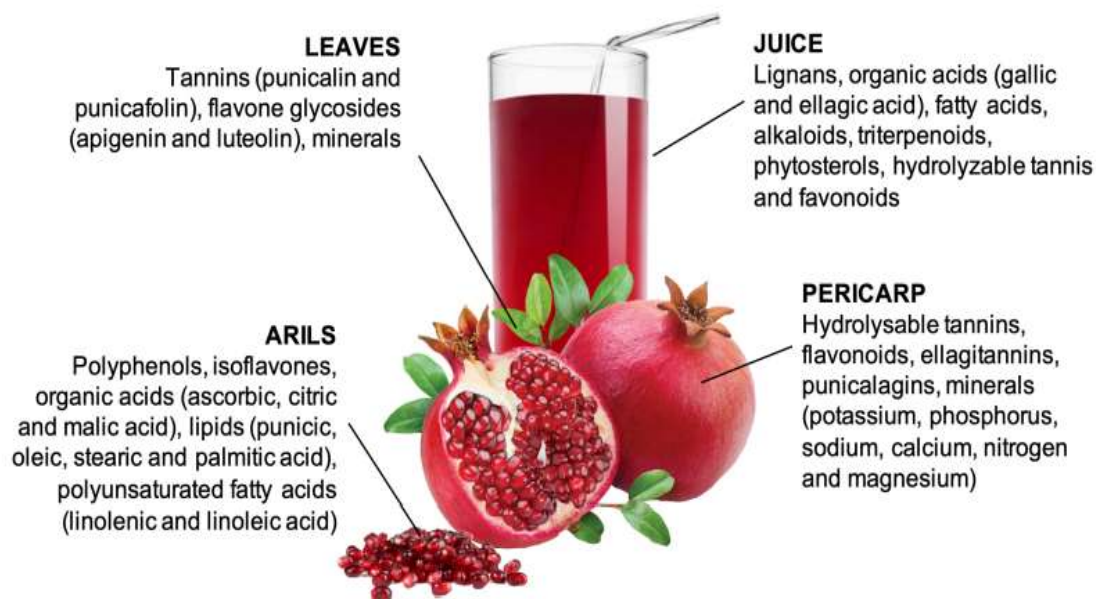


Figure 1: Chemical constituents of pomegranate

Antioxidant mechanism

Pomegranate extracts were shown to have antioxidant activity that was two- to three-times higher than that of red wine or green tea, according to a recent scientific study. Pomegranate extracts have been shown to boost the plasma antioxidant capacity of humans, as well as lessen the amount of lipid peroxidation and oxidative stress that macrophages experience in experimental animal models [27]. In studies that used animal models, it was found that extracts of pomegranate that were made using the whole fruit but left out the juice had antioxidant properties. These extracts were tested on mouse peritoneal macrophages (MPM), where they demonstrated a 53% increase in reduced glutathione levels and a 20% reduction in oxidative stress. It was shown that the antioxidant content of fermented pomegranate juice extract was significantly higher than that of extracts of red wine and green tea. In another experiment, pre-treating pomegranate peel extract with catalase and super oxide dismutase enhanced the enzymes' ability to scavenge free radicals and reduced lipid peroxidation by 50% compared to rats who weren't treated and had carbon tetra chloride cause damage to their livers. This was compared to rats who weren't treated and had carbon tetra chloride cause damage to their livers [28].

Apple juice has been shown to have a lower antioxidant capability than PPJ, according to a study that was conducted utilising PPJ on humans. According to the findings of a second study, the plasma antioxidant capacity of healthy individuals who consumed 250 millilitres of PPJ on a daily basis for a period of four weeks saw a rise from 1.33 millimoles to 1.46 millimoles. People who drank apple juice, on the other hand, did not exhibit any discernible alterations in their antioxidant capabilities. The concentrations of vitamins E and C, as well as reduced glutathione, did not change substantially between the groups. The results of this research strongly suggested that the surprising discoveries may have been caused by secondary metabolites found in pomegranates [29].

Typically, a succession of chain reactions that are started, propagated, and stopped by free radicals constitute the autoxidation process. From a molecular perspective, antioxidants can be generally categorised into major and

secondary types [30]. Primary antioxidants, also known as chain-breaking antioxidants, are known to be radical scavengers. This is due to the fact that they provide peroxy free radicals with the reactive hydrogen that they require in order to create products, therefore disrupting radical chain sequences in the process. Hydroperoxides and secondary antioxidants, which are often also referred to as hydroperoxide decomposers, combine with one another to form byproducts that are not reactive [31]. When two different categories are combined, there is the potential for stabilising effects. According to research conducted on antioxidants, anthocyanins have the potential to serve as radical scavengers, reducing agents, hydrogen donors, metal chelators, and singlet oxygen quenchers. Reducing activity, quenching single oxygen, scavenging lipid peroxy radicals, complexing pro-oxidants, and scavenging free radicals are some of the strategies that fall under this category. Flavonoids, which are typically considered to be powerful antioxidants, display their antioxidant activity through three primary processes: radical scavenging, metal chelation, and interactions with other antioxidants. Radical scavenging is the most important of these methods [32]. The majority of earlier investigations have attempted to elucidate the two ways that anthocyanins act as antioxidants: by scavenging free radicals and by inhibiting the creation of new radicals by chelating metals, particularly iron. Pomegranate peel reportedly has minimal chelating action despite being a significant radical scavenger, indicating that it has high primary antioxidant activity but poor secondary antioxidant activity. On the other hand, Orak et al. showed that the ability of pomegranate peel, juice, and seed to chelate metals was considerably influenced by the cultivar and solvent. As a result, the antioxidative potential of pomegranates as measured by metal chelation activity is yet unknown [33, 34].

Pomegranate peel polyphenol compounds

The main natural source of antioxidants may be pomegranate peel, and its extract has a comparatively high antioxidant activity [35]. Pomegranate peel has been utilised for various illnesses since ancient times due to its excellent therapeutic capacity. It contains great nutritional value, including vitamins A, B6, C, E, folate, potassium, and oxalic acid, in addition to its therapeutic properties. More therapeutic properties of pomegranate peel, including its abortifacient, analgesic, anti-amoebic, antibacterial, anticonvulsant, antifungal, antiviral, antispasmodic, diuretic, hypoglycemic, hypothermic, and antioxidant activity, have been researched recently [36]. According to Li et al., the peel of the pomegranate contains 63 high molecular weight phenolic compounds, as well as proanthocyanidins, ellagitannins, complex flavonoids, polysaccharides, and significant amounts of microelements. Each of these components possesses potent anti-mutagenic, antioxidant, antimicrobial, and antiapoptotic properties. About half of the weight of a pomegranate is made up of the peel [37].

Antioxidant Activity

Pomegranate peel extracts have potent antioxidant and phytochemical properties. Pomegranate peel extract's strong antioxidant capacity may be due to the primary polyphenolics it contains, like asellagic acid activity. Singh et al. provided the explanation for the very first report of the antioxidant activity of pomegranate peel extract [38]. The antioxidant capacity of pomegranate peel extract is ten times more than that of pulp extract. Pomegranate peel extract also has a remarkable ability to neutralise superoxide and hydroxyl radicals. The antioxidant and aldose reductase-suppressing properties of pomegranates have been cited as two of the benefits associated with their consumption. Pomegranate products, such as juice, peel, and seed oil, are rich sources of polyphenolic chemicals, which give them powerful antioxidant capabilities. These substances are found in pomegranate. Extracts of pomegranate peel contain cyclooxygenases and lipoxygenases, two types of enzymes that have the ability to reduce the activity of enzymes that are involved in the production of inflammation. Polyphenolic flavonoids have been shown to have an antiatherogenic impact in research that has been conducted using rats with liver impairment in both in vitro and in vivo settings. Polyphenolic flavonoids suppress atherogenesis and prevent macrophages from oxidising LDL [39]. Polyphenolic flavonoids also have anti-inflammatory properties. According to study carried out by Al-Olayan and colleagues using a rat model, drinking pomegranate juice bolsters the body's natural antioxidant defences, which in turn protects against the reproductive damage caused by carbon tetrachloride (CCl₄). Because of this, it is possible that it could be utilised as a treatment for conditions that are caused by free radicals. An in-vivo study on rats that were administered the fruit found that the pomegranate peel offered some protection against the effects of carbon tetrachloride (CCl₄) poisoning. The expression of matrix metalloproteinases (MMPs) and the tissue damage produced by interleukin-1 (IL-1) may be reduced by the use of an extract of pomegranate pulp, which has the ability to do so. Pomegranate extracts contain phytochemicals that

have the power to give free radicals hydrogen, according to Barathikannan et al. Extract from pomegranate peel has the ability to convert the stable radical diphenylpicrylhydrazyl (DPPH) into the more reactive diphenylpicrylhydrazine. Pomegranate peel extract can give protons when it aggregates with hydroxyl groups to stabilise free radicals, which may explain why it is so effective at neutralising DPPH radicals [40, 41].

Pomegranate can be used as a table fruit or juice in human nutrition because of its antioxidant capabilities, They make their presence known through the many different contributions made by lipophilic and hydrophilic components. The rinds, which are generally thrown away but have the most antioxidant activity, produced aqueous extracts that were nearly as effective as the complete rind. This indicates that it may be possible to use this type of extract as an additional supply of antioxidant components in the diets of humans [42].

Anti-inflammatory Action

Inflammation is the first line of defence that the human immune system employs in its fight against harmful microorganisms and damaged tissue. The occurrence of it passes through phases that might be acute as well as chronic. However, if it lasts for an extended period of time, inflammation can be detrimental to the body. Several diseases, including inflammatory bowel disease, rheumatoid arthritis, and chronic obstructive pulmonary disease, have been associated to persistent inflammation. Dysfunctional inflammatory responses have been related to many other non-communicable diseases such as obesity, diabetes, insulin resistance, atherosclerosis, and neurological disorders. According to the results of numerous studies conducted by scientists over the course of several decades, Chronic illness risk is reduced with a diet high in fruits and vegetables. The interest of the scientific community has been piqued by the fact that the bioactive components found in these functional foods have the ability to preserve overall health. As a result, a growing number of researchers have investigated the potential anti-inflammatory effects of pomegranates and their derived compounds [43].

Both punicalagin and ellagic acid, the two most essential pomegranate pericarp polyphenols previously identified, have demonstrated anti-inflammatory properties. Punicalagin's concentration has been determined to be 464.48 mg/g, whereas ellagic acid's concentration is 71.50 mg/g. Using a murine megaphage cell line (RAW264.7), The polyphenol content of pomegranate pericarp was 57.09%, punicalagin was treated at 0.100 M, ellagic acid was treated at 0.100 M, and both were treated with polyphenols at 0.200 g/ml [44]. During inflammatory processes, nitric oxide (NO) and prostaglandin E2 (PGE2) are two important mediators that are typically elevated. In a concentration-dependent manner, all of the investigated polyphenols significantly decreased the levels of both of these mediators. Similarly, Both COX-2 and iNOS (inducible nitric oxide synthase) production were inhibited by all treatments [45]. These enzymes are crucial for the formation of an inflammatory response. Researchers looked on the creation of pro-inflammatory cytokines in the same cell line. There was a marked decrease in the production of interleukin (IL) 1, IL 1, and IL 6 after pomegranate phytochemicals were given. Finally, we looked into whether or not pomegranate triggered or inhibited the mitogen-activated protein kinases (MAPKs) pathway. After treatment with polyphenols, the expression levels of p38 MAPK, Jun N terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) decreased significantly. According to the previously described in vitro study, even the inedible portions of pomegranates exhibit anti-inflammatory properties. This finding suggests that the pericarp of pomegranates may be beneficial in the development of novel organic therapies for inflammatory processes [46].

Anti-aging properties

Numerous clinical problems, such as osteoporosis and neurological disorders, are brought on by the biological process of ageing. The main cause of neurodegenerative illnesses is the gradual death of brain cells brought on by the buildup of misfolded proteins, a class of proteins with altered physicochemical properties [47, 48]. Key factors in the development of neurodegenerative diseases include proteins such as Synuclein in Parkinson's, amyloid in Alzheimer's, huntingtin in Huntington's, prion protein in Creutzfeldt-Jakob, and superoxide dismutase 1 in amyotrophic lateral sclerosis are all proteins implicated in neurodegenerative disorders. It is essential to develop novel, effective preventive strategies as well as novel, effective therapies for cases that are discovered because the clinical manifestations of these illnesses often don't occur until after a certain amount of time has passed since their origin. In a decade's worth of research, pomegranate and its derivatives have emerged as a potential adjuvant for the prevention of neurodegenerative disorders [49–51].

Conclusion

Numerous substances, such as polyphenols, alkaloids, and vitamins with strong free radical scavenging activities, can be found in pomegranates. Free radicals have the potential to generate oxidative stress, which can harm biomolecules and result in a variety of chronic diseases, including cancer, diabetes, atherosclerosis, Alzheimer's disease, nephrotoxicity, hepatotoxicity, pain, and other degenerative conditions. The presence of certain substances, such as phenolic compounds and ascorbic acid, such as punicalin, punicalagin, gallic acid, anthocyanins and ellagic acid, has been linked to the pomegranate's antioxidant action. The most prevalent polyphenols with significant free radical scavenging abilities are pomegranate tannins, particularly ellagitannins. Bacteria in the intestine transform punicalagins and ellagitannins into urolithins, which have antioxidant properties. Anthocyanins, such as cyanidin, pelargonidin glycosides, and delphinidin, which have strong antioxidant activity, are thought to be responsible for the pomegranate juice's red colour. The development of fruits has an impact on these substances with antioxidant action. The earliest fruits (20 days) have been found to have the highest antioxidant activity. Because the amount of ascorbic and phenolic acids decreases as the fruit ages, the antioxidant activity decreases. Additionally, different pomegranate plant kinds have varying antioxidant activities. Because of this, different pomegranate kinds might not have the same therapeutic properties, and it is best to eat them when they are still young and fresh.

Declarations

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Not applicable.

Consent for publication:

All the authors approved the manuscript for publication.

Availability of data and material

All required data is available.

Competing interests

All authors declare no competing interests.

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