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# Pomegranate as a natural source of phenolic antioxidants: a review

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## Abstract

Pomegranate, a recognized source of phenolic compounds, has been associated with health-promoting benefits, mostly due to its antioxidant activity. Ellagic and gallic acids, anthocyanins, and ellagitannins are the main phenolics in pomegranate, showing antioxidant activity. For this reason, pomegranate has been used in foods, such as meat products, as an attempt to retard lipid oxidation and increase shelf-life. In recent years, *in vitro*, *in vivo*, and human studies reported the antioxidant activity of pomegranate, especially its peels, with reduced incidence of chronic diseases (e.g., cardiovascular ailments, cancer, neurodegenerative disease, type 2 diabetes, chronic kidney disease). This review aims to present the main antioxidant compounds on pomegranate and their biological effects, the antioxidant activity of pomegranate-based foods, the application of pomegranate as a natural antioxidant food additive, the role of pomegranate in the prevention and management of chronic diseases, as well as the trends and prospects regarding the application of pomegranate in innovative food and health.

**Keywords**: Ellagitannins; Anthocyanin; Antioxidant; Polyphenols.

## 1. Introduction

Existing data suggest that between 16–57% of adults in developed countries develop two or more chronic non-communicable diseases simultaneously. The increasing incidence of these conditions has encouraged scientific research in this field (Hajat and Stein, 2018). Reports have shown that the accumulation of free radicals (FR) in the human body as a result of environmental, lifestyle, and pathological conditions contribute to an increased risk of chronic non-communicable diseases such as type 2 diabetes mellitus, Alzheimer's, cancer, and cardiovascular diseases. This accumulation often results in an imbalance of reduction-oxidation homeostasis that is likely one of the processes that regulate gene expression in such pathological conditions (Wilcox et al., 2004).

In order to diminish oxidative stress, research has focused on foods and natural compounds displaying antioxidant activity (AA) that can contribute to delay or prevent oxidation. With that being said, epidemiological studies point out a significant inverse relationship between regular consumption of fruits and vegetables and a decrease in the incidence of chronic non-communicable diseases. This correlation is a result of the biologically active antioxidants present in these foods carrying the potential to protect cells and tissues against damage caused by FR (Magrone et al., 2012; Frozza et al., 2013; Kandylis and Kokkinomagoulos, 2020).

Among the sources of bioactive compounds, pomegranate (*Punica granatum* L.), one of the most traditionally consumed fruits worldwide, stands out for being associated with health-promoting

benefits linked to its consumption. These biological properties have been attributed mainly to the phenolic compounds (PC) present in this fruit (Ismail et al., 2017). Given that oxidative stress is a biomarker for numerous chronic non-communicable diseases, the high *in vitro* AA of pomegranate has stimulated studies aiming at investigating its effects on human health (Islam, 2016).

Pomegranate is widely promoted, with or without scientific support, to consumers as a superfood capable of fighting a variety of diseases. This fruit, which has been consumed and used as a functional food in the Middle East for thousands of years, has recently gained global popularity (Johanningsmeier and Harris, 2011).

Pomegranate is usually consumed fresh, with the skin being discarded as waste. Pomegranate peel (PP) corresponds to about 50% of the total weight of the fruit, and it is a source of PC, such as ellagic acid (EA) and its derivatives, and ellagitannins, such as punicalin and punicalagin (Gullon et al., 2016). Moreover, PP presents up to 10 times more bioactive compounds than pulp and seeds (Li et al., 2006). Therefore, pomegranate extracts are used as food additives on meat products, typical Brazilian pastry product and others (Veloso et al., 2020).

Therefore, this review aims to highlight the current state-of-the-art concerning the phenolic composition of pomegranate, the antioxidant potential of pomegranate-based foods, the use of PP as a natural antioxidant, its biological effect on the prevention of chronic diseases, as well as to suggest future trends and prospects about the application of pomegranate in new functional foods.

## 2. Pomegranate

Pomegranate has been used in traditional medicine since ancient times. This species was described by Linnaeus in 1758, who suggested the following classification: Kingdom: Plantae, Order: Myrtales, Family: Lythraceae, Genus: *Punica* Species: *Punica granatum*. It is a small tree or shrub originated in the region encompassing Iran to Afghanistan, from where it spread to India and the Mediterranean and can grow up to 8 m tall (Andrade et al., 2019; Kyriacou et al., 2020).

Currently, there are more than 500 cultivars of pomegranate all over the world (Kandylis and Kokkinomagoulos, 2020), grown in Tunisia, Turkey, Spain, Egypt, Morocco, USA, China, India, Argentina, Israel, and South Africa (Singh et al., 2018), as well as Portugal and Brazil at a less extent. The increased production and consumption of pomegranate fruit may be related to the mounting evidence of its numerous benefits to human health, especially in what comes to the prevention and/or reduction of risk factors for chronic diseases (Akhtar et al., 2015; Yang et al., 2016; Singh et al., 2018), such as cancer (Hertog et al., 1997), atherosclerosis (Al-Jarallah et al., 2013) and Alzheimer's (Subash et al., 2015; Morzelle et al., 2016).

The pomegranate tree thrives under arid and semi-arid conditions (Robert et al., 2010). In Asia, pomegranate has economic and cultural importance due to its high profitability and easy adaptation to various agroclimatic conditions, being commercially cultivated in the subtropical, tropical, and temperate regions of the continent (Bhatia and Asrey, 2019). Similarly to the majority of fruits, the chemical composition of pomegranate fruit varies according to soil and climate conditions where the plant is grown, as well as the fruit's maturation stage at harvest period (Andrade et al., 2019).

Pomegranate is a round-shaped edible fruit of 5–12 cm in diameter, with thick skin, usually pink or red. The core of the fruit has a spongy white tissue that creates spaces full of edible bags, known as arils (Christaki et al., 2011; Kandylis and Kokkinomagoulos, 2020;). The approximate ratio of peel, arils, and seeds is described to be 50:40:10 (Andrade et al., 2019).

## 3. Pomegranate as functional food

The biological role of pomegranate has been attributed, at least in part, to the presence of PC, mainly gallic acid (GA), ellagic acid (EA), hydrolysable and condensed tannins as well as anthocyanins, potent antioxidants (Ambigaipalan et al., 2016; 2017). These compounds have been related to numerous health effects, including the prevention of Alzheimer's disease, cancer, cardiovascular disease, and diabetes (Johanningsmeier and Harris, 2011; Salgado et al., 2012; Shahidi et al., 2019). They will be presented and discussed below.

### *3.1. Phenolic compounds (PC)*

PC are a large group of natural antioxidants commonly found in plant material, especially fruits. They can modulate gene expression, inflammation, antioxidant, and immune functions, exerting a strong influence on human health (Tota et al., 2010; Kang et al., 2011). PC are secondary plant metabolites derived from the shikimic and malonic acid pathways. In foods, they can occur as soluble (free or esterified to fatty acids) or insoluble-bound (covalently bound to proteins, cellulose, pectin, among others) compounds. Structurally, they present at least one aromatic ring substituted with one or more hydroxyl groups, and their AA is related to the number and position/distribution of such groups (Giada, 2013; Shahidi and Ambigaipalan, 2015). The antioxidant action of phenolics comes from their ability to scavenge FR through the donation of a hydrogen atom, which derives from the hydroxyl groups. In general, the higher the number of hydroxyl groups with no steric hindrance in the molecule, the greater the antioxidant potential. Besides, based on structural features, phenolics can be grouped into several sub-classes (e.g., flavonols, phenolic acids, anthocyanins, proanthocyanidins, hydrolysable tannins), yielding different properties (Shahidi and Ambigaipalan, 2015).

The concentration of phenolics changes according to pre-harvest (cultivation, harvesting, and weather conditions) and post-harvest (storage and transport) conditions (McCune et al., 2011). Derakhshan et al. (2018) evaluated pomegranate seed, peel and pulp from different regions of Iran (Natanz, Shahreza and Doorak), and found that PP of Doorak has 50% more AA compared with the other regions. Likewise, the characteristics of the solvent used to extract the compounds, as well as the operational conditions used to concentrated fruit-based extracts, have a strong influence on the nature of the obtained compounds.

The main PC found in pomegranate are shown in Table 1.

#### 3.1.1. Phenolic acids

GA and its dimer derivative EA are phenolic acids belonging to the derivatives of benzoic acid class (Shahidi et al., 2019). GA has a low molecular weight, and it is formed by an aromatic ring carrying three hydroxyl groups and a carboxylic acid group. It has antioxidant, anticarcinogenic, and antimicrobial activity, as well as protection of cells against oxidative stress, being one of the primary phenolic acids in vegetables and fruits, such as pomegranates. The concentration of GA in pomegranate juice is significantly lower when compared with the peel (Fernandes and Salgado 2016; Dludla et al., 2018; Choubey et al., 2018).

**Table 1. Phenolic compounds (mg·g$^{-1}$) of pomegranate pulp and peel**

| | Pulp | Peel | Reference |
|---|---|---|---|
| *Anthocyanin* | | | |
| Delphinidin-3,5-diglucoside | 9.43 | 50.64 | Morzelle et al., 2019 |
| cyanidin-3,5-diglucoside | 5.57 | 0.021–23.57 | Morzelle et al., 2019, Mehrizi et al., 2017 |
| cyanidin-3-glucoside | 0.76 | 0.007–22.83 | Morzelle et al., 2019; Mehrizi et al., 2017 |
| pelargonidin-3,5-diglucoside | 0.87 | 0.005–8.05 | Morzelle et al., 2019, Mehrizi et al., 2017 |
| *Hydrolyzable tannins* | | | |
| Punicalagin A | 0.063 | 1.48–7.5 | Morzelle et al., 2019, Rahnemoon et al., 2018 |
| Punicalagin B | 0.066 | 2.38–6.24 | Morzelle et al., 2019, Rahnemoon et al., 2018 |
| *Phenolic acids* | | | |
| Gallic acid | 0.07–0.19 | 0.025–1.01 | Morzelle et al., 2019, Li et al., 2016, Song et al., 2016 |
| Ellagic acid | 0.54–2.11 | 0.029–7.07 | Li et al., 2016, Song et al., 2016 |
| Chlorogenic acid | – | 0.004 | Song et al., 2016 |
| *p*-coumaric acid | 0.006 | 0.023 | Morzelle et al., 2019 |
| *Flavonoids* | | | |
| Catechin | – | 12.8 | Ambigaipalan et al., 2016 |
| Epicatechin | 0.019 | 0.010–0.198 | Morzelle et al., 2019; Song et al., 2016 |
| *Soluble Procyanidins* | | | |
| procyandin dimer | 42.1 | – | Ambigaipalan et al., 2016 |
| procyanidin dimer B1 | 9.09 | – | Ambigaipalan et al., 2016 |
| procyanidin dimer B2 | 27.8 | – | Ambigaipalan et al., 2016 |
| procyanidin dimer B3 | 37.9 | – | Ambigaipalan et al., 2016 |

The biological effect of GA has been previously studied. Liu et al. (2020a) investigate the neuroprotective effect of daily orally administered GA. Adult male Sprague Dawley rats (250–350 g) were randomly divided into three groups (n = 7/group) treated either with saline solution (control group) or orally administrated GA at 50 mg/kg or 100 mg/kg via an intragastric needle 1 h prior to an intranigral infusion of lipopolysaccharides (LPS), 4µg/µL, to induce neuroinflammation. The animals continued to receive GA daily for another seven days, and after this period, they were sacrificed by decapitation. Administration of GA (100 mg/kg) significantly reduced the effects caused by the LPS-infused in the substantia nigra of rat brain. More specifically, GA attenuated LPS effects in glial fibrillary acidic protein (a biomarker of activated astrocytes), ED-1 (a biomarker of activated microglia), inducible NO synthase (a pro-inflammatory enzyme) and interleukin 1β (IL-1β) (a pro-inflammatory cytokine). The results also showed that GA was capable of inhibiting LPS-induced oxidative stress and protein conjugation since it attenuated LPS-induced elevation in heme oxygenase-1 level (a redox-regulated protein) and α-synuclein aggregation (a hallmark of central nervous system neurodegeneration). Furthermore, GA inhibited LPS-induced apoptosis and necroptosis in the nigrostriatal dopaminergic system of rat brain by avoiding LPS-induced caspase 3 activation (a biomarker of programmed cell death) and LPS-induced increases in receptor-interacting protein kinase (RIPK)-1 and RIPK-3 levels (biomarkers of necroptosis). Therefore, these outcomes suggest that GA at 100 mg/kg contributed to the reduction in oxidative stress and the inhibition of neuroinflammation. Other authors (Bai et al., 2020; Panghal et al., 2020; Trivedi et al., 2020; Abdel-Moneim et al., 2017) also confirmed the antioxidant potential of GA.

EA can be found in the free form (less frequent), glycosylated, or as an ellagitannin. This phenolic acid can be encountered in various fruits, such as strawberry, red guava, persimmon, raspberry, plum, and pomegranate. EA has four rings in its structure, consisting of two phenols with two hydroxyl groups each. Studies have demonstrated its anti-inflammatory and AA, which results in the prevention of several chronic diseases (Ismail et al., 2012; Shakeri et al., 2018; Lima et al., 2019).

Allam et al. (2016) verified the protective effect of EA in male MF1 rats (n = 15/group) with induced friction through the subcutaneous application of 0.02 mL of Complete Freund's Adjuvant (CFA) containing heat-killed *Mycobacterium tuberculosis* in a concentration of 5 mg/mL. For this evaluation, the rats were divided into four groups: normal control group (treated with 2% dimethyl sulfoxide-DMSO), normal treatment group (treated with EA), control group with arthritis (2% DMSO + CFA) and arthritis treatment group (CFA + EA). The animals received EA (700 mg/kg) intraperitoneally, divided into three injections a week (58.33 mg/kg each) for four weeks. The treatment began one week before the induction of arthritis by CFA and continued for three weeks after the induction of arthritis. At the end of the experiment, the animals were sacrificed, and serum levels of IL-1β, interleukin 10 (IL-10), interleukin 17 (IL-17), tumor necrosis factor α (TNF-α), interferon-gama (IFN-γ), and transforming growth factor beta (TGF-β) were measured. EA contributed to the downregulation of

pro-inflammatory cytokines and upregulation of anti-inflammatory cytokines. Serum levels of IL-1β, TNF-α, and IL-17, which are pro-inflammatory cytokines, were reduced. However, serum levels of IL-10 and IFN-γ significantly increased, while serum levels of TGF-β did not significantly alter with EA treatment. Other recent studies (Chen et al., 2016; Baluchnejadmojarad et al., 2017; Liu et al., 2020b;) have confirmed the antioxidant and anti-inflammatory potential of EA.

#### 3.1.2. Hydrolysable tannins

Hydrolyzable tannins comprise intermediate to high-molecular-weight phenolics, weighing up to 30,000 Da. Their structure is composed of esters of GA (gallotannins) or EA (ellagitannins) with a glucose core, being readily hydrolyzed by acids or enzymes into monomeric products (Shahidi et al., 2019). Their gastrointestinal (GI) tract absorption is slow, and they are hydrolyzed into several other compounds, such as EA and its derivatives (e.g., urolithins). Hydrolyzable tannins occur naturally in fruits, such as strawberries, raspberries, blackberries, and pomegranates. Ellagitanins and gallotannins are heavily present in seeds, pericarp, and peel of pomegranate (Rodrigues et al., 2019; Kandylis and Kokkinomagoulos, 2020).

Punicalagin belongs to the ellagitannins group and gives the pomegranate skin its yellow color. This compound can also end up in pomegranate juice during the fruit's processing. Studies report anti-cancer, anti-inflammatory, and antioxidant properties (Cerdá et al., 2003; Berköz and Allahverdiyev, 2017; Liu et al., 2019) for this compound.

The antioxidant capacity of punicalagin was observed by Chu and Han (2018) in an *in vitro* model of Parkinson's disease (neuroblastoma cells SH-SY5Y treated with 6-hydroxydopamine (6-OHDA). At 2 h prior to 6-OHDA treatment, SH-SY5Y cells were pre-treated with punicalagin at different concentrations (0, 50, 100, and 200 μM) or dimethyl sulfoxide (DMSO, 0.1%, v/v). The following parameters were analyzed: cell viability using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) bromide assay; cell damage by the presence of lactate dehydrogenase (LDH); intracellular production of Reactive Oxygen Species (ROS) with a 2′, 7′-dichlorofluorescein diacetate (DCFH-DA) probe; and the superoxide dismutase (SOD) activity. All tested concentrations of punicalagin exhibited protective action, contrarily to the control treatment (cells treated with DMSO): cell viability increased, released LDH was significantly eliminated, intracellular ROS values were restored, and there was a rise in SOD activity.

Liu et al. (2019) observed the antioxidant potential of punicalagin on the acute hyperlipidemic mouse model (male C57BL6 rats from 6 to 8 weeks of age). Animals were divided into four groups: control group (n = 8), hyperlipidemia group (n = 7, P407 group), low dose group (50 mg punicagalin/kg/day), high dose group (200 mg of punicagalin/kg/day). The intervention lasted nine days and was performed by oral gavage. On the tenth day, rats were induced to have acute hyperlipidemia by applying 0.5 g/kg of poloxamer 407 (P407) via intraperitoneal injection, whereas animals in the control group received the same volume of sterile saline. The dose of 200 mg/kg was chosen for later trials because it partially normalized the levels of triacylglycerols and cholesterol in the serum, as well as ROS in the thoracic aorta compared to the P407 group, which had high levels of these compounds. The structure of the artery endothelial cells was checked by H&E staining. The group treated with punicalagin showed positive results, with no rupture of the elastic membrane, thus resulting in a normal structure. In addition, there was an improvement in mitochondrial function due to high levels of complex proteins I, II, and IV, and an increase in the expression of forkhead box O1 (Fox 01), different from the P407 group.

The antioxidant potential of punicalagin has already been reported by many researchers such as Clementi et al. (2018), Kim et al. (2017), Pathakoti et al. (2017) and Berköz and Allahverdiyev (2017) among others, which contributes to continuous and increasing interest in this compound. Taking into consideration the reported evidence, supplements containing punicalagin represent a promising intervention tool for the prevention and/or treatment of human cardiovascular diseases.

#### 3.1.3. Anthocyanins

Anthocyanins are PC belonging to the subgroup of flavonoids. Their chemical structures are composed of glycosides whose aglycones are derived from polyhydroxy or polymethoxy of 2-phenylbenzopyrryl salts. They are water-soluble vegetable pigments responsible for the color blue, purple, and red in fruits and flowers (Bendokas et al., 2019). Due to their ability to reproduce colors and low toxicity, anthocyanins can have several applications in the food industry (Shen et al., 2020).

Among the compounds identified as anthocyanins, delphinidin-3-glucoside is present in greater quantity compared to other anthocyanins in fruits. Delphinidins are the anthocyanins with highest antioxidant power due to the high number of hydroxyl groups in the B ring (Lee et al., 2015). Cyanidin and delphinidin have antioxidant activity superior to vitamin C (Kim and Lee, 2004).

Over the past two decades, the attention has shifted to the cardioprotective effects displayed by anthocyanins. Reis et al. (2016) concluded through a systematic review that anthocyanin is a potentially favorable agent in the prevention of cardiovascular diseases, as it inhibits inflammatory processes, endothelial dysfunction, and vasodilators production. Its mechanism of action involves antioxidant activity, scavenging of FR and/or anions, inhibiting xanthine oxidase (XO), ion metal chelation, targeting arachidonic acid, and nuclear factor κ light-chain enhancer of activated B cells (NF-κB), TNF-α, and adhesion molecules, and suppression of heme oxygenase-1. According to the authors, there are still positive effects on the oxidation of low density lipoprotein (LDL), very low-density lipoproteins (VLDL), high-sensitive C-reactive protein (CRP), and total triacylglycerols, thus improving the clinical status of patients with cardiovascular diseases.

Krga and Milenkovic (2019) reported that anthocyanins and its metabolites seem to regulate different cellular processes involved in the development of cardiovascular diseases, controlling the activity of cell signaling proteins and transcription factors, modulating the expression of genes and miRNA, also suggesting that the modulation of inflammatory responses and improvements in endothelial function are probably the most important actions of these compounds. Other evidence, such as the increase in high density lipoprotein (HDL), cholesterol levels in prehypertensive and non-dyslipidemic men, were observed by Hassellund et al. (2013).

Despite the rising evidence based on epidemiological, clinical, and *in vitro* studies about the benefits of dietary anthocyanins in assisting the prevention of cardiovascular diseases, its mode of action is still not entirely clear. Thereupon, further well-designed research is essential to thoroughly explain the molecular mechanisms through which anthocyanins ameliorate cardiovascular diseases. Also, research is needed in order to possibilitate the use of these compounds in the clinical management of such conditions,

**Table 2. Phenolic compounds in pomegranate based-foods**

| Pomegrante-based products | | GA | EA | Punicalagin |
|---|---|---|---|---|
| *Wine* (mg/L)<br>(Akalin et al., 2018) | | 80.4–108.8 | – | – |
| *Fermented milk* (µg/g)<br>(Al-Hindi and El Ghani., 2020) | PP 150 mg/L[a]<br>PP 300 mg/L[a] | 152.4–167<br>182.1–195.7 | 9.62–15.4<br>13.2–19.6 | 111.2–162.5<br>190.8–211.6 |
| *Juice*<br>(Cano-Lamadrid et al., 2016) | Conventional Organic (mg/L) | –<br>– | Tr<br>Tr | 201<br>104 |
| *Juice*<br>(Gil et al., 2000; Fischer et al., 2011; Özgüvem et al., 2019) | commercial (mg/L) | 1.1–10.72 | 2.1–37.9 | 1259.8 |
| *Juice*<br>(Hmid et al., 2017) | commercial (mg/g) | 0.05–0.14 | 0.02 | 0.01–0.70 |
| *Juice*<br>(Gil et al., 2000) | concentrate (mg/L) | – | 172.8 | 1,353.1 |
| *Juice*<br>(Gil et al., 2000; Hmid et at., 2017) | with arils (mg/L) | 12.42–88.51 | 8.7–95.02 | 22.8–25.5 |

[a]Suplemented with pomegranate peel extract; [b]Impure montmorillonite and extract of pomegranate fruit waste (%). GA: Gallic acid; EA: Ellagic acid.

in addition to assessing a suitable effective dose, duration of treatment, and lasting effects.

### 3.2. *Antioxidant activity of pomegranate juice, pulp, and peel*

Pomegranate juice has more than 30 nutrients and 79 bioactive compounds, mainly phenolics, such as flavonoids, phenolic acids, and hydrolyzable tannins (Ambigaipalan et al., 2016; Khomich et al., 2019), as can be observed in Table 2. Antioxidant phenolics of pomegranate-based foods are shown in Table 2.

Due to its high antioxidant activity, pomegranate has been applied in different types of food in order to avoid loss of bioactive components. Moreover, because of the growing interest in using natural preservatives in foods, pomegranate could be a feasible alternative to improve quality, limit the growth of undesirable microorganisms, and decrease lipid oxidation (Derakhshan et al., 2018). In several studies, pomegranate extracts and juices have demonstrated superior antioxidant potential than foods popular for their antioxidant properties, with values up to three times more antioxidant activity than red wine and green tea (Gil et al., 2000; Johanningsmeier and Harris, 2011). *In vitro* assays of antioxidant activity of pomegranate pulp, peel, and juice are shown in Table 3.

The processing to obtain industrialized pomegranate juice affects the product's phenolic composition, especially when compared with homemade juice, which will consequently impact the antioxidant activity and availability of PC in this source. Dżugan et al. (2018) characterized and compared industrialized and homemade pomegranate juices, suggesting that industrialized juices have an antioxidant capacity superior to that found in homemade

**Table 3. *In vitro* assays of antioxidant activity of pomegranate peel, pulp, seed and juice**

| | *In vitro* assay | Extract | Origin | Range | Reference |
|---|---|---|---|---|---|
| Peel | β-carotene bleaching test (Antioxidant activity %) | ethanol | Iran | 45–58 | Derakhshan et al., 2018 |
| Seed | β-carotene bleaching test (Antioxidant activity %) | ethanol | Iran | 34–54 | Derakhshan et al., 2018 |
| Juice | β-carotene bleaching test (Antioxidant activity %) | ethanol | Iran | 9–10 | Derakhshan et al., 2018 |
| Juice[a] | FRAP (mmol TE/L of juice) | Aqueous | India | 22.09–25.68 | Dżugan et al., 2018 |
| Juice[b] | FRAP (mmol TE/L of juice) | Aqueous | Turkey<br>Israel Azerbaijan<br>Russia<br>Azerbaijan | 57.17<br>30.86<br>70.33<br>8.23<br>47.96 | Dżugan et al., 2018 |
| Extract[c] | Scavenger Effect on Superoxide Anion (% of inhibition) | ethanol | n.i. | 95 | Sorrenti et al., 2019 |
| Peel | ORAC (µmol TE/g DW) | ethanol | United States | 7423.0 | Morzelle et al., 2019 |
| Pulp | ORAC (µmol TE/g DW) | ethanol | United States | 323.8 | Morzelle et al., 2019 |

[a]Homemade juice; [b]Commercial juice; [c]0.028 mg·mL$^{-1}$. n.i.: not identified.

**Table 4. Use of pomegranate as a natural antioxidant in foods**

| Reference | Type of food | Results |
|---|---|---|
| Ahmed et al., 2017 | broiler meat | improved nutritional quality, fatty acid profile, and shelf life |
| Ahmed et al., 2015 | broiler meat | improved fatty acid profile and reduced lipid oxidation |
| Berizi et al., 2018 | rainbow trout | prevented the oxidation of fats and proteins and antimicrobial activity |
| Devatkal et al., 2010 | goat meat patties | reduced lipid oxidation (TBARS) |
| Devatkal et al., 2011 | salted chicken patties | reduced lipid oxidation (TBARS) |
| Dua et al., 2016 | fat rich meat | lower TBARS values |
| Gomalkani et al., 2020 | Linseed oil | improved oxidative stability |
| Ismail et al., 2019 | Minced Shrimps | inhibited TBARS production during 28 days of refrigerated storage |
| Martínez et al., 2019 | Fish Patties | delayed lipid oxidation, measured as volatile compounds, and the microbiological spoilage |
| Morsy et al., 2018 | meatballs | Reduced contents of peroxide, TBARS, and total volatile base nitrogen (TVB-N) |
| Natalello et al., 2020 | lamb meat | reduced lipid oxidation, greater concentration of vitamin E and polyunsaturated fatty acids |
| Naveena et al., 2008b | chicken patties | inhibited lipid oxidation |
| Qin et al., 2013 | Pork Meat | reduced lipid oxidation |

juices. According to the authors, this outcome can be explained by the fact that usually, the fruit is used entirely by the industry, including its the peels, which have higher phenolic content than the pulp. On the other hand, in handmade juice production, the peels are usually discarded. Despite that, the content of anthocyanins in homemade juices was higher than their industrialized counterparts.

The scientific community has studied the composition of agro-industrial by-products in order to ensure that they are properly used, avoiding an excessive accumulation of waste in the environment. In addition, a large proportion of consumers demand natural ingredients due to their health claims, especially the ones obtained from sustainable sources (Melo et al., 2015; Gómez et al., 2016). It should be pointed out that agro-industrial waste has considerable amounts of bioactive substances recognized for their health-promoting properties and technological application as antioxidants, potentially prebiotic ingredients, or even as food dyes (Vásquez-Olivo et al., 2018).

Pomegranate by-products have the potential to be reused. According to the literature, 37 kg of waste is generated for every 100 kg of processed pomegranate. Of this total, 23 kg corresponds to the peel and 14 kg to the seeds. From these residues, 180 g of microencapsulated phenolics can be recovered from the peels (Gullon et al., 2015).

PP is widely known for its phytochemicals levels, with compounds that carry medicinal and nutritional significance, as well as a higher antioxidant activity than pulp and seeds (Morzelle et al., 2019). Due to its high antioxidant power, pomegranate extract is an excellent alternative to be used as a food preservative, contributing to extend shelf life. Lipid oxidation is among the major causes of deterioration in meat, ultimately causing undesirable sensory, nutritional, and physicochemical changes (Horbańczuk et al., 2019). With that being said, and taking into consideration the cost-effective aspect, studies concerning the use of PP as natural antioxidants have grown over the years (Smaoui et al., 2020).

Martínez et al. (2019) carried out *in vitro* tests (FRAP, ORAC) to measure the antioxidant activity of PP and evaluate the ability of the extracts (concentration of 200 ppm) to prevent oxidation of fish burgers stored for 11 days at 4 °C. PP extract delayed lipid oxidation, measured by the formation of volatile compounds (1-penten-3-ol, hexanal, 2-nonanone, 1,6-octadien-3-ol, nonanal and pentadecane).

Studies conducted by Naveena et al. (2008a, 2008b) showed that PP (5 to 20 mg tannic acid equivalents/100 g meat) was able to inhibit lipid oxidation of chicken patties (cooked to an internal temperature of 80 °C, and stored in low-density polyethylene pouches for 15 days at 4 °C) to a much greater extent than synthetic antioxidant (BHT). Moreover, PP did not have a significant impact on the overall sensory attributes of the finished product.

In another study (Ismail et al., 2019), the effect of hydro-alcoholic extracts of PP on the control of lipid oxidation of shrimp meat was investigated. Minced shrimp meat was treated with the extract at different concentrations (0,5%, 1.0%, and 2.0%), and thiobarbituric reactive substances (TBARS) were measured from day 0 to day 28 of storage at 4 °C. The rate of TBARS production was significantly lower in samples marinated with 1.0% and 2.0% of the extract in comparison to samples treated with a synthetic antioxidant (BHT, 0.05%). Moreover, a slight increase (10%) in TBARS in shrimp samples treated with 2.0% extracts of PP from day 0 to day 28 of storage was identified. Thereupon, hydro-alcoholic extract of PP was found to protect shrimp meat against lipid peroxidation.

The use of pomegranate as a natural antioxidant in foods is shown in Table 4.

Pomegranate can increase the antioxidant activity of juice, tea, and other beverages. Lyophilized PPs were added to tomato and orange juices with strawberry at different concentrations (0.5, 1.0, 1.5, and 2.0%). Orange and tomato juice samples enriched with higher dried extract concentration (2.0%) showed an increase of over 30 and 25 times, respectively, in antioxidant activity as compared to the juice control (without extract). However, although both flavors of enriched juices had high levels of antioxidants, orange juice with a concentration of 2% of the dry extract was rejected in the sensory analysis due to the astringent flavor of the PP (Salgado et al., 2012).

González-Molina et al. (2009) produced a polyphenol-rich drink based on lemon and pomegranate juice in different propor-

tions (25%, 50%, and 75% for both juices) and the results suggested that the formulation of 75% pomegranate juice and 25% lemon juice presents the potential for the development of new functional drinks, emphasized by its high antioxidant capacity. However, a sensory analysis was not performed in order to detect the acceptability of this product. The phenolic-driven sensory changes in functional foods has been discussed by de Camargo and Schwember (2019).

Despite the feasibility of using PP as a natural antioxidant, extraction methods should be improved, aiming at sustainable and cost-effective approaches. Similarly, their biological activities should always be examined in comparison with a synthetic antioxidant, as well as their efficacy to prevent lipid oxidation in different foods. Also, *in vitro* assays and pre-clinical and clinical trials should be carried out to address their potential toxic effects on human health in order to mitigate risks to the consumers (Andrade et al., 2019).

## 4. Health effects of pomegranate phenolics

### *4.1. Cellular antioxidant activity*

Oxygen plays a vital role in the human organism, being part of metabolic processes. Under normal circumstances, a small percentage of the electrons passing through the electron transport chain leaks out of the mitochondria, combines with molecular oxygen, and forms ROS (Valko et al., 2007). These radical and non-radical chemical species can be harmful to the organism if produced in excess, causing cellular damage. In order to prevent this, cells contain endogenous antioxidant defenses, such as the enzymes SOD, glutathione peroxidase (GPx), and catalase (CAT) (Niederländer et al., 2008).

External factors (e.g., diseases, drugs, pollution, poor eating habits) can contribute to increased production of ROS, leading to the biological condition known as oxidative stress. Besides, internal factors such as enzymes from the P450 complex, XO, and nicotinamide adenine dinucleotide (NADPH) are sources of oxidative stress (Sosa et al., 2013).

The oxidative stress condition caused by the prevalence of ROS and reactive nitrogen species (RNS) is detrimental to cellular functions since they can damage proteins, lipids, and genetic material (DNA and RNA) (Brigelius-Flohe, 1999; Islam, 2016). Several degenerative and cardiovascular diseases, cancer, diabetes, and a decline in the immune system involve cellular damage caused by oxidative stress. This association shows that the incidence of these ailments is closely related to the prevalence of reactive substances in the body (Rauter et al., 2012; Sosa et al., 2013; Islam, 2016)

There is mounting evidence about the function of dietary antioxidants in human health. Antioxidant compounds from fruits, such as pomegranate, are able to neutralize FR present in the body, thus helping to protect cells and tissues. Consequently, this mechanism of action contributes to the prevention of aging and the increased incidence of chronic non-communicable diseases (McCune et al., 2011; Pereira et al., 2012).

Numerous *in vitro* and *in vivo* studies have been carried out to understand the mechanisms through which pomegranate could improve oxidative stress and prevent chronic non-communicable diseases. Most studies were done with the bioactive compounds alone or together with the food matrix. However, studies must be conducted to show the biological effect, focusing on the mechanism of action by biotransformed forms (de Camargo et al., 2018). Urolithin A is a metabolite generated from ellagitannins and EA upon pomegranate consumption. Casedas et al. (2020) evaluated the cytoprotective effect of this metabolite on neuronal cells (Neuro-2a) subjected to oxidative stress through treatment with hydrogen peroxide ($H_2O_2$), as well as its direct antioxidant activity and inhibitory properties against oxidases. Cells treated with urolithin A (0.5 and 1 μM) and $H_2O_2$ showed a more effective response to oxidative stress than the control. Mitochondrial activity (MTT assay), redox state (ROS formation and lipid peroxidation), and the activity of antioxidant enzymes (CAT, SOD, GPx) were significantly ameliorated. Additionally, urolithin A enhanced the expression of cytoprotective peroxiredoxins 1 and 3. Finally, the inhibition of oxidizing enzymes, such as monoamine oxidase A and tyrosinase, was also detected in a dose-dependent manner.

Fazio et al. (2018) treated cell culture of murine fibroblasts (3T3–L1) and human embryonic renal epithelium (Hek-293) with pomegranate acetonic and methanolic extracts (15, 30, 60 and 120 μg/mL). The cells had previously been induced to oxidative stress with menadione. As a result, both extracts showed potential ROS scavenging activity, in addition to being able to contribute to the antitumor function.

### *4.2. Type 2 diabetes*

Studies have indicated that oxidative stress plays an essential role in the pathogenesis of type 2 diabetes. Overload of glucose and oxidative phosphorylation enhances the generation of ROS through various tissues and metabolic processes in the mitochondria (Burgos-Moron et al., 2019).

Katz et al. (2007) discussed the relationship between pomegranate extracts or juice and type 2 diabetes. The authors stated that the mechanism was not clear, with the studies showing that the antioxidant activity of pomegranate may be involved in the process. However, Ambigaipalan et al. (2016,) demonstrated that phenolics from pomegranate inhibit the activity of alpha-glucosidase, a carbohydrate-hydrolysing enzyme present in the small intestinal brush border that participates in the breakdown of complex carbohydrates and enables their absorption. Other studies have shown the effects of PP and other fractions on metabolic variables associated with the pathologic markers of type 2 diabetes (Medjakovic and Jungbauer, 2013; Banihani et al., 2013; Chukwuma et al., 2020).

Pomegranate affects type 2 diabetes by reducing oxidative stress and lipid peroxidation. This reduction may occur by directly scavenging FR, increasing the activity of antioxidant enzymes, metal chelation, reducing resistin formation, influencing NO production and modulating selected transcriptional factors, such as NF-κB (Katz et al., 2007; Makino-Wakagi et al., 2012; Banihani et al., 2013). Also, pomegranate enhances peroxisome proliferator-activated receptor-gamma (PPAR-γ), a transcriptional factor key to carbohydrate metabolism (Huang et al., 2005).

Polar and non-polar extracts of PP, the fruit's edible parts, arils, and seeds reduced lipid peroxidation and modulated antioxidant status of diabetic and oxidative stress-induced rats. Besides, pomegranate juice, extracts, or their polyphenols reduce blood glucose, increase glycogen on liver and insulin secretion, modulate insulin terminating factors, improve lipid profile, and glucose tolerance (Banihani et al., 2013) .

Huang et al. (2005) showed that pomegranate flower extracts, with a high concentration of GA, enhanced PPAR-γ mRNA in human THP-1-differentiated macrophage cells.

Chukwuma et al. (2020) described that acetonic extract of PP has 3.5 times greater α-amylase inhibitory activity than aqueous extracts. The inhibitory effect of α-amylase promoted by PP was associated with the presence of ferulic acid, known for its phar-

macological potential of inhibiting this metabolic enzyme. The authors also found that the acetone extract of PP possesses compounds with antidiabetic and antioxidant effects, with minimal toxicity.

Clinical trials have tried to establish a connection between pomegranate consumption and reduced diabetes risk, mainly using pomegranate juice. Pomegranate juice (50 mL/d, 3 months) has been reported to oxidize a N-linoleoyl tyrosine, synthetic oxidative stress marker, on diabetic patients (Szuchman et al., 2008).

Studies with pomegranate extracts, polar or non-polar, can give the best results for those in which pomegranate juice is used (Jelodar et al., 2007).

### 4.3. Cardiovascular diseases

Cardiovascular diseases are a major cause of death worldwide, with oxidative stress playing a key role in the development of these ailments. Plant-based bioactive compounds have strong antioxidant and anti-inflammatory properties, exhibiting cardioprotective effects.

Evidence suggests that pomegranate may be included in a heart-healthy diet. Cardioprotective effects of pomegranate polyphenols include decreased serum cholesterol, reduced lipid peroxidation levels, reduced intima-media thickness, diminished levels of NO, reduced blood pressure and angiotensin-converting enzyme (ACE) activity, inhibition of LDL oxidation, reduced TNF-α, IL-6 and CRP (Basu and Penugonda, 2009; Wang et al., 2020).

Atherosclerosis is a degenerative artery disease, where the role of oxidative stress on its initiation and progression is well established. Pomegranate reduced atherosclerotic lesion areas in immune-deficient mice (Basu and Penugonda, 2009). Aviram et al (2008) evaluated *in vivo* and *in vitro* antiatherogenic effects of phenolics from PPs, arils, seed, and flowers. The *in vivo* study was conducted with atherosclerotic apolipoprotein E-deficient mice, which consumed pomegranate extracts for three months. Pomegranate phenolics reduced 70% atherosclerotic lesion area (except for pomegranate seed), 15% oxidized LDL, and 53% peroxide content. Pomegranate, especially pomegranate juice and flowers, reduced serum lipids, and glucose levels.

Punicalagin is able to activate FoxO1 (forkhead box O1), the main regulator of enzyme antioxidant defense, and through this mechanism, punicalagin can prevent vascular dysfunction and promote mitochondrial biogenesis and increased cellular paraoxonase 2 (PON2) activity (Liu et al., 2019).

Furthermore, pomegranate flower extract decreased cardiac fibrosis in rats through the modulation of the NF-κB pathway and cardiac endothelin-1, a protein involved in blood vessel constriction and increased blood pressure (Huang et al., 2005).

### 4.4. Chronic kidney disease

Increases in both systemic inflammation and oxidative stress are established as non-traditional critical elements involved in the immune dysregulation of patients undergoing hemodialysis. Patients suffering from chronic kidney disease (CKD) have low levels of antioxidants, such as glutathione and superoxide, and high levels of prooxidants substances circulating in their bodies.

Given the connection between oxidative stress and many hemodialysis comorbidities, antioxidant consumption could be a low-cost non-drug strategy, and probably an effective therapy to attenuate the decline of antioxidant defense in patients on dialysis.

Shema-didi et al. (2012) conducted a randomized placebo-controlled double-blind study to investigate the effect of ingesting pomegranate juice three times a week for one year on oxidative stress and inflammatory processes of hemodialysis patients. Patients were randomly assigned to treatment group (n = 66) receiving 100 mLof pomegranate juice, or control group (n = 35) receiving 100 mLof placebo juice (similar to pomegranate juice in color and taste). The primary outcomes were the levels of oxidative stress and inflammation biomarkers, whereas the secondary outcomes were hospitalizations due to infections and the progression of the atherosclerotic process. The results indicated that the intake of pomegranate juice resulted in a significant reduction of protein oxidation, lipid oxidation, and inflammatory biomarker levels. Additionally, the intake of pomegranate juice resulted in a significantly lower incidence of hospitalization due to infections. The beneficial effects lasted up to three months postintervention. Furthermore, 25% of patients receiving pomegranate juice improved, and only 5% progressed in the atherosclerotic process. Conversely, more than 50% of patients in the group receiving placebo showed progression, and none showed any improvement in the atherosclerotic process. The authors concluded that the ingestion of pomegranate juice for a prolonged period improved non-traditional risk factors for cardiovascular disease, attenuated the progression of the atherosclerotic process, strengthened innate immunity, and, therefore, may contribute to reducing morbidity among patients undergoing hemodialysis.

Another study demonstrated in a crossover trial that the consumption of 100 mL pomegranate juice immediately after hemodialysis three times a week during eight weeks promoted significant reduced levels of oxidative stress of patients (n = 41), which was measured by the total antioxidant capacity and malondialdehyde levels (Boldaji et al., 2020).

Although the beneficial effects of consuming pomegranate juice are observed in patients, studies indicate that supplementation with isolated polyphenolic compounds extracted from the fruit would not have the same beneficial action. Patients undergoing hemodialysis consumed a food supplement with 1,000 mg of purified pomegranate polyphenolic extract for six months, and no significant effects were observed on oxidative stress markers (Wu et al., 2015).

### 4.5. Neurodegenerative disease

Excessive production of ROS and nitrogen species (RNS) has also been linked to neurodegenerative diseases, including Alzheimer's diseases (AD), Amyotrophic lateral sclerosis, Huntington's disease, Multiple sclerosis, and Parkinson's diseases (Islam, 2016). Functional foods to prevent and/or treat neurodegenerative diseases represent a promising field of study currently gaining popularity (Morzelle et al., 2016).

Loren et al. (2005) evaluated if neonatal protection against hypoxic-ischemic encephalopathy could be achieved by supplementing the maternal diet with pomegranate juice. Hypoxic-ischemic encephalopathy is an important cause of morbidity and mortality, requiring effective therapies for prevention and treatment. Results have shown that pomegranate juice in the maternal diet resulted in a decreased loss of brain tissue (>60%) and inhibition of caspase-3. Pomegranate juice, when included in maternal diet possibly has a neuroprotective effect on the neonatal brain.

The neurodegenerative disease has an accumulation of specific proteins such as PrPSc príons in Creutzfeldt Jacob's disease and β-amyloid in AD, and share common characteristics such as neuronal death and oxidative damage. Mizhari et al. (2014) evaluated whether the reduction in oxidation through the consumption of

natural antioxidants from pomegranate seeds alters the manifestation of Creutzfeldt Jacob's disease in transgenic mice. The pomegranate seed oil has a natural antioxidant compound—a punic acid—a polyunsaturated acid and significantly delayed the onset of the disease when administered to asymptomatic animals and postponed the worsening of the problem in animals induced to the disease. The treatment reduced lipid oxidation and neuronal loss, which indicates a strong neuroprotective effect.

Bookheimer et al. (2013) showed the effect of pomegranate juice (eight ounces for four weeks) in elderly individuals (n = 34) with age-related memory loss. After four weeks, pomegranate juice promoted an increase in plasma Trolox-equivalent antioxidant capacity (TEAC) and a significant improvement in the Buschke selective reminding test.

Braidy et al. (2013) evaluated the neuroprotective effect of pomegranate on an *in vitro* model for Parkinson's disease. Results indicated that the juice extracted from the pomegranate pulp had interesting properties in order to delay age-related neurodegeneration.

Studies have shown pomegranate as neuroprotective towards Alzheimer's disease (Choi et al., 2001; Hartman et al., 2006; Rojanathammanee et al., 2013; Subash et al., 2015). Pomegranate phenolics, mainly punicalagin, may be responsible for this neuroprotective effect (Rojanathammanee et al., 2013; Braidy et al., 2013).

Injuries caused by FR are precedents of amyloid deposition in the brain, which raises the hypothesis that possibly such stress would be the start for amyloidogenesis (Nunomura et al., 2006). Besides, FR are closely related to synaptic dysfunction, cascades of apoptosis, tau protein hyperphosphorylation, which causes impairment of cognitive ability (Mattson, 2004).

Transgenic mice model of Alzheimer's disease supplemented with nanodroplet formulation of pomegranate seed oil showed decreased lipid oxidation and neuronal loss (Mizrahi et al., 2014).

The consumption of pomegranate juice promoted benefits, behavioral and neurological, in transgenic mice ($APP_{SW}$/Tg2576) (Hartman et al., 2006). Results showed that the consumption of 5 mL/day of pomegranate juice promoted a more than 50% decrease of βA on the hippocampus.

Neuroprotective potential of pomegranate pulp extract (800 mg/kg/dia for 30 days) on mice after acute infusion with Amyloid-β Peptide were analyzed by Choi et al. (2011). Rojanathammanee et al. (2013) analyzed the effect of consumption of pomegranate pulp extract for three months in transgenic mice (APP/PS1) models of AD. The consumption of pomegranate pulp extract had an anti-inflammatory effect on the brain that could possibly slow the progression of AD. The PC present in the extract were tested in isolation in cell cultures, and the results showed that the active compounds were punicalagin and ellagic acid.

Subash et al. (2015) studied whether transgenic AD rats (APPsw / Tg2576) supplemented with pomegranate for 15 months have an improvement in memory, anxiety, and learning. In the experiment, animals with four months of age received a diet containing 4% pomegranate inserted directly into the feed (pellets) until they were 19 months old. The results suggest that pomegranate dietary supplementation slowed the progression of cognitive and behavioral changes in AD.

EA significantly decreased neurotoxicity induced by $βA_{1–42}$ in a human cell line (SH-SY5Y) (Feng et al., 2009). Moreover, quercetin 3-*O*-glucuronide, also found in pomegranate, significantly reduced the production of βA peptide in primary neuronal cultures generated from an AD model animal (Ho et al., 2013). Another study indicated that pre-treatment of primary cultures of the hippocampus with quercetin significantly attenuated cytotoxicity induced by $βA_{1–42}$ (Ansari et al., 2009).

Acetylcholinesterase is a key enzyme in Alzheimer's disease. High levels of acetylcholinesterase, and consequently low levels of the neurotransmitter acetylcholine, are commonly found in patients with AD. Drugs used to attenuate the symptoms of AD are anticholinesterasics. Morzelle et al. (2019) evaluated the anticholinesterase effect of PP and methanolic pulp extracts. Phenolics from PP showed inhibition of acetylcholinesterase, which was dependent on the phenolic concentration. PP extract (3 mg/mL) showed 58% of inhibition. Increasing the options of natural compounds bearing acetylcholinesterase could be helpful for the management of AD.

Morzelle et al. (2016) demonstrated the effect of PP extract (PPE) on biomarkers of oxidative stress (lipid peroxidation and SOD activity) in a mouse model of neurodegeneration. Male C57Bl/6 mice were chronically infused for 35 days with amyloid-β peptide 1–42 (Aβ) using mini-osmotic pumps and treated with PPE (800 mg/kg/day). The levels of malondialdehyde (MDA) and SOD activity were evaluated on the liver and brain, respectively. Lipid peroxidation, probably caused by the generation of FR during the Aβ deposit, has been linked to AD, and these oxidative events can lead to neuronal death, contributing to cognitive decline in patients with AD. PP promoted a reduction of lipid peroxidation in the liver but did not increase the SOD activity in the brain. Such data suggest that the antioxidant effect of the extract is independent of the endogenous antioxidant capacity. The intake of PP extract could contribute to neuroprotection as an antioxidant and by stabilizing or reverting injury caused by oxidative stress. This antioxidant effect is also related to the high content of PC (mainly punicalagin and GA) in the extract (Morzelle et al., 2019). The proposed mechanism for antioxidant activity is the capacity of the extract to promote hydroxyl radical scavenging.

## 5. Conclusion

Previous studies have shown that pomegranate is a functional fruit with a myriad of benefits on chronic non-communicable diseases, such as type 2 diabetes, cardiovascular disease, CKD, and neurodegenerative disease. Pomegranate pulp, peel, and seed extracts represent an excellent alternative to be used in the industry as a preservative, contributing to extend food's shelf life. The effect of pomegranate on foods and the biological benefits were associated with PC, especially anthocyanins and hydrolyzable tannins. However, the mechanism behind the action of phenolic metabolites from pomegranate and its by-products deserves further investigation.

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