Pomegranate (Punica granatum L.), one of the oldest known edible fruits, is nowadays broadly consumed throughout the world. Its fruits and seeds as well as other anatomical compartments (e.g., flowers and leaves) are rich in numerous bioactive compounds and therefore, the scientific interest in this plant has been constantly growing in recent years. It has been shown that pomegranate and its extracts exhibit potent antioxidative, antimicrobial, and anticarcinogenic properties. The present review summarizes some recent studies on pomegranate, highlighting mainly its vasculoprotective role attributed to the presence of hydrolyzable tannins ellagitannins and ellagic acid, as well as other compounds (e.g., anthocyanins and flavonoids). These in vitro and in vivo studies showed that substances derived from pomegranate reduce oxidative stress and platelet aggregation, diminish lipid uptake by macrophages, positively influence endothelial cell function, and are involved in blood pressure regulation. Clinical studies demonstrated that daily intake of pomegranate juice lessens hypertension and attenuates atherosclerosis in humans. Altogether, the reviewed studies point out the potential benefits of a broader use of pomegranate and its constituents as dietary supplements or as adjuvants in therapy of vascular diseases, such as hypertension, coronary artery disease, and peripheral artery disease.

Keywords: pomegranate, antioxidant, blood pressure, cardiovascular disease, vasculoprotective

INTRODUCTION

Pomegranate (Punica granatum L.), belonging to Punica L. genus, Punicaceae family, is an ancient fruit native to Central Asia in regions spanning from Iran and Turkmenistan to northern India as well as in the Mediterranean area and the Middle East (Holland et al., 2009). Archaeologists have found carbonized pomegranate exocarps originated from the Early Bronze Age (3000 BC), e.g., in Jericho and from the Late Bronze Age in Cyprus (Ward, 2003; Boncuk, 2014). Pomegranate has been highly appreciated since centuries by different cultures. For example, in Ancient Egypt it was not only a part of the supply of fruits for pharaoh’s residence (at around 1600 B.C.), but pomegranate was also painted on walls and tombs to symbolize life after death (Ward, 2003; Boncuk, 2014). Pomegranate used to

Pomegranate (Punica granatum L.), one of the oldest known edible fruits, is nowadays broadly consumed throughout the world. Its fruits and seeds as well as other anatomical compartments (e.g., flowers and leaves) are rich in numerous bioactive compounds and therefore, the scientific interest in this plant has been constantly growing in recent years. It has been shown that pomegranate and its extracts exhibit potent antioxidative, antimicrobial, and anticarcinogenic properties. The present review summarizes some recent studies on pomegranate, highlighting mainly its vasculoprotective role attributed to the presence of hydrolyzable tannins ellagitannins and ellagic acid, as well as other compounds (e.g., anthocyanins and flavonoids). These in vitro and in vivo studies showed that substances derived from pomegranate reduce oxidative stress and platelet aggregation, diminish lipid uptake by macrophages, positively influence endothelial cell function, and are involved in blood pressure regulation. Clinical studies demonstrated that daily intake of pomegranate juice lessens hypertension and attenuates atherosclerosis in humans. Altogether, the reviewed studies point out the potential benefits of a broader use of pomegranate and its constituents as dietary supplements or as adjuvants in therapy of vascular diseases, such as hypertension, coronary artery disease, and peripheral artery disease.

Keywords: pomegranate, antioxidant, blood pressure, cardiovascular disease, vasculoprotective
play an important role in different religions, including Zoroastrianism, Judaism, Buddhism, Christianity, and Islam (Langley, 2000; Jurenka, 2008). It was praised, e.g., by the Old Testament of the Bible as “a sacred fruit conferring powers of fertility, abundance, and good luck” (Jurenka, 2008). Besides being a part of the mythology and consumed as a fruit, pomegranate has been known for its medical use. For example, the Ebers papyrus originating from about 1550 BC noted that the roots of the pomegranate tree were used to treat tapeworm parasites (Svenja, 2018). In addition, pomegranate was employed to treat diabetes by Indians (Saxena and Vikram, 2004) and to lessen tapeworm infestation also by Romans (Langley, 2000). The persisting significance of the medical use of pomegranate can be illustrated, for example, by the fact that in Great Britain the coats of arms of three royal colleague and the British Medical Association are decorated with the figure of this herb (Langley, 2000).

Besides native regions spreading from Iran to northern India and the Mediterranean area and the Middle East, pomegranate is nowadays cultivated in subtropical Africa as well as in California, Arizona, and Mexico, as this plant requires high exposure to sunlight during summer and temperature not lower than ~12°C in winter (Levin, 2006; Holland et al., 2009). The pomegranate tree is about 2–3 m tall, glabrous, with multiple trunks and bushy appearance. The surface of the leaves is smooth and hairless, with a glossy appearance on the upper part of the leaf (Figure 1). The fruit ripens within 5–8 months after it has begun to form. During this process, the color of the external part of the fruit changes from yellow, green, or pink to fully red, pink, or deep purple (Figure 1). An edible juicy layer of a fruit varies in color from white to deep red (Holland et al., 2009).

Studies accomplished over the last several decades showed that pomegranate and its components exhibit potent antioxidative (Gil et al., 2000; Les et al., 2015), anti-inflammatory (Adams et al., 2006; Rasheed et al., 2009) as well as antibacterial, antimicrobial, and antifungal properties (Niaz et al., 2007; Fawole et al., 2012; Elsherbiny et al., 2016; Wafa et al., 2017). In addition to these in vitro studies, in vivo and in vitro studies showed that pomegranate exhibits anti-hypertensive (Mohan et al., 2010; Dos Santos et al., 2016; Arun et al., 2017) and anti-proliferative properties (Albrecht et al., 2004; Malik et al., 2005; Malik and Mukhtar, 2006). Pomegranate and its constituents have been tested for their use as adjuvant therapy for treatment of several forms of oncological diseases, mainly of prostate cancer (Lansky and Newman, 2007; Paller et al., 2013; Panth et al., 2017; Sharma et al., 2017). Furthermore, numerous pre-clinical studies have pointed out the beneficial effects of intake of pomegranate juice or pomegranate extracts in a variety of conditions. For example, such treatment improved sperm quality in mice (Türk et al., 2008), lowered amyloid deposition in a mouse model of Alzheimer’s disease (Hartman et al., 2006), and lessened neuronal damage in a mouse neonatal hypoxic-ischemic brain injury model (Loren et al., 2005). In addition, single intraperitoneal injection with pomegranate extract applied to fishes that had been naturally infected with lymphocystis disease virus, stimulated their innate immune response, and reduced their mortality due to lymphocystis infection (Harikrishnan et al., 2010). In humans, oral administration of pomegranate extract enriched with ellagic acid is beneficial for minimizing ultraviolet-induced skin damage (Kasai et al., 2006), while hydro-alcoholic extracts of pomegranate have a significant antibacterial activity and are therefore useful for treatment of dental plaques (Menezes et al., 2009). Many studies also demonstrated potent vasculoprotective effects of pomegranate and its constituents, as presented below.

**BIOACTIVE CONSTITUENTS OF POMEGRANATE**

Bioactive substances of pomegranate include, for example, hydrolyzable tannins (gallotannins and ellagittannins), ellagic acid and its derivatives, gallic acid, anthocyanins/anthocyanidins, proanthocyanidins, flavonoids, vitamins, as well as sterols, lignans, saccharides, fatty acids, organic acids, terpenes, and terpenoids, among others. Ellagittannins and gallotannins together with ellagic acid and its derivatives are crucial bioactive compounds of pomegranate (Amakura et al., 2000a; Gil et al., 2000; Fischer et al., 2011a; Borger and Crozier, 2012; Brightenti et al., 2017). Furthermore, ellagitannins and gallotannins are hydrolyzed to ellagic acid and glucose or gallic acid and glucose, respectively (Arapitas, 2012). In addition, pomegranate is a source of numerous (poly)phenolic compounds (Fischer et al., 2011a). Anthocyanins present in pomegranate comprise mainly delphinidin 3-glucoside, delphinidin 3,5-diglucoside, pelargonidin 3-glucoside, pelargonidin 3,5-diglucoside, cyanidin 3-glucoside, and cyanidin 3,5-diglucoside (Alighourchi et al., 2008; Fischer et al., 2013; Lantzouraki et al., 2015), and the characteristic colors of pomegranate fruits are attributed to them. Pomegranate seeds contain different fatty acids with the most represented punicic acid (Schubert et al., 1999; Kaufman and Wiesman, 2007; Pande and Akoh, 2009; Verardo et al., 2014; Görnaš and Rudzinska, 2016). Flavol-3-ols, flavonoid glycosides, phenolic acids, and hydrolyzable tannins represent main phenolic compounds in pomegranate seed residue (He et al., 2011). In pomegranate peel, gallic acid is a major phenolic constituent while kaempferol-3-O-glucoside is the most represented flavonoid (Ambigaipalan et al., 2016). Triterpenoids oleanolic acid and ursolic acid are present in pomegranate flower (Fu et al., 2014). Volatile components of pomegranate comprise monoterpenes, monoterpenoids, aldehydes, alcohols, and linear hydrocarbons monoterpenes, especially represented by alpha-terpinene, alpha-terpineol, and 3-carene (Vázquez-Araújo et al., 2011; Carbonell-Barrachina et al., 2012). An overview of compounds identified in pomegranate is outlined in Table 1.

**VASCULOPROTECTIVE EFFECTS OF VARIOUS PARTS OF POMEGRANATE REVEALED IN IN VITRO AND IN VIVO MODELS**

Many pomegranate-derived compounds exhibit a wide range of vasculoprotective effects. Various pomegranate parts
(components) have proven to reduce oxidative stress, lipid peroxidation, and generation of foam cells, to positively influence endothelial cell function (by increasing NO levels and lowering glucose levels), to attenuate platelet aggregation and diminish hypertension, thus altogether improving vascular function, as presented below. In addition, pomegranate and its components are protective against toxicity induced by chemicals or drugs (Table 2 and the text below).

### Pomegranate Juice and Extract

In 2000s, Gil et al. in their pivotal study pointed out the strong antioxidant properties of pomegranate juice enriched with tannin punicalagin, anthocyanins, ellagic acid derivatives, as well as other phenolic substances. Using different analytical methods, the authors revealed potent antioxidant activities of pomegranate juice that were three times higher than the well-known antioxidative properties of red wine or green tea (Gil et al., 2000). These findings were confirmed by subsequent studies that additionally pointed to vasculoprotective effects of pomegranate products, as presented below.

In a study involving mice as well as human volunteers, pomegranate juice intake attenuated oxidative stress (Aviram et al., 2000). More specifically, in apolipoprotein E-deficient mice, food supplementation with pomegranate juice reduced by 44% the size of atherosclerotic lesions and diminished the number of foam cells in such lesions (Aviram et al., 2000). In humans, intake of pomegranate juice diminished the susceptibility of low-density lipoproteins (LDLs) to aggregate and enhanced by up to 20% the activity of serum paraoxonase (Aviram et al., 2000), an esterase that is associated with high-density lipoproteins (HDLs) and can protect lipids against peroxidation (Chistiakov et al., 2017). Pomegranate juice also inhibited the oxidized LDL (oxLDL) uptake and cholesterol biosynthesis in a J774.A1 macrophage-like cell line (Fuhrman et al., 2005). A study utilizing diabetic mice model suggested that these protective effects might be due to the presence of unique complex sugars and/or phenolic sugars in pomegranate juice (Rozenberg et al., 2006). Another study involved high and low exercise lifestyle mimicking rats (high- and low-capacity runners) fed with pomegranate juice for 3 weeks (Rosenblat et al., 2015). While the effects were stronger in a group of low-capacity runners, the consumption of pomegranate juice decreased the cellular oxidation and increased the paraoxonase 2 activity in peritoneal macrophages from both animal groups when compared with non-treated cohorts of animals (Rosenblat et al., 2015).

In cultured human coronary artery endothelial cells exposed to high shear stress, pomegranate juice down-regulated the expression of redox sensitive genes ELK-1 and p-JUN and increased the expression of endothelial nitric oxide synthase (eNOS) (De Nigris et al., 2005) that is necessary for the proper functioning of blood endothelial cells (Vallance and Chan, 2001). In addition, an intake of pomegranate juice by LDL receptor-deficient mice fed with high-cholesterol diet, lessened progression of atherogenesis at different stages of the disease (De Nigris et al., 2005). Another in vitro study using cultured bovine pulmonary artery endothelial cells showed that the presence of even very low amounts of pomegranate juice in the cultivation medium protects the generated nitric oxide (NO) against its oxidative destruction (via an inhibition of a superoxide anion-mediated disappearance of NO, leading to an enhancement of the bioavailability of NO) (Ignarro et al., 2006). Another study of this group showed that presence of pomegranate juice in human coronary artery endothelial cells reverts down-regulation of the expression of eNOS caused by the addition of oxLDL (De Nigris et al., 2006). In a study accomplished in hypercholesterolemic mice, an intake of pomegranate juice enriched with punicalagin increased the eNOS expression and decelerated the progression of atherosclerosis, as well as enhanced nitrates levels (De Nigris et al., 2007). In pigs, an intake of the commercial pomegranate extract Pomanox® made from dried pomegranate skin or husk could reduce coronary endothelial dysfunction induced by hyperlipidemia (Vilahur et al., 2015). These beneficial effects included an activation of the protein kinase B (Akt)/eNOS pathway and an attenuation of vascular inflammation as well as of vascular damage induced by oxidative stress (Vilahur et al., 2015).

Furthermore, pomegranate juice attenuated the aggregation of human platelets exposed to collagen or arachidonic acid ex vivo (Aviram et al., 2000; Mattiello et al., 2009), by attenuating calcium mobilization, thromboxane A2 production, and hydrogen peroxide formation (Mattiello et al., 2009). These effects were assigned to the presence of polyphenols in pomegranate products (Mattiello et al., 2009). It was also shown that pomegranate fruit extract was active at a 2.0 μM concentration that is possible to be achieved after polyphenol-rich food intake by humans (Mattiello et al., 2009). On the other side, pomegranate seed oil inhibited cyclooxygenase (COX)
| Pomegranate phytochemicals | Pomegranate part | References |
|-----------------------------|------------------|------------|
| **(1) ALKALOIDS**           |                  |            |
| Caffeine                    | Peel*            | Elsherbiny et al., 2016 |
| N-(2′,5′-dihydroxyphenyl) pyridium chloride | Leaf | Nawwar et al., 1994b |
| Peeliterine                 | Peel, bark       | Neuhof et al., 1993; Vidal et al., 2003 |
| **(2) ANTHOCYANINS/ANTHOCYANIDINS** |          |            |
| Cyanidin glucosides and derivatives | Juice, seed, peel | Hernandez et al., 1999; Noda et al., 2002; Alighourchi et al., 2008; Türkylmaz, 2013; Ambigaipalan et al., 2016; Wafa et al., 2017 |
| Delphinidin glucosides and derivatives | Juice, peel | Hernandez et al., 1999; Noda et al., 2002; Alighourchi et al., 2008; Türkylmaz, 2013; Ambigaipalan et al., 2016; Wafa et al., 2017 |
| (Epi) afzelchin-delphinidin-3-O-hexoside | Seed | Ambigaipalan et al., 2017 |
| Malvidin glucosides and derivatives | Juice | Borges and Crozier, 2012; Pérez-Ramírez et al., 2018 |
| Pelargonidin glucosides and derivatives | Juice, peel | Hernandez et al., 1999; Noda et al., 2002; Alighourchi et al., 2008; Türkylmaz, 2013; Wafa et al., 2017 |
| Peonidin-3-O-(6″-O-acetyl)glucoside | Juice | Borges and Crozier, 2012 |
| Vitisin A                   | Juice            | Borges and Crozier, 2012 |
| **(3) ELLAGIC ACID AND DERIVATIVES** |          |            |
| Ellagic acid                | Juice, peel, seed, flower | Amakura et al., 2000b; Gil et al., 2000; Wang et al., 2004; Jain et al., 2011; Wafa et al., 2017 |
| Ellagic acid glucosides and derivatives | Juice, peel | Gil et al., 2000; Wafa et al., 2017 |
| **(4) FATTY ACIDS**         |                  |            |
| Arachidic acid, behenic acid, docosadienoic acid, eicosapentaenoic acid, erucic acid, gondoic acid, lignoceric acid, inoleic acid, linolealaidic acid, linolenic acid, myristic acid, margaric acid, nervonic acid, oleic acid, palmitic acid, palmtoleic acid, punicic acid, stearic acid, cis-vaccenic acid | Seed | Hopkins and Chisholm, 1968; Schubert et al., 1999; Kaufman and Wiesman, 2007; Pande and Akoh, 2009; Elalleh et al., 2011; Verardo et al., 2014; Siano et al., 2016 |
| **(5) FLAVONOIDS AND DERIVATIVES** |          |            |
| Acetyl prunin, diosmetin glucoside | Juice | Fanali et al., 2016 |
| Apigenin                    | Leaf            | Nawwar et al., 1994b |
| Apigenin-rhamnoside, chrysin | Juice | Lantzouraki et al., 2015 |
| Catechin                    | Juice, seed, peel | De Pascual-Teresa et al., 2000; Mphahlele et al., 2014; Ambigaipalan et al., 2016 |
| Datisin-hexoside            | Juice            | Mena et al., 2012 |
| Dihydroxygalocatechin       | Peel             | Ambigaipalan et al., 2016 |
| Epicatechin                 | Juice, peel      | De Pascual-Teresa et al., 2000; Mphahlele et al., 2014 |
| Eriodictyol 7-O-β-glucoside  | Juice            | Mphahlele et al., 2014 |
| Flavan-3-ol                 | Juice, peel      | De Pascual-Teresa et al., 2000 |
| Gallocatechin               | Peel             | Wafa et al., 2017 |
| Hesperidin                  | Juice            | Mphahlele et al., 2014 |
| Kaempferol                  | Peel             | Van Elsrijk et al., 2004 |
| Kaempferol glucoside(s)     | Juice, seed, peel | Van Elsrijk et al., 2004; Mphahlele et al., 2014; Lantzouraki et al., 2015; Ambigaipalan et al., 2016 |
| Luteolin                    | Peel, fruit      | Van Elsrijk et al., 2004; Han et al., 2015 |
| Myricetin and its glucoside | Juice            | Naz et al., 2007; Lantzouraki et al., 2015 |
| Naringin                    | Juice, peel      | Kim et al., 2002; Mphahlele et al., 2014 |
| Phloretin                   | Peel, seed, juice | Han et al., 2015 |
| Phloridzin                  | Juice            | Hmid et al., 2017 |
| Pinocembrin                 | Juice            | Calani et al., 2013 |

(Continued)
| Pomegranate phytochemicals | Pomegranate part | References |
|----------------------------|-----------------|------------|
| Quercetin and its derivatives | Juice, seed, peel | Artik, 1998; Naz et al., 2007; Borges and Crozier, 2012; Han et al., 2015; Lantzouraki et al., 2015; Ambigaipalan et al., 2016 |
| Rutin | Juice, peel | Artik, 1998; Mphahlele et al., 2014 |
| Taxifolin and its glycosides | Peel, seed, juice | Calani et al., 2013; Han et al., 2015 |
| **(6) LIGNANS** | | |
| Isolariocresinol, mataresinol, medioresinol, pinoresinol, secoisolariocresinol, syringaresinol | Fruit, seed | Bonzanini et al., 2009 |
| **(7) ORGANIC ACIDS** | | |
| Citric acid | Juice | Poyrazoglu et al., 2002; Carbonell-Barrachina et al., 2012; Gundogdu and Yilmaz, 2012; Legua et al., 2012; Lantzouraki et al., 2015 |
| Fumaric acid | Juice | Poyrazoglu et al., 2002; Gundogdu and Yilmaz, 2012 |
| Lactic acid | Juice | Gundogdu and Yilmaz, 2012 |
| Malic acid | Juice | Poyrazoglu et al., 2002; Carbonell-Barrachina et al., 2012; Lantzouraki et al., 2015 |
| Methylmalonic acid | Juice | Alper et al., 2011 |
| Oxalic acid | Juice | Legua et al., 2012 |
| Quinic acid | Juice, peel | Artik, 1998; Amakura et al., 2000a; Ehling and Cole, 2011 |
| Succinic acid | Juice | Poyrazoglu et al., 2002; Alper et al., 2011 |
| Tartaric acid | Juice | Poyrazoglu et al., 2002; Ehling and Cole, 2011; Legua et al., 2012 |
| Uronic acid | Peel | Hasnaoui et al., 2014 |
| **(8) OTHER PHENOLIC COMPOUNDS** | | |
| 3-Hydroxytyrosol | Peel | Elsherbiny et al., 2016 |
| Benzaldehyde | Peel | Hadrich et al., 2014 |
| Benzoic acid | Peel | Hadrich et al., 2014 |
| Brevifolin carboxylic acid | Fruit, juice | Fischer et al., 2011a,b |
| Caffeic acid and its hexoside | Juice, peel | Artik, 1998; Amakura et al., 2000a; Lantzouraki et al., 2015 |
| Chlorogenic acid | Juice, peel | Artik, 1998; Amakura et al., 2000a; Hasnaoui et al., 2014 |
| Cinnamic acid | Juice | Lantzouraki et al., 2015 |
| Coniferyl 9-O-[(β-α-piofuranosyl) (1→6)-O-β-d-glucopyranoside | Seed | Wang et al., 2004 |
| Cyanidin-pentoside-hexoside | Fruit | Fischer et al., 2011a |
| Ethyl cinnamate | Juice | Cadwallader et al., 2010 |
| Ferulic acid and its hexoside | Juice | Lantzouraki et al., 2015 |
| Gallic acid | Juice, seed, peel | Amakura et al., 2000b; Huang et al., 2005a; Jan et al., 2011; Mphahlele et al., 2014; Ambigaipalan et al., 2016; Fanali et al., 2016 |
| Protocatechuic acid | Juice, seed, peel | Ambigaipalan et al., 2016; Fanali et al., 2016 |
| p-Coumaric acid | Juice, peel, seed | Artik, 1998; Amakura et al., 2000a; Ambigaipalan et al., 2017 |
| Salicylic acid | Peel | Elsherbiny et al., 2016 |
| Sesamin, 4-hydroxysemin | Peel | Jiang et al., 2012 |
| Vanillic acid | Juice | Mena et al., 2012 |
| **(9) PROANTHOCYANIDINS** | | |
| Procyanidin dimer B2 and B3 | Peel | Ambigaipalan et al., 2016 |
| Arabinose, xylose, galactose, glucose, mannose, rhamnose | Peel | Hasnaoui et al., 2014 |
| Pomegranate phytochemicals | Pomegranate part | References |
|---------------------------|-----------------|------------|
| **(10) SACCHARIDES**     |                 |            |
| Glucose, fructose, maltose, sucrose | Juice | Carbonell-Barrachina et al., 2012; Legua et al., 2012; Vegara et al., 2014; Conidi et al., 2017 |
| **(11) STEROLS**         |                 |            |
| β-Sitosteryl acetate      | Peel            | Jiang et al., 2012 |
| Avenasterol, Δ7-avenasterol, campesterol, cycloartenol, Δ7-stigmasterol, stigmastanol, β-sitosterol | Seed | Górnaś and Rudzinska, 2016 |
| Campesterol               | Seed            | Abd El Wahab et al., 1998 |
| Daucoesterol              | Seed            | Wang et al., 2004 |
| Stigmasterol              | Seed            | Abd El Wahab et al., 1998 |
| **(12) TANNINS (GALLOTANNINS AND ELLAGITANNINS AND THEIR DERIVATIVES)** | | |
| 1,2,3-Tri-O-galloyl-β-4C1-glucose | Leaf | Nawwar et al., 1994a |
| 2-O-Galloylpunicin        | Juice           | Borges and Crozier, 2012 |
| 3,3′-Di-O-methyllellagic acid | Seed         | Wang et al., 2004 |
| 3,3′,4′-Tri-O-methyllellagic acid | Seed         | Wang et al., 2004 |
| Castalagin                | Juice, peel     | Fischer et al., 2011a |
| Castalin                  | Fruit, juice    | Fischer et al., 2011b |
| Casuarrin (Galloyl-bis-HHDP-hexoside) | Peel | Satomi et al., 1993; Ambigaipalan et al., 2016 |
| Corilagin (Galloyl-HHDP-hexoside) | Peel, leaf | Satomi et al., 1993; Nawwar et al., 1994a; Ambigaipalan et al., 2016 |
| Epicatechin gallate       | Peel            | Ambigaipalan et al., 2016 |
| Flavogallonic acid        | Peel            | Jiang et al., 2012 |
| Gallagic acid             | Peel, juice     | Tzulker et al., 2007 |
| Gallaglidacton            | Peel            | Satomi et al., 1993; Anibal et al., 2013 |
| Granatin A/B              | Peel            | Tanaka et al., 1990; Wafa et al., 2017 |
| Lagerstannin C (Galloyl-HHDP-glucronic) | Peel | Wafa et al., 2017 |
| Pedunculagin I (bis-HHDP-hexoside) | Juice, peel | Satomi et al., 1993; Lantzouraki et al., 2015; Wafa et al., 2017 |
| Penta-galloylgucopyranose | Seed            | He et al., 2011 |
| Punicocaritin A, B, C, and D | Peel, bark | Tanaka et al., 1986a; Anibal et al., 2013 |
| Punicarin                 | Leaf            | Nawwar et al., 1994a |
| Punicalagin (HHDP-gallagyl-hexoside) | Juice, peel, leaf | Tanaka et al., 1986b; Jain et al., 2011; Anibal et al., 2013; Lantzouraki et al., 2015 |
| Punicalin α and β         | Peel, juice, leaf | Tanaka et al., 1986b; Tzulker et al., 2007; Jain et al., 2011; Wafa et al., 2017 |
| Punicatannin C            | Flower          | Yuan et al., 2013 |
| Pungilaguin (Digalloyl-HHDP-glucoside) | Peel | Wafa et al., 2017 |
| Tellimagrandin            | Peel            | Satomi et al., 1993 |
| Tergallaglic acid-O-glucose | Juice       | Borges and Crozier, 2012 |
| Valoneic acid bilactone   | Juice           | Fischer et al., 2011a,b |
| **(13) TERPENES AND TERPENOIDS** | | |
| 3-Carene, α-terpinene, α-terpineol, eugenol | Juice | Carbonell-Barrachina et al., 2012 |
| Asiatic acid              | Flower          | Batta and Rangaswami, 1973 |
| Betulinol, 24-methyleneoctanol, cycloartenol, squalene | Seed | Verardo et al., 2014 |
| Camphor                   | Peel            | Hadrich et al., 2014 |
| Eugenol                   | Juice           | Carbonell-Barrachina et al., 2012 |
| Mastin acid               | Flower          | Batta and Rangaswami, 1973 |
| Oleanolic acid            | Flower          | Huang et al., 2005b; Fu et al., 2014 |
| α/β-Pinenes, limonene, terpineol, β-farnesene, β-caryophyllene, bisabolene | Juice | Vázquez-Araújo et al., 2011 |

(Continued)
**TABLE 1** | Continued

| Pomegranate phytochemicals | Pomegranate part | References |
|----------------------------|------------------|------------|
| Punicaone, 1α,6-hydroxy-3-oxoolean-12-en-28-oic acid, 3β,24-dihydroxyurs-12-en-28-oic acid, betulin, betulinic acid, borneol, friedelin, lantanolic acid, lupeol, oleanic acid | Peel | Jiang et al., 2012 |
| Ursolic acid | Seed, flower | Ahmed et al., 1995; Huang et al., 2005a; Fu et al., 2014 |

**TABLE 2** | Vasculoprotective effects of pomegranate determined in vitro and in vivo pre-clinical studies.

| Vasculoprotective effects | Pomegranate part | References |
|---------------------------|------------------|------------|
| Antioxidative properties in vitro and in vivo | Juice, fruit extract, peel extract | Gil et al., 2000; Les et al., 2015; Delgado et al., 2016 |
| Suppression of peroxidation of plasma lipids, induction of serum paraoxonase activity, lowering lipid uptake by macrophages, and diminishing development of atherosclerosis in mice | Juice, fruit extract | Aviram et al., 2000; Fuhrman et al., 2005; Rosenblat et al., 2015; Mollazadeh et al., 2016 |
| Improvement of endothelial cell function in vitro, in mice and pigs [due to an activation of the protein kinase B (Akt)/eNOS pathway, an inhibition of a superoxide anion-mediated disappearance of NO, and reduction of vascular inflammation] | Juice, fruit extract | De Nigris et al., 2005; de Nigris et al., 2006; De Nigris et al., 2007; Ignarro et al., 2006; Vilahur et al., 2015 |
| Reduction the collagen- and arachidonic acid-induced platelet aggregation ex vivo | Juice, fruit extract | Aviram et al., 2000; Mattiello et al., 2009 |
| Reduction in activity of angiotensin-converting enzyme (ACE); decrease in mean arterial blood pressure in rats | Juice, fruit extract, peel extract | Mohan et al., 2010; Dos Santos et al., 2016; Arun et al., 2017 |
| Lessening cardiac toxicity induced by drugs or smoking (diminishing lipid peroxidation and increasing levels of antioxidant enzymes) | Juice, fruit extract | Jadeja et al., 2010; Al Hariri et al., 2016 |
| Reduction of blood glucose levels in a variety of mouse and rat models [effects mediated via upregulation of PPAR-γ leading to an increase in insulin sensitivity] | Seed-, flower-, and peel-extract | Das et al., 2001; Huang et al., 2005a; Li et al., 2005; Vroegrijk et al., 2011; Salwe et al., 2015 |
| Lowering fatty acid, triglycerides and total cholesterol plasma levels as well as cardiac triglycerides (in Zucker diabetic fatty rats) | Flower extract | Huang et al., 2005b |

*Peel (pericarp, rind, and hull are synonyms).*

(Schubert et al., 1999), the key enzyme catalyzing the conversion of arachidonic acid to prostaglandin (PGI2) (Grosser et al., 2006). The latter substance is known as a potent vasoprotective factor inhibiting platelet adhesion and thrombus formation on endothelium (Weiss and Turitto, 1979). In addition, feeding of rats with pomegranate extract diminished in colonic mucosa levels of COX-2, prostaglandin E2 (PGE2) as well as inducible nitric oxide synthase (iNOS) (Larrosa et al., 2010b).

Some other works investigated how pomegranate affects arterial hypertension, an important risk factor for cardiovascular diseases (Pickering, 1972). For example, in a study involved the use of Wistar rats in which diabetes was induced by streptozotocin administration, and the animals were additionally challenged by a subcutaneous administration of angiotensin II to induce hypertension, a prolonged administration of pomegranate juice (for 4 weeks) reduced activity of angiotensin converting enzyme (ACE), as well as decreased mean arterial blood pressure in comparison with non-treated animals (Mohan et al., 2010).

Pomegranate fruit extracts were also studied regarding their protective effect against cardiac toxicity induced by drugs or smoking. For example, detrimental effects of a cardiotoxic drug isoproterenol (known to cause a cardiac necrosis leading to a myocardial infarction) were reduced upon pre-treatment of rats with pomegranate juice for 30 consecutive days before isoproterenol treatment (Jadeja et al., 2010). Such pre-treatment significantly lessened an increase in the heart weight, infarction size, plasma marker enzymes, lipid peroxidation levels as well as levels of Ca$^{2+}$ ATPase (Jadeja et al., 2010). The protective effects of pomegranate juice intake were also demonstrated in a study using rats in which a cardiac hypertrophy was induced by cigarette smoke exposure (Al Hariri et al., 2016).
Pomegranate Seed Oil

Pomegranate seeds comprise about 3% of the pomegranate weight and contain about 12–20% seed oil (Lansky and Newman, 2007) that is rich in fatty acids and contains mainly punicic acid (Kaufman and Wiesman, 2007; Verardo et al., 2014; Górnaś and Rudzinska, 2016).

In rats with streptozotocin-induced diabetes, oral feeding with seed extracts significantly reduced blood glucose levels (Das et al., 2001). In mice, an intake of pomegranate seed oil counteracted their obesity induced by a high-fat diet by enhancing peripheral insulin sensitivity (Vroegrijk et al., 2011). Oral treatment of the above cited diabetic rats with pomegranate seed oil significantly decreased peroxidation of plasma lipids (Mollazadeh et al., 2016). In addition, such treatment diminished malondialdehyde content in homogenates from the heart and kidney tissues, and reduced triglyceride levels in treated animals in comparison to the control cohort (Mollazadeh et al., 2016).

Pomegranate Flower, Peel, and Leaf Extracts

A 6-week oral administration of pomegranate flower extracts suppressed plasma glucose levels in Zucker diabetic fatty rats following their exposure to glucose-loading. In addition, such treatment in these animals increased cardiac peroxisome proliferator-activated receptor gamma (PPAR-γ) mRNA expression as well as restored the down-regulated cardiac glucose transporter (GLUT)-4 mRNA, altogether improving insulin sensitivity (Huang et al., 2005a). These beneficial effects were assigned mainly to the presence of gallic acid (Huang et al., 2005a). A long-term treatment of Zucker diabetic fatty rats with pomegranate flower extracts was cardioprotective, as it lowered their fatty acid-, triglyceride-, and total cholesterol plasma levels as well as reduced the cardiac triglycerides content (Huang et al., 2005b). In another study, oral administration of pomegranate flower extracts decreased plasma glucose levels in non-fasted diabetic rats (but not in fasted-diabetic rats or in normal rats). This study also showed that pomegranate flower extracts inhibit α-glucosidase (a key enzyme for carbohydrate digestion in intestines) and administration of pomegranate flower extracts may improve postprandial hyperglycemia in type 2 diabetes, and altogether diminish the risk of cardiovascular dysfunctions (Li et al., 2005). In mice fed with a high-fat diet to induce obesity, treatment with pomegranate leaf extract decreased body weight, energy intake as well as total cholesterol, triglyceride, and glucose levels (Lei et al., 2007). Administration of hydroalcoholic peel or leaf extracts of pomegranate for 28 days decreased blood glucose levels in a Wister rat model of diabetes induced by streptozotocin (Salwe et al., 2015). Hydroalcoholic peel extracts of pomegranate were also tested in spontaneously hypertensive ovariectomized female rats (an animal model for menopause characterized by an increase in the superoxide anion levels; Delgado et al., 2016). Such treatment diminished elevation of superoxide anion levels and lessened oxidative stress in this animal model (Delgado et al., 2016). Treatment of spontaneously hypertensive rats of different ages for 30 days with pomegranate peel extracts, significantly reduced systolic blood pressure, ACE activity, oxidative stress as well as vascular remodeling (Dos Santos et al., 2016). A recent in vitro study showed that pomegranate peel methanolic extracts potently scavenge superoxide and hydroxyl radicals, protect LDL against oxidation and suppress ACE activity (Arun et al., 2017). Altogether, these studies demonstrated that also the non-edible parts of pomegranate—peel and leaves—exhibit vasculoprotective effects.

VASCULOPROTECTIVE EFFECTS OF PURE COMPOUNDS DERIVED FROM POMEGRANATE

Studies presented above showed the numerous vasculoprotective effects of different parts of the pomegranate. It was suggested that many of these protective effects are caused by the presence of hydrolyzable tannins (ellagitannins and gallotannins), their derivative ellagic acid, or their common metabolites urolithins (Table 3 and the text below).

Pomegranate ellagitannins and a single high molecular weight ellagitannin punicalagin, attenuated the inflammatory cell signaling in colon cancer cells (Adams et al., 2006). Punicalagin and gallic acid induced in isolated macrophages the expression of paraoxonase 2 (Shiner et al., 2007). These substances also reduced oxidative stress in macrophages via activation of transcription factors PPAR-γ and activator protein 1 (AP-1; Shiner et al., 2007).

Single components (e.g., punicalin, punicalagin, ellagic acid, and gallic acid) isolated from pomegranate fruit suppressed the formation of advanced glycation end products (AGEs, known to contribute to a number of diseases including diabetic complications and arteriosclerosis) from bovine serum albumin and sugar in antglycation assays in vitro (Kumagai et al., 2015). Pomegranate fruit extracts also reduced the accumulation of AGEs in mice fed with a high-fat and high-sucrose diet (Kumagai et al., 2015). In addition, punicalagin and ellagic acid inhibited lipid metabolism in mouse and human adipocytes ex vivo (Les et al., 2017).

Effects of ellagic acid on reactive oxygen species (ROS) generation were also investigated in endothelial cells. Pretreatment of HUVECs with ellagic acid attenuated ROS production and prevented eNOS downregulation induced by oxLDL (Lee et al., 2010; Ou et al., 2010). Ex vivo, ellagic acid stimulated vasorelaxation of the rat thoracic aorta via an endothelium-dependent mechanism and an inhibition of calcium influx (Yilmaz and Usta, 2013). Nevertheless, as ellagitannins and ellagic acid in vivo metabolize into urolithins that enter systemic circulation (Cerdà et al., 2005; Larrosa et al., 2010a), researchers also studied how these metabolites affect the vascular function.

The antioxidant properties of different urolithins were evaluated in a cell-based assay and the results showed that urolithin C and D were more potent antioxidants than the parental substance ellagic acid and punicalagin (Bialonska et al., 2014).
In a subsequent study, urolithin A inhibited the adhesion of monocytes to endothelial cells, partly by counteracting eNOS-dependent decrease in NO production. Reduction in myocardial ischemia/reperfusion injury and myocardial infarct size in vivo might be partly mediated by urolithin A glucuronide (Gimenez-Bastida et al., 2012). In addition, a recent in vitro study showed potent anti-atherogenic properties of ellagic acid and some urolithins (Mele et al., 2016). All these compounds reduced the adhesion of THP-1 derived macrophages to HUVECs and diminished secretion of soluble vascular cell adhesion molecule-1 (VCAM-1) and inflammatory interleukin-6 (IL-6) (Mele et al., 2016). In a study utilizing cultured human artery endothelial cells, urolithin A attenuated endothelial dysfunction induced by oxLDL (Han et al., 2016). These effects were partly mediated by counteracting eNOS-dependent decrease in NO production (Han et al., 2016). In addition, urolithin A reduced the expression of intracellular adhesion molecule-1 (ICAM-1) and monocyte chemotactic protein 1 (MCP-1), upon adhesion of THP-1 cells to the endothelial cells. Urolithin A also suppressed the expression of tumor necrosis factor-α (TNF-α), IL-6 and endothelin-1, increased PPAR-γ mRNA expression, and downregulated phosphorylation of the extracellular signal-regulated protein kinase 1/2 (ERK1/2) (Han et al., 2016). In another study, urolithin A inhibited heme peroxidases [myeloperoxidase (MPO) and lactoperoxidase (LPO)] more effectively than its parent compound ellagic acid (Saha et al., 2016). Animal experiments using C57BL/6 mice revealed potent anti-inflammatory properties of urolithin A, as it efficiently reduced phorbol myristate acetate (PMA)-induced mouse ear edema formation (Saha et al., 2016). Urolithin A also lessened myocardial ischemia/reperfusion injury and reduced myocardial infarct size in mice via the phosphoinositide 3-kinase/Akt (PI3K/Akt) pathway (Tang et al., 2017).

In addition to the above presented effects of hydrolyzable tannins (ellagitannins and gallotannins), their derivative ellagic acid, or their common metabolites urolithins, but also other substances were shown to contribute to beneficial effects of pomegranate products. These include (poly)phenolic compounds anthocyanins (Alighourchi et al., 2008; Fischer et al., 2011a) and flavonoids (Sudheesh and Vijayalakshmi, 2005; Ricci et al., 2006), as well as fatty acids (Kaufman and Reshef et al., 2005). For example, anthocyanins exhibit anti-inflammatory activities (Vendrame and Klimis-Zacas, 2015). Flavonoid naringin abundantly present in pomegranate juice (Mphahlele et al., 2014) is considered to contribute (together

---

**TABLE 3 | Vasculoprotective effects of pomegranate-derived substances or their metabolites, as determined in vitro and in vivo pre-clinical studies.**

| Vasculoprotective effects                                                                 | Vasculoprotective substances                      | References                      |
|-------------------------------------------------------------------------------------------|--------------------------------------------------|---------------------------------|
| Induction of paraoxonase 2 and reduction in oxidative stress in isolated macrophages       | Punicalagin, gallic acid                          | Shiner et al., 2007             |
| Attenuation of reactive oxygen species (ROS) generation and prevention of eNOS downregulation induced by oxLDL in HUVECs. Stimulation of vasorelaxation of the rat thoracic aorta ex vivo, via an endothelium-dependent mechanism and through an inhibition of calcium influx | Elagic acid                                       | Lee et al., 2010; Ou et al., 2010; Yilmaz and Usta, 2013 |
| Suppression of formation of advanced glycation end products (AGEs) in vitro and in mice    | Punicalin, punicalagin, ellagic acid, gallic acid | Kumagai et al., 2015            |
| Inhibition of lipid metabolism in adipocytes                                               | Punicalagin, ellagic acid                         | Les et al., 2017                |
| Antioxidative properties in a cell-based assay in vitro                                    | Urolithins                                       | Bialonska et al., 2009          |
| Inhibition of adhesion of monocytes to endothelial cells, of secretion of a cellular adhesion molecule (VCAM-1) and pro-inflammatory cytokine (IL-6). Decrease in the accumulation of cholesterol in THP-1-derived macrophages | Elagic acid, urolithin A glucuronide, other urolithins | Gimenez-Bastida et al., 2012; Mele et al., 2016 |
| Attenuation of endothelial dysfunction induced by oxLDL in cultured human artery endothelial cells, partly by counteracting eNOS-dependent decrease in NO production. Reduction in myocardial ischemia/reperfusion injury and myocardial infarct size in vivo | Urolithin A                                      | Han et al., 2016; Tang et al., 2017 |
| Anti-hypertensive effects of sweetie juice in humans                                       | Naringin                                         | Reshef et al., 2005             |
| Amelioration of glucose tolerance and diminishing obesity-related inflammation via activation of PPAR-γ and -α | Puninic acid                                     | Fontecillas et al., 2009        |

(2009). Nonetheless, although an in vitro antioxidant potential of urolithin A was relatively low in comparison with other urolithins, its plasma concentrations was the highest among them (Bialonska et al., 2009). In a subsequent study, urolithin A glucuronide inhibited adhesion of monocytes to endothelial cells in the micromolar range (5-15µM), suggesting that the beneficial effects of pomegranate intake on the vasculature might be partly mediated by urolithin A glucuronide (Gimenez-Bastida et al., 2012). In addition, a recent in vitro study showed potent anti-atherogenic properties of ellagic acid and some urolithins (Mele et al., 2016). All these compounds reduced the adhesion of THP-1 derived macrophages to HUVECs and diminished secretion of soluble vascular cell adhesion molecule-1 (VCAM-1) and inflammatory interleukin-6 (IL-6) (Mele et al., 2016).
with flavonoid naritutin) to the anti-hypertensive effects of sweetie juice in humans (Reshef et al., 2005). Puninic acid was shown to ameliorate glucose tolerance and diminish obesity-related inflammation via an activation of PPAR-γ and α (Hontecillas et al., 2009). Quercetin present in juice, seed, and peel of pomegranate (Artik, 1998; Borges and Crozier, 2012; Ambigaipalan et al., 2016) is known to mediate endothelium-dependent vasodilatation via stimulation of both the NO/cyclic guanyllyl monophosphate (cGMP) pathway and endothelium-derived hyperpolarizing factor (EDHF) (Khoo et al., 2010).

**CLINICAL STUDIES ON POMEGRANATE IN THE CONTEXT OF CARDIOVASCULAR DISEASES**

Many clinical studies investigating the effects of pomegranate in the context of CVDs were performed in the last two decades. These works profusely demonstrated the vasculoprotective properties of pomegranate products (Table 4). Nevertheless, some of these studies pointed to the fact that when applying pomegranate for a longer period or in high amounts, certain possible side effects of such treatment (mainly diarrhea) might occur (Paller et al., 2013).

In hypertensive patients, daily consumption of pomegranate juice for 2 weeks reduced the activity of ACE by 36% as well as diminished systolic blood pressure by 5% (Aviram and Dornfeld, 2001). The same group also reported that a long-duration intake of pomegranate juice (for 3 years) by patients with carotid artery stenosis significantly reduced their blood pressure, LDL oxidation and common carotid intima-media thickness (Aviram et al., 2004). A 4-week consumption of pomegranate juice reduced significantly blood pressure in a cohort of 51 healthy women (without significantly changing serum ACE activity; Lynn et al., 2012). Another study involving 13 hypersensitive men demonstrated that intake of pomegranate juice lowered blood pressure (Asgary et al., 2013). However, in these patients the levels of some clinical parameters, such as serum concentrations of C-reactive protein (CRP), E-selectin, VCAM-1, ICAM-1, and IL-6 remained unchanged (Asgary et al., 2013). A subsequent study involving 21 hypertensive patients showed that consumption of pomegranate juice significantly reduced systolic as well as diastolic blood pressure (Asgary et al., 2014). In addition, a double blind, randomized, placebo controlled pilot study revealed that the pomegranate peel hydroalcoholic extract reduced cardiovascular risk factors in obese women with dyslipidemia (Haghighian et al., 2016).

Although a meta-analysis evaluating the effects of pomegranate consumption on CRP concentrations did not reveal a significant correlation between these parameters (Sahebkar et al., 2016), the effects of pomegranate consumption on blood pressure regulation in accomplished animal and human studies seem to be clinically relevant. In a recent review it was concluded that both pomegranate juice and seed oil can effectively lower blood pressure (Asgary et al., 2017). Another recently accomplished meta-analysis came to the same conclusions, as intake of pomegranate juice decreased levels of systolic blood pressure regardless of the duration and dose of the juice consumed in the evaluated studies, whereas doses more than 240 cc (eight ounces) exhibited a borderline significant effect in reducing of a diastolic blood pressure (Sahebkar et al., 2017). The authors of this meta-analysis determined a constant benefit of pomegranate juice intake on blood pressure, which may be considered clinically relevant. Additional information of how pomegranate affects

**TABLE 4 | Outcome of clinical studies involving intake of pomegranate juice or peel hydro alcoholic extract.**

| Type of the study/Number of probands | Clinical outcome | References |
|--------------------------------------|-----------------|------------|
| Daily consumption of pomegranate juice for 2 weeks by hypertensive patients (N = 10) | Reduction in ACE activity by 36% and of a systolic blood pressure by 5% | Aviram and Dornfeld, 2001 |
| A long-duration intake of pomegranate juice (for 3 years) by patients with carotid artery stenosis (N = 19) | Reduction in systolic blood pressure by 12%, decrease in common carotid intima-media thickness up to 30% | Aviram et al., 2004 |
| A 4-week consumption of pomegranate juice by healthy women (N = 51) | A mild, but significant reduction in blood pressure (without significantly changing serum ACE activity) | Lynn et al., 2012 |
| Intake of pomegranate juice by hypersensitive men (N = 13) | Decrease in blood pressure while other parameters (serum concentrations of CRP, E-selectin, VCAM-1, ICAM-1, and IL-6) remain unchanged | Asgary et al., 2013 |
| Consumption of pomegranate juice by hypertensive patients (N = 21) | Significant reduction in systolic as well as diastolic blood pressure | Asgary et al., 2014 |
| Intake of pomegranate peel hydro alcoholic extract by obese women with dyslipidemia (N = 38) | Significant reduction in systolic blood pressure | Haghhighian et al., 2016 |
| A meta-analysis focusing on effects of pomegranate consumption on CRP | No significant correlation between pomegranate consumption and CRP levels | Sahebkar et al., 2016 |
| A meta-analysis focusing on blood pressure lowering effects of intake of pomegranate juice | Decrease in systolic blood pressure levels (regardless of the duration and dose of the juice consumed in the evaluated studies). A borderline significant effect in reducing of diastolic blood pressure by doses higher than 240 cc (eight ounces) | Sahebkar et al., 2017 |
vasculature can be found in some other reviews (Lansky and Newman, 2007; Aviram and Rosenblat, 2013; Hyson, 2015; Zheng et al., 2017). In addition to many described beneficial effects of pomegranate on endothelial function, pomegranate juice was also found to enhance the inhibitory effect of NO on vascular smooth muscle cell proliferation (Ignarro et al., 2006). This aspect might be clinically relevant and a subject of further studies, as vascular smooth muscle cell proliferation plays an important role in the development and progression of atherosclerosis and restenosis (Uhrin et al., 2018; Wang et al., 2018).

**CONCLUSION**

Pomegranate, an ancient and highly distinctive fruit, is a rich source of natural bioactive constituents. Various studies showed that pomegranate and its products exhibit protective effects on the cardiovascular system. These vasculoprotective effects include diminishing of oxidative stress, positive influencing macrophage-, endothelial cell-, and platelet function, lowering lipid oxidation, reducing blood glucose levels, vasodilatory effects as well as decreasing blood pressure via an inhibition of ACE activity. In light of the altogether promising outcome of numerous preclinical and clinical studies, pomegranate is advocated to be used as a dietary supplement for prevention and treatment of cardiovascular diseases, thus representing a supplementary non-pharmacological therapy for cardiovascular diseases.

**AUTHOR CONTRIBUTIONS**

DW, CÖ, IA-R, SC, JP, PU, and AA wrote the first draft of the manuscript. JH and AJ prepared Tables 2–4 during the revision and NT improved the revised version of the manuscript.

**ACKNOWLEDGMENTS**

The authors are grateful to the Polish KNOW (Leading National Research Centre) Scientific Consortium Healthy Animal—Safe Food, decision of Ministry of Science and Higher Education (No. 05-1/KNOW2/2015), the Homing grant from Foundation for Polish Sciences, the Peter und Traudl Engelhorn Foundation for the promotion of Life Sciences for financial support. The funding agency did not have any role in writing or submitting this review for publication.

**REFERENCES**

Abd El Wahab, S. M., El Fiki, N. M., Mostafa, S. F., and Hassan, A. E. B. (1998). Characterization of certain steroid hormones in Punica granatum L. seeds. *Bull. Facul. Pharm. (Cairo Univ.)* 36, 11–15.

Adams, L. S., Seeram, N. P., Aggarwal, B. B., Takada, Y., Sand, D., and Heber, D. (2006). Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflammatory cell signaling in colon cancer cells. *J. Agric. Food Chem.* 54, 980–985. doi: 10.1021/jf050955r

Ahmed, R., Iftal, S. M., Safiuddin, A., and Nazeer, M. (1995). Studies on *Punica granatum*-l isolation and identification of some constituents from the seeds of *Punica granatum*. *Pak. J. Pharm. Sci.*, 69–71.

Albrecht, M., Jiang, W., Kumi-Diaka, J., Lansky, E. P., Gomersall, L. M., Patel, A., et al. (2004). Pomegranate extracts potentely suppress proliferation, xenograft growth, and invasion of human prostate cancer cells. *J. Med. Food* 7, 274–283. doi: 10.1089/jmf.2004.7.274

Al Hariri, M., Zibara, K., Farhat, W., Hashem, Y., Soudani, N., Al Ibrahim, F., et al. (2016). Cigarette smoking-induced cardiac hypertrophy, vascular inflammation and injury are attenuated by antioxidant supplementation in an animal model. *Front. Pharmacol.* 7:397. doi: 10.3389/fphar.2016.00397

Alighourchi, H., Barzegar, M., and Abbasi, S. (2008). Anthocyanins characterization of 15 Iranian pomegranate (*Punica granatum L*) varieties and their variation after cold storage and pasteurization. *Eur. Food Res. Technol.* 227, 881–887. doi: 10.1007/s00217-007-0799-1

Alper, N., Onsekizoglu, P., and Acar, J. (2011). Effects of various clarification treatments on phenolic compounds and organic acid compositions of pomegranate (*Punica granatum L*) juice. *J. Food Process. Preserv.* 35, 313–319. doi: 10.1111/j.1745-4549.2009.00458.x

Amakura, Y., Okada, M., Tsuji, S., and Tonogai, Y. (2000a). Determination of phenolic acids in fruit juices by isocratic column liquid chromatography. *J. Chromatogr.* A 891, 183–188. doi: 10.1016/S0021-9673(00)00625-7

Amakura, Y., Okada, M., Tsuji, S., and Tonogai, Y. (2000b). High-performance liquid chromatographic determination with photodiode array detection of ellagic acid in fresh and processed fruits. *J. Chromatogr. A* 896, 87–93. doi: 10.1016/S0021-9673(00)00414-3

Ambigaipalan, P., De Camargo, A. C., and Shahidi, F. (2016). Phenolic compounds of pomegranate byproducts (outer skin, mesocarp, divider membrane) and their antioxidant activities. *J. Agric. Food Chem.* 64, 6584–6604. doi: 10.1021/acs.jafc.6b02950

Ambigaipalan, P., de Camargo, A. C., and Shahidi, F. (2017). Identification of phenolic antioxidants and bioactive of pomegranate seeds following juice extraction using HPLC-DAD-ESI-MSn. *Food Chem.* 221, 1883–1894. doi: 10.1016/j.foodchem.2016.10.058

Anbil, P. C., Peixoto, I. T., Foglio, M. A., and Höfling, J. F. (2013). Antifungal activity of the ethanolic extracts of *Punica granatum* L. and evaluation of the morphological and structural modifications of its compounds upon the cells of Candida spp. *Braz. J. Microbiol.* 44, 839–848. doi: 10.1590/S1517-838220130005000060

Araptisas, P. (2012). Hydrolyzable tannin analysis in food. *Food Chem.* 135, 1708–1717. doi: 10.1016/j.foodchem.2012.05.096

Artik, N. (1998). Determination of phenolic compounds in pomegranate juice by using HPLC. *Fruit Process.* 8, 492–499.

Arun, K. B., Jayamurphy, P., Anusha, C. V., Mahesh, S. K., and Nisha, P. (2017). Studies on activity guided fractionation of pomegranate peel extracts and its effect on antidiabetic and cardiovascular protection properties. *J. Food Process. Preserv.* 41:e13108. doi: 10.1111/jfpp.13108

Asgary, S., Keshvari, M., Sahebkar, A., Hashemi, M., and Rafiean-Kopaei, M. (2013). Clinical investigation of the acute effects of pomegranate juice on blood pressure and endothelial function in hypertensive individuals. *ARYA Atheroscler.* 9, 326–331.

Asgary, S., Keshvari, M., Sahebkar, A., and Sarrafzadegan, N. (2017). Pomegranate consumption and blood pressure: a review. *Curr. Pharm. Des.* 23, 1042–1050. doi: 10.2174/1381612822666161010103339

Asgary, S., Sahebkar, A., Afshani, M. R., Keshvari, M., Haghihooryvanmard, S., and Rafiean-Kopaei, M. (2014). Clinical evaluation of blood pressure lowering, endothelial function improving, hypolipidemic and anti-inflammatory effects of pomegranate juice in hypertensive subjects. *Phytother. Res.* 28, 193–199. doi: 10.1002/ptr.4977

Aviram, M., and Dornfeld, L. (2001). Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. *Atherosclerosis* 158, 195–198. doi: 10.1016/S0021-9150(01)00412-9

Aviram, M., Dornfeld, L., Rosenblat, M., Volkova, N., Kaplan, M., Coleman, R., et al. (2000). Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans.
and in atherosclerotic apolipoprotein E-deficient mice. Am. J. Clin. Nutr. 71, 1062–1076. doi: 10.1093/ajcn/71.5.1062

Aviram, M., and Rosenblat, M. (2013). Pomegranate for your cardiovascular health. Rambam Maimonides Med. J. 4:e00013. doi: 10.5041/RMMJ.10113

Aviram, M., Rosenblat, M., Gattini, D., Nitecki, S., Hoffman, A., Dornfeld, L., et al. (2004). Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. Clin. Nutr. 23, 423–433. doi: 10.1016/j.clnu.2003.10.002

Batta, A. K., and Rangaswami, S. (1973). Crystalline chemical components of some vegetable drugs. Phytochemistry 12, 214–216. doi: 10.1016/S0031-9422(00)84654-3

Bialonska, D., Kasimsetty, S. G., Khan, S. I., and Ferreira, D. (2009). Urolithins, ellagic acid and related compounds. J. Agric. Food Chem. 57, 10181–10186. doi: 10.1021/jf9025794

Boncuk, M. (2014). Word Origin, Nar, Pomegranate. Available online at: http://maviboncuk.blogspot.ch/2014/08/word-origin-nar-pomegranate.html?m=0 (accessed April 24, 2018).

Bonzanini, F., Bruni, R., Palla, G., Serlataite, N., and Calligiani, A. (2009). Identification and distribution of lignins in Punica granatum L. fruit endocarp, pulp, seeds, wood kernels and commercial juices by GC–MS. Food Chem. 117, 745–749. doi: 10.1016/j.foodchem.2009.04.057

Borges, G., and Crozier, A. (2012). HPLC-PDA-MS fingerprinting to assess the authenticity of pomegranate beverages. Food Chem. 135, 1863–1867. doi: 10.1016/j.foodchem.2012.05.108

Brighenti, V., Groothuis, S. F., Precipe, F. P., Amir, R., Benvenuti, S., and Pellati, F. (2017). Metabolite fingerprinting of Punica granatum L. (pomegranate) polyphenols by means of high-performance liquid chromatography with diode array and electrospray ionization-mass spectrometry detection. J. Chromatogr. A 1480, 20–31. doi: 10.1016/j.chroma.2016.12.017

Cadwallader, K. R., Tamamoto, L. C., and Sajuti, S. C. (2010). “Aro ma components

Dos Santos, R. L., Delucaqua, L. O., Delgado, N. T., Rouver, W. N., Podratz, P. L., Lima, L. C., et al. (2016). Pomegranate peel extract attenuates oxidative stress by decreasing coronary angiotensin-converting enzyme (ACE) activity in hypertensive female rats. J. Toxicol. Environ. Health A 79, 998–1007. doi: 10.1080/15287394.2016.1213690

Dumlu, M. U., and Gurkan, E. (2007). Elemental and nutritional analysis of Punica granatum from Turkey. J. Med. Food 10, 392–395. doi: 10.1089/jmf.2006.295

Ehling, S., and Cole, S. (2011). Analysis of organic acids in fruit juices by liquid chromatography-mass spectrometry: an enhanced tool for authenticity testing. J. Agric. Food Chem. 59, 2229–2234. doi: 10.1021/jf104527e

Elalleh, W., Ying, M., Nasi, N., Sheng-Hua, H., Guasmi, F., and Ferchichi, A. (2011). Fatty acids from Tunisian and Chinese pomegranate (Punica granatum L.) seeds. Int. J. Food Sci. Nutr. 62, 200–206. doi: 10.1002/10963748.2010.526932

Elsherbiny, E. A., Amin, B. H., and Baka, Z. A. (2016). Efficiency of pomegranate (Punica granatum L.) peels extract as a high potential natural tool towards Fusarium dry rot on potato tubers. Postharvest Biol. Technol. 111, 256–263. doi: 10.1016/j.postharvbio.2015.09.019

Fanali, C., Belluomo, M. G., Cirilli, M., Cristofori, V., Zecchin, M., Cacciola, F., et al. (2016). Antioxidant activity evaluation and HPLC-photodiode array/MS polyphenols analysis of pomegranate juice from selected italian cultivars: a comparative study. Electrotherapies 37, 1947–1955. doi: 10.1002/cpts.201500501

Fawole, O. A., Makunga, N. P., and Opara, U. L. (2012). Antibacterial, antioxidant and tyrosinase-inhibition activities of pomegranate fruit peel methanolic extract. BMC Complement. Altern. Med. 12:200. doi: 10.1186/1472-6882-12-200

Fischer, U. A., Carle, R., and Kammerer, D. R. (2011a). Identification and quantification of phenolic compounds from pomegranate (Punica granatum L.) peel, mesocarp, aril and differently produced juices by HPLC-DAD-ESI/MS(n). Food Chem. 127, 807–821. doi: 10.1016/j.foodchem.2010.12.156

Fischer, U. A., Carle, R., and Kammerer, D. R. (2013). Thermal stability of anthocyanins and colourless phenolics in pomegranate (Punica granatum L.) juices and model solutions. Food Chem. 138, 1800–1809. doi: 10.1016/j.foodchem.2012.10.072

Fischer, U. A., Dettmann, J. S., Carle, R., and Kammerer, D. R. (2011b). Impact of processing and storage on the phenolic profiles and contents of pomegranate (Punica granatum L.) juices. Eur. Food Res. Technol. 233, 797–816. doi: 10.1007/s00217-011-1560-3

Fu, Q. J., Zhang, L. H., Cheng, N. N., Jia, M., and Zhang, Y. H. (2014). Extraction optimization of oleoanolic and ursolic acids from pomegranate (Punica granatum L.) flowers. Food Bioprod Process 92, 321–327. doi: 10.1016/j. bjop.2012.12.006

Fuhrman, B., Volkova, N., and Aviram, A. (2005). Pomegranate juice inhibits oxidized LDL uptake and cholesterol biosynthesis in macrophages. J. Nutr. Biochem. 16, 570–576. doi: 10.1016/j.jnutbio.2005.02.009

García-Muñoz, C., and Vaillant, F. (2014). Metabolic fate of ellagitannins: implications for health, and research perspectives for innovative functional foods. Crit. Rev. Food Sci. Nutr. 54, 1584–1598. doi: 10.1080/10408398.2011.644643

Gil, M. I., Tomás-Barberán, F. A., Hess-Pierce, B., Holcroft, D. M., and Kader, A. A. (2000). Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. J. Agric. Food Chem. 48, 4581–4589. doi: 10.1021/jf000404a

Giménez-Bastida, J. A., González-Sarrías, A., Larrosa, M., Tomas-Barberan, F., Espin, J. C., and Garcia-Conesa, M. T. (2012). Ellagittannin metabolites, urolithin A glucuronide and its aglycone urolithin A, ameliorate...
acids, sugars, and anthocyanins. Int. J. Food Prop. 15, 481–494. doi: 10.1080/10942912.2010.491931

Lei, F., Zhang, X. N., Wang, W., Xing, D. M., Xie, W. D., Su, H., et al. (2007). Evidence of anti-obesity effects of the pomegranate leaf extract in high-fat diet induced obese mice. Int. J. Obes. (Lond.). 31, 1023–1029. doi: 10.1038/sj.ijo.0803502

Les, F., Carpene, C., Arbones-Mainar, J. M., Decaunes, P., Valero, M. S., and Lopez, V. (2015). Effects of pomegranate juice supplementation on pulse wave velocity and blood pressure in healthy young and middle-aged men and women. Plant Foods Hum. Nutr. 67, 309–314. doi: 10.1111/sf.2015.02.030

Lipinski, L., Klewickska, E., and Sójka, M. (2014). The structure, occurrence and biological activity of ellagittannins: a general review. Acta Sci. Pol. Technol. Aliment. 13, 289–299. doi: 10.17306/J.AFS.2014.5.7

Loren, D. J., Seeram, N. P., Schulman, R. N., and Holtzman, D. M. (2005). Maternal dietary supplementation with pomegranate juice is neuroprotective in an animal model of neonatal hypoxic-ischemic brain injury. Pediatr. Res. 57, 858–864. doi: 10.1203/01.PDR.0000157722.07810.15

Lynn, A., Hamadeh, H., Leung, W. C., Russell, J. M., and Barker, M. E. (2012). Prostate cancer prevention through Punica granatum (pomegranate) juice: antioxidant, antiproliferative and enzyme inhibiting activities. Food Funct. 6, 2049–2057. doi: 10.1039/C5FO00426H

Levin, G. M. (2006). Pomegranate Roads: A Soviet Botanist’s Exile from Eden. Edited by B. L. Bae (Foster Creek, CA: Florapress), 15–183.

Li, Y., Wen, S., Kota, B. P., Peng, G., Li, Q. G., Yamahara, J., et al. (2005). Punica granatum flower extract, a potent alpha-glucosidase inhibitor, improves postprandial hyperglycemia in Zucker diabetic fatty rats. J. Ethnopharmacol. 99, 239–244. doi: 10.1016/j.jep.2005.02.030

Malik, A., Afqaf, F., Sarfaraz, S., Adhami, V. M., Syed, D. N., and Mukhtar, H. (2005). Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. Proc. Natl. Acad. Sci. U.S.A. 102, 14813–14818. doi: 10.1073/pnas.0508701102

Malik, A., and Mukhtar, H. (2006). Prostate cancer prevention through pomegranate fruit. Cell Cycle 5, 371–373. doi: 10.4161/cc.5.4.2486

Mattielli, T., Trifirò, E., Jotti, G. S., and Pulcinelli, F. M. (2009). Effects of pomegranate juice supplementation on pulse wave velocity and blood pressure in healthy young and middle-aged men and women. Plant Foods Hum. Nutr. 67, 309–314. doi: 10.1111/sf.2015.02.0295-z

Melnik, A., Afqaf, F., Sarfaraz, S., Adhami, V. M., Syed, D. N., and Mukhtar, H. (2005). Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. Proc. Natl. Acad. Sci. U.S.A. 102, 14813–14818. doi: 10.1073/pnas.0508701102

Melnik, A., and Mukhtar, H. (2006). Prostate cancer prevention through pomegranate fruit. Cell Cycle 5, 371–373. doi: 10.4161/cc.5.4.2486

Mattielli, T., Trifirò, E., Jotti, G. S., and Pulcinelli, F. M. (2009). Effects of pomegranate juice and extract polyphenols on platelet function. J. Med. Food 12, 334–339. doi: 10.1089/jmf.2007.0640

Mele, L., Mena, P., Piemontese, A., Marino, V., López-Gutiérrez, N., Bernini, F., et al. (2016). Antithrombotic effects of ellagic acid and urolithins in vitro. Arch. Biochem. Biophys. 599, 42–50. doi: 10.1016/j.jbc.2016.02.017

Mena, P., Calani, L., Dall’asta, C., Galaverna, G., García-Viguera, C., Bruni, R., et al. (2012). Rapid and comprehensive evaluation of (poly)phenolic compounds in pomegranate (Punica granatum L.) juice by UHPLC-MSn. Molecules 17, 14821–14840. doi: 10.3390/molecules171214821

Menezes, S. M., Cordeiro, L. N., and Viana, G. S. (2009). Punica granatum (pomegranate) extract is active against dental plaque. J. Herb. Pharmacother. 6, 79–92. doi: 10.1080/15750602.07

Moham, M., Waghulde, H., and Kasture, S. (2010). Effect of pomegranate juice on angiotensin II-induced hypertension in diabetic Wistar rats. Phytother. Res. 24(Suppl. 2), S196–203. doi: 10.1002/tr.2090

Mollazadeh, H., Sadeghnia, H. R., Hoseini, A., Farzadnia, M., and Boroushaki, M. T. (2016). Effects of pomegranate seed oil on oxidative stress markers, serum biochemical parameters and pathological findings in kidney and heart of streptozotocin-induced diabetic rats. Ren. Fail. 38, 1256–1266. doi: 10.1080/0886022X.2016.1207053

Mphahlele, R. R., Stander, M. A., Fawole, O. A., and Opara, U. L. (2014). Effect of fruit maturity and growing location on the postharvest contents of flavonoids, phenolic acids, vitamin C and antioxidant activity of pomegranate juice (cv. Wonderful). Sci. Hort. 179, 36–45. doi: 10.1016/j.scienta.2014.09.007

Nawwar, M. A. M., Hussein, S. A. H., and Merfort, I. (1994a). NMR spectral analysis of polyphenols from Punica granatum. Phytochemistry 36, 793–798. doi: 10.1016/S0031-9422(00)88920-9

Nawwar, M. A. M., Hussein, S. A. M., and Merfort, I. (1994b). Leaf phenolics of Punica granatum L. Phytochemistry 37, 1175–1177. doi: 10.1016/S0031-9422(00)89552-7

Nawwar, M. A. M., Hussein, S. A. H., and Merfort, I. (1994a). NMR spectral analysis of polyphenols from Punica granatum. Phytochemistry 36, 793–798. doi: 10.1016/S0031-9422(00)88920-9

Nawwar, M. A. M., Hussein, S. A. M., and Merfort, I. (1994b). Leaf phenolics of Punica granatum L. Phytochemistry 37, 1175–1177. doi: 10.1016/S0031-9422(00)89552-7

Nawwar, M. A. M., Hussein, S. A. H., and Merfort, I. (1994a). NMR spectral analysis of polyphenols from Punica granatum. Phytochemistry 36, 793–798. doi: 10.1016/S0031-9422(00)88920-9

Nawwar, M. A. M., Hussein, S. A. M., and Merfort, I. (1994b). Leaf phenolics of Punica granatum L. Phytochemistry 37, 1175–1177. doi: 10.1016/S0031-9422(00)89552-7

Nawwar, M. A. M., Hussein, S. A. H., and Merfort, I. (1994a). NMR spectral analysis of polyphenols from Punica granatum. Phytochemistry 36, 793–798. doi: 10.1016/S0031-9422(00)88920-9

Nawwar, M. A. M., Hussein, S. A. M., and Merfort, I. (1994b). Leaf phenolics of Punica granatum L. Phytochemistry 37, 1175–1177. doi: 10.1016/S0031-9422(00)89552-7
Salwe, K. J., Sachdev, D. O., Bahrurupi, Y., and Kumarappan, M. (2015). Evaluation of antioxidant, hypolipidemic and antioxidant activity of hydroalcoholic extract of leaves and fruit peel of *Punica granatum* in male Wistar albino rats. *J. Nat. Sci. Biol. Med.* 6, 56–62. doi: 10.4103/0976-9668.149085
Satomi, H., Umemura, K., Ueno, A., Hatano, T., Okada, T., and Noro, T. (1993). Carboxy anhydrase inhibitors from the pericarps of *Punica granatum* L. *Biochim. Biophys. Acta.* 16, 787–790. doi: 10.1016/biba.16.787
Saxena, A., and Vikram, N. K. (2004). Role of selected Indian plants in management of type 2 diabetes: a review. *J. Altern. Complement. Med.* 10, 369–378. doi: 10.1089/107553903432062365
Schubert, S. Y., Lansky, E. P., and Neeman, I. (1999). Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids. *J. Ethnopharmacol.* 66, 11–17. doi: 10.1016/S0378-8749(98)00220-2
Sharma, P., McCloud, S. E., and Afaq, F. (2017). Pomegranate for prevention and treatment of cancer: an update. *Molecules* 22, 177. doi: 10.3390/molecules2201177
Shiner, M., Fuhrman, B., and Aviram, M. (2007). Macrophage paraoxonase 2 (PON2) expression is up-regulated by pomegranate juice phenolic anti-oxidants via pPAR gamma and AP-1 pathway activation. *Atherosclerosis* 195, 313–321. doi: 10.1016/j.atherosclerosis.2007.01.007
Siano, F., Straccia, M. C., Paolucci, M., Fasulo, G., Boscaino, F., and Volpe, M. G. (2016). Physico-chemical properties and fatty acid composition of pomegranate, cherry and pumpkin seed oils. *J. Sci. Food Agric.* 96, 1730–1735. doi: 10.1002/jsfa.7277
Sudheesh, S., and Vijayalakshmi, N. R. (2005). Flavonoids from *Punica granatum*-potential antiperoxidative agents. *Fitoterapia* 76, 181–186. doi: 10.1016/j.fitote.2004.11.002
Svenja (2018). *Tapeworms in Time: Ancient Egypt and the Ebers Papyrus*. Available online at: https://diagnos-t-x.de/ancient-egypt-and-the-ebers-papyrus/ (accessed April 24, 2018).
Tanaka, T., Nonaka, G. I., and Nishioka, I. (1986a). Tannins and related compounds. XLII. Isolation and characterization of novel ellagitannins, punnicaricetins A, B and C and punigluconin from the bark of *Punica granatum* L. *Chem. Pharm. Bull.* 34, 656–663. doi: 10.1248/cpb.34.656
Tanaka, T., Nonaka, G. I., and Nishioka, I. (1990). Tannins and related compounds. C. Reaction of dehydroxyaldehydedrosylic acid esters with bases, and its application to the structure determination of pomegranate tannins, *granutins a and b*. *Chem Pharm Bull* 38, 9424–9428. doi: 10.1248/cpb.38.2424
Tanaka, T., Nonaka, G., and Nishioka, I. (1986b). Tannins and related compounds. XL. Revision of the structures of punicin and punicalin, and isolation and characterization of 2-O-galloylpunicin from the bark of *Punica granatum* L. *Chem. Pharm. Bull.* 34 650–653. doi: 10.1248/cpb.34.650
Tang, L., Mo, Y., Li, Y., Zhong, Y., He, S., Zhang, Y., et al. (2017). Urolithin A alleviates myocardial ischemia/reperfusion injury via PI3K/Akt pathway. *Biochim. Biophys. Res. Commun.* 486, 774–780. doi: 10.1016/j.bbrc.2017.03.119
Tomás-Barberan, F. A., Gonzalez-Sarrias, A., Garcia-Villalba, R., Nunez-Sanchez, V., Tanaka, T., Nonaka, G. I., and Nishioka, I. (2015). Polyphenol-enriched diet prevents coronary endothelial dysfunction by activating the Akt/eNOS pathway. *Rev. Esp. Cardiol. (Engl. Ed).* 68, 216–225. doi: 10.1016/j.recesp.2014.03.023
Vroegrijk, I. O., Van Diepen, J. A., Van Den Berg, S., Westbroek, I., Keizer, H., Gambelli, L., et al. (2011). Pomegranate seed oil, a rich source of y-rubiflavonoids, prevents diet-induced obesity and insulin resistance in mice. *Food Chem. Toxicol.* 49, 1426–1430. doi: 10.1016/j.fct.2011.03.037
Wafa, B. A., Makni, M., Ammar, S., Khannous, L., Hassana, A. B., Bouaziz, M., et al. (2017). Antimicrobial effect of the Tunisian Nana variety *Punica granatum* L. extracts against Salmonella enterica (serovars Kentucky and Enteritidis) isolated from chicken meat and phenolic composition of its peel extract. *Int. J. Food Microbiol.* 241, 123–131. doi: 10.1016/j.ijfoodmicro.2016.10.007
Wang, D., Uhrin, P., Mocan, A., Waltenberger, B., Breuss, J. M., Tewari, D., et al. (2018). Vascular smooth muscle cell proliferation as a therapeutic target. Part I: molecular targets and pathways. *Biotechnol. Adv.* doi: 10.1016/j.biotechadv.2018.04.006. [Epub ahead of print].
Wang, R. F., Xie, W. D., Zhang, X., Xing, D. M., Ding, Y., Wang, W., et al. (2004). Bioactive compounds from the seeds of *Punica granatum* (pomegranate). *J. Nat. Prod.* 67, 2096–2098. doi: 10.1021/jn0498051
Ward, C. (2003). Pomegranates in eastern Mediterranean contexts during the Late Bronze Age. *World Archaeol.* 34, 539–541. doi: 10.1080/0043824021000026495
Weiss, H. J., and Turitto, V. T. (1979). Prostacyclin (prostaglandin I2, PGI2) inhibits platelet adhesion and thrombus formation on subendothelium. *Blood* 53, 244–250.
Yilmaz, B., and Usta, C. (2013). Ellagic acid-induced endothelium-dependent and endothelium-independent vasorelaxation in rat thoracic aortic rings and the underlying mechanism. *Phytother. Res.* 27, 285–289. doi: 10.1002/ptr.4716
Yuan, T., Wan, C., Ma, H., and Seeram, N. P. (2013). New phenolics from the flowers of *Punica granatum* and their in vitro alpha-glucosidase inhibitory activities. *Planta Med.* 79, 1674–1679. doi: 10.1055/s-0033-1350925
Zhang, J., Zhou, Y., Li, S., Zhang, P., Zhou, T., Xu, D. P., et al. (2017). Effects and mechanisms of fruit and vegetable juices on cardiovascular diseases. *Int. J. Mol. Sci.* 18, 1–15. doi: 10.3390/ijms18030555

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.