Beneficial Effects of Pomegranate Fruit Consumption in Cardiovascular Diseases Prevention

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Abstract: Oxidative stress, dyslipidemia, hypercoagulability, endothelial dysfunction and inflammation are key elements in the development of atherosclerosis. Oxidative stress has been implicated as well in most of the key steps in the pathophysiology of atherosclerosis and the consequential clinical manifestations of cardiovascular diseases. In addition to the formation of atherosclerosis, oxidative stress acute thrombotic events, including dyslipidemia, the oxidation of low-density lipoproteins (LDLs) and plaque rupture leading to atherothrombosis and myocardial infarction. In the last decades, multiple experimental studies and clinical trials have demonstrated that diet plays a central role in the prevention of atherosclerosis. Pomegranate (*Punica granatum* L.) is one of nature's most concentrated sources of antioxidants. It contains some very potent antioxidants (*i.e.* tannins, anthocyanins and flavonoids), which provide a wide spectrum of action against free radicals and are considered to be potent anti-atherogenic products. These properties make pomegranate a healthy fruit with a high potential in preventing cardiovascular diseases. In this review, we give an overview on the newest insights in the role of pomegranate in therapy of vascular diseases.

Keywords: Pomegranate, atherosclerosis, antioxidants, cardiovascular diseases, oxidation.

1. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in modern society, accounting for 16.7 million deaths each year. Atherosclerosis is the underlying cause of the majority of CVD, resulting in a high rate of mortality in the population. The development of atherosclerotic lesions results from a complex interplay between the activation, dysfunction and structural alterations of the endothelium leading to sub-endothelial retention of lipid components from the plasma, such as low-density lipoproteins (LDLs) [1]. In addition, the fundamental priming step for the atherosclerotic process is the transport of oxidized low-density lipoproteins (LDLs) across the endothelium into the arterial sub-endothelial space [2]. In 1984, Steinbrecher *et al*. [3], reported that incubation of LDL with endothelium cells convert native LDL into a modified form that not recognized by LDL-receptor, increasing the rate of cholesterol uptake by macrophages in a non-regulated manner through the scavenger-receptor pathway, which leads to cholesterol accumulation and foam cell formation. On the other hand, dysfunctional high-density lipoproteins (HDLs) induced by structural modifications (*i.e.* oxidative stress), may lead to a loss of their antioxidant and anti-inflammatory properties as well as their ability to promote cholesterol efflux and reverse cholesterol transport; thereby highly contributing to the acceleration of atherogenesis [4]. Since increased oxidative stress plays a key role in atherogenesis, its inhibition by nutritional antioxidants was demonstrated to delay the progression of the disease. Diet plays a fundamental role in cardiovascular prevention and in maintaining physiological homeostasis [2]. Polyphenols are common nutrient antioxidants found largely in the fruits, vegetables and traditional medicinal herbs, and are generally involved in defence against cancers, metabolic [5] and neurodegenerative diseases [6]. Animal and clinical studies have suggested that polyphenol-rich diets may protect against cardiovascular diseases [7-10]. They may delay the onset of atherosclerosis by interacting with some cell receptor and intracellular signalling and/or gene expression regulation during atherosclerotic progressions.

In the past few years there has been an increasing interest in determining relevant dietary sources of antioxidant phenolic compounds, several of which contribute to the bright colour of many fruits and vegetables. Thus, red fruit juices such as grape and different berry juices have received attention due to their high antioxidant activity. Pomegranate juice is rich in some specific flavonoids with potent antioxidant properties, especially punicalagin, unique tannins, and several anthocyanins. The polyphenolic fraction of pomegranate appears to be responsible for most of the health benefits owing to the strong antioxidant activity, anti-inflammatory and anti-carcinogenic effects [11].

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Pomegranate has been used for a long time to treat infections [12] and it has been described to decrease blood pressure, to positively affect cardiovascular risk factors in several clinical studies [13] and to show neuroprotective effects against Alzheimer's disease (AD) in several animal studies [14,15].

2. POMEGRANATE

In the last decades, nutrition science has focused on the role of functional foods due to their potential for providing health benefits. There has been an increased interest in determining dietary sources of antioxidant polyphenols. Thus, red fruit juices such as grape, berry and pomegranate have received attention due to their antioxidant activity. Belonging to *Punica* L. genus, *Punicaceae* family, pomegranate *(Punica granatum* L.) is an ancient fruit-bearing deciduous shrub native from the Himalayas in northern India to Iran, where pomegranates had been under cultivation for thousands of years. Pomegranate has been cultivated and naturalized since ancient times over the entire Mediterranean region to the Turkish European borders and American southwest, California and Mexico [16,17]. The fruit can be divided into 3 parts: the seeds, about 3% of the weight of the fruit, the juice, about 30% of the fruit weight, and the peels (pericarp) characterized by membranes internal network [16] which contain different phytochemical components such as punicalagin, which is good antioxidant with potent free-radical scavenging properties [18].

Research on the pomegranate as a medicinal and nutritional food source has grown. Pomegranate and its derivates such as peel, juice and seeds are rich source of several high-value compounds with beneficial physiological activities. Pomegranate juice has recently become more popular in diet because of the attribution of health benefits, it is one of the main products of today's pomegranate fruit production and represents about a third of the fruit's weight [19]. Its high antioxidant activity has led to applications in functional food formulation, mainly for heart health. However, for medical use, extracts of other parts of the plant, including the flowers, bark, roots, and leaves may also be of interest, since they all contain bioactive compounds. Indeed, most pomegranate parts have been documented in ethnomedicine.

3. BIOACTIVE COMPONENTS OF POMEGRANATE

The antioxidant activity of pomegranate is associated with its phenolic compounds in the form of flavonoids (flavonols, flavanols, and anthocyanins), condensed tannins (proanthocyanidins), and hydrolysable tannins (ellagitannins and gallotannins). Amongst the seed, peel and juice, the peel is the richest in polyphenols, mainly punicalagins, the ellagitannins typical of pomegranate [20,21]. Pomegranate leaves contain tannins (punicalin and punicafolin) and flavone glycosides, including luteolin and apigenin, whereas the plant's flower contains gallic acid and its roots and bark contain ellagitannins, including punicalin and punicalagin [22]. These are summarized, with their structures, in Table **1**. Specifically, the main antioxidant compounds in pomegranate juice are anthocyanins, ellagic acid, gallic acid, catechin, epigallocatechin gallate, and quercetin. Gil *et al*. [22] reported that during the juice processing, the whole fruit is pressed and ellagitannins are extracted into pomegranate juice in significant quantities, reaching levels of over 2g/L. Amongst the large variety of chemical components in pomegranate, ellagic and punic acids, ellagitannins (mainly punicalagins), anthocyanins, flavonols, flavan-3-ols, and flavones seem to be the ones responsible for most of the plant's therapeutic effects [18]. Moreover, pomegranate accession as well as varieties, geographical region and harvesting periods play an important role in the fruit composition and consequently its potential effects.

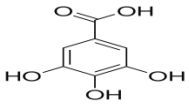
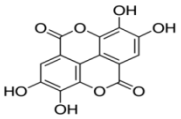
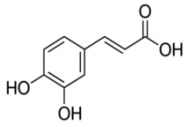
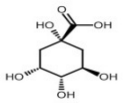
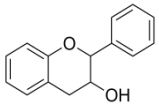
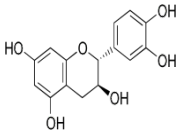
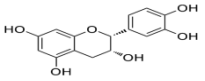
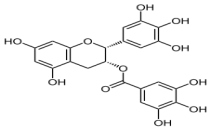
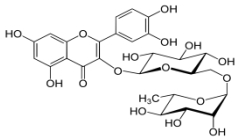
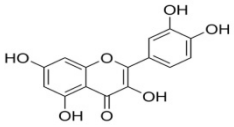
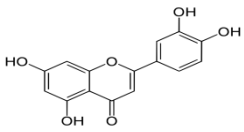
4. NUTRACEUTICAL PROPERTIES OF POMEGRANATE

4.1. Antioxidant Potential and Cardiovascular Protective Role

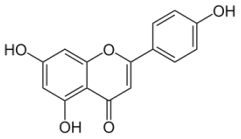
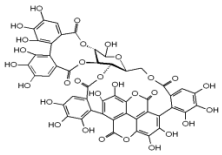
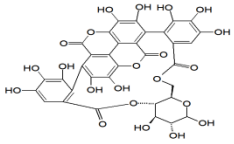
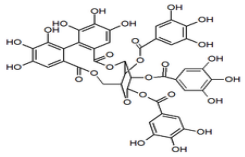
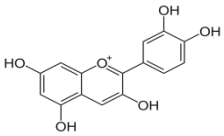
Nowadays, it is widely accepted that the beneficial health effects of diets rich in fruits and vegetables, in the context of CVD prevention, are related to the bioactive compounds present in these foods [43]. However, oxidative stress processes have been given growing attention and constitute an etiological factor and a main cause of diseases with increasing incidence in the world societies, mainly cardiovascular, neurodegenerative diseases and cancer [44]. In 1950s, Harman was the first to propose the free radical theory of aging [45], which stipulates that enhanced and unopposed metabolically-driven oxygen free radical plays a major role in diverse chronic age-related diseases and in accelerated aging [46].

Ethnobotanical data shows that the therapeutic potential of pomegranate has been widely recognized. Several health disorders such as cough, diarrhoea,

Table 1: Phytochemical Compounds of *Punica granatum*

Chemical class	Compound name	Compound structure	Plant part	References
Hydroxybenzoic acids	Gallic acid		Juice, seed, peel and flower	Amakura et al. [23] Huang et al. [24] Mphahlele et al. [25] Fanali et al. [26]
Hydroxybenzoic acids	Ellagic acid		Juice and flower	Amakura et al. [23] Wang et al. [27] Jain et al. [28] Wafa et al. [29]
Hydroxycinnamic (phenylpropanoids)	Caffeic acid		Juice and peel	Amakura et al. [30] Lantzourak et al. [31]
Cyclitol carboxylic acids and their salts	Quinic acid		Juice	Amakura et al. [30] Ehling and Cole [32]
Flavan-3-ols	Flavan-3-ol		Juice and peel	de Pascual-Teresa et al. [33]
Flavan-3-ols	Catechin		Juice and peel	de Pascual-Teresa et al. [33] Mphahlele et al. [25] Ambigaipalan et al. [34]
Flavan-3-ols	Epicatechin		Juice and peel	de Pascual-Teresa et al. [33] Mphahlele et al. [25]
Flavan-3-ols	Epigallocatechin 3-gallate		Peel and juice	de Pascual-Teresa et al. [33]
Flavonol glycosides	Rutin		Peel and juice	Mphahlele et al. [25]
Flavonols	Quercetin		Juice, seed and peel	Borges and Crozier [35] Han et al. [36] Ambigaiplan et al. [34]
Flavones	Luteolin		Peel	Van Elswijk et al. [37] Han et al. [36]

(Table 1). Continued.

Chemical class	Compound name	Compound structure	Plant part	References
Flavones	Apigenin		Leaf	Nawwar et al. [38]
Ellagitannins	Punicalagin		Peel, leaf, juice and bark	Jain et al. [28] Gil et al. [22] Anibal et al. [39] Lantzouraki et al.[31]
Ellagitannins	Punicalin		Peel, juice, leaf and bark	Tzulker et al. [40] Jain et al. [28] Wafa et al. [29]
Ellagitannins	Punicafolin		Leaf	Nawwar et al. [38]
Anthocyanidins	Cyanidin		Peel	Noda et al. [41] Fischer et al. [42]

inflammation, intestinal worms, infertility and some bacterial infections have been treated with pomegranate extracts [47]. *In vitro* and *in vivo* studies have notably paid particular attention to the plant's antioxidant activities [11], several of them confirming that pomegranate ranks among the best fruits in this context. Indeed, the comparison of antioxidant activities and total phenolic contents among twelve polyphenol-rich beverages showed that pomegranate juice (PJ) had the highest antioxidant activity [48]. A similar study carried out by Fu *et al*. [49], out of the 62 species tested, the pomegranate was one of the seven best fruits to exhibit the highest antioxidant activity. PJ was shown to possess an antioxidant activity three times higher than that of green tea [49]. Also, Javad *et al*. demonstrated that pomegranate juice contains higher levels of total tannins, phenolics and showed a higher antioxidant activity [50].

Another determination of the free radical scavenging capacity of various juices, also revealed that PJ was the most potent one, whereas orange juice, grapefruit juice, and peach juice showed very low free radicals scavenging capacities [51]. Not surprisingly, a generally strong correlation was reported between the scavenging activity of pomegranate preparations toward oxygen free radicals and their content in total polyphenols as well as flavonoids [52]. Indeed, Aviram *et al*. demonstrated that PJ contains a higher concentration of total polyphenols (5mM) than several other fruit juices (orange, grapefruit, grape, cranberry, pear, pineapple, apple, and peach juices) that contain only 1.3 to 4mM of total polyphenols [51]. In the clinic, ingestion of a polyphenol-rich pomegranate extract by healthy human volunteers increases the antioxidant capacity of plasma towards peroxyl radicals, but no significant change was observed in the generation of ROS [53]. In parallel, Seeram *et al*. showed that ellagic acid (EA) can be detected in 1h postprandial plasma samples in healthy human subjects who consumed pomegranate juice containing 25mg EA [54], suggesting that it could contribute to the fruit's therapeutic potential.

Concerning the different parts of the pomegranate fruit, the antioxidant activity was higher in juice extracted from whole pomegranate than that obtained from arils only, highlighting the importance of

considering the whole fruit during the processing of pomegranate juice [22]. Finally, the antioxidant potential and bioactive components of whole pomegranate fruit also depend on cultivars and growing location, as recently reported by Kalaycioglu and Erim [55]. Antioxidant activities associated with different pomegranate parts are summarized in Table **2**. As previously mentioned, biochemical modifications of LDL and HDL under oxidative stress contribute greatly to enhance the injurious potential of lipoproteins and their involvement in the development of cardiovascular diseases. In an *in vitro* study, Nigris *et al*. [56] Show that pomegranate juice reduces LDL oxidation and its subsequent effect on the endothelial nitric oxide-synthase in human coronary endothelial cells. Consumption of PJ for 1 and 2 weeks by healthy volunteers increased the resistance of LDL and HDL to copper-induced oxidation, as shown by the prolongation of the lag time required for the oxidative initiation process of LDL and HDL [57,58].

Results from various human and animal studies led to suggest PJ as the "heart-healthy" fruit juice. In fact, as reported by Basu and Penugonda [59], consumption of PJ (Wonderful variety, 240 ml/day for 1 year) in 73 patients with the cardiovascular risk factor, showed trends to increased arterial elasticity [59]. These results are consistent with those obtained by Khatteb et al., which demonstrated that daily consumption of PJ for 3 months on myocardial perfusion in 45 coronary heart disease (CHD) patients, significantly decreases the extent of stress-induced ischemia [60]. Aviram et al. [58] investigated the effects of long-term consumption of PJ in patients with carotid artery stenosis (CAS) on carotid lesion size, in association with changes in oxidative stress. Results showed that patients' carotid intima-media thickness (CIMT) was increased by 10% in untreated-group, while in the PJ-group it results in a significant reduction by 35% upon 1 year of PJ consumption. However, Davidson *et al*., suggest that in subjects at moderate CHD risk, PJ consumption had no significant effect on overall CIMT progression rate but slowed CIMT progression in subjects with increased oxidative stress and disturbances in the TG-rich lipoprotein/HDL axis [61]. In another hand, animals studies showed that PJ supplementation reduced the atherosclerosis progression and atherosclerotic lesions formation in atherosclerotic apoE-deficient mice [57] as well as in hypercholesterolemic LDL-receptors deficient

Table 2: Potential Antioxidant and Cardiovascular Protection of Pomegranate

Effects	Pomegranate part	References
Three times higher antioxidant activity than that of green tea or red wine.	Juice	Gil et al. [22] Seeram et al. [48]
Pomegranate juice strongest antioxidant of almost 62 fruits tested.	Juice	Fu et al. [49]
Strong antioxidant and antiproliferative activities.	Juice, arils, peels, rinds, fruit extract	Ricci et al. [72] Les et al. [73] Asgary et al. [11] Javad et al. [50] Aviram et al. [51] Masci et al. [52]
Prevents LDL oxidation, atherosclerotic plaque formation and increasing the activity of serum paraxonase in macrophages.	Juice	Aviram et al. [57]
Reduces LDL oxidation and its subsequent effect on the endothelial nitric oxide-synthase in human coronary endothelial cells.	Juice	de Nigris et al. [56] Arun et al. [74]
Reduction of cellular lipid peroxidation lowering cellular uptake of oxidized LDL and inhibition of cholesterol biosynthesis, attenuation of atherosclerosis development.	Juice	Aviram et al. [57] Fuhrman et al. [70]
Reduction in activity of angiotensin-converting enzyme (ACE) and arterial blood pressure in rats.	Juice, peel extract	Mohan et al. [75] Santos et al. [76] Arun et al. [74]
Lowering fatty acids, triglycerides and total cholesterol plasma levels in Zucker diabetic fatty (ZDF) rats.	Flower extract, Juice	Huang et al. [77]
Induction of PON 1 et 2, lowering cholesterol and triglyceride, reduction in oxidative stress in isolated macrophages.	Flower extract, Juice	Estrada et al. [67] Fuhrman et al. [65] Shiner et al. [78]

mice when compared to control [62]. These findings are in agreement with those reported by Al-Jarallah et al., which demonstrated that pomegranate extract reduced aortic sinus and coronary artery atherosclerosis in SR-BI/apoE double knockout mice [63]. According to these authors, treatment with pomegranate extract substantially reduced the levels of oxidative stress, monocytes chemotactic protein-1 (MCP-1), lipid accumulation, macrophages infiltration and fibrosis in the myocardium; which attenuated cardiac enlargement and abnormalities development in ER-BI/apoE dKO mice [63].

Paraoxonase 1 (PON1) is an HDL-associated protein, which is principally synthesized and secreted by the liver cells. It has been widely reported that PON1 expression is associated with low CVD risk because of its potent antioxidant effect and its capacity to promote cholesterol efflux process [64]. Polyphenol-rich dietary, which be able to enhance PON1 expression and activities will greatly contribute to preventing CVD development. Interestingly, Khateeb et al., have recently reported that Pomegranate juice as well as its major polyphenols mainly Punicalagin and gallic acid, upregulate hepatocyte PON1 expression via the intracellular signalling cascade PPARγ-PKA-cAMP [60]. Moreover, Fuhrman et al., [65] reported in a study conducted in diabetic patients that the impairment of PON1 binding to HDL in diabetic patients was reversed by 4 wk uptake of PJ. Consumption of PJ in type 2 diabetes patients for 6 weeks also results in a significant increase of PON1 (paraoxonase and arylesterase) activities and reduction of lipid profiles (triglycerides, total cholesterol and C-LDL), lipoproteins oxidation as well as fasting blood sugar, while no change was reported in respect to C-HDL [66]. These results may be supported by those obtained from Estrada-Luna study, which demonstrated that consumption of PJ in diabetic mice induced PON1 gene expression and activity [67]. The above results were confirmed also in an in-vitro study where incubation of serum from diabetic patients with PJ or punicalagin results in an increment of PON1 binding to isolated HDL [51]. This effect on the PON1 gene expression and activity is of particular interest because of its role in managing oxidative stress and CVD progression.

Excessive lipids accumulation can lead to the foam cells formation, which plays an important role in promoting the occurrence of atherosclerosis process. Interestingly, it was reported that PJ inhibited macrophage foam cell formation by reduction of cholesterol biosynthesis and ox-LDL degradation [68]. Moreover, Zhao et al. reported that polyphenols from pomegranate peel reduced efficiently CD36 protein expression which may explain the reduction of macrophages cholesterol influx [69]. At the cholesterol efflux process level, the results are controversial since in-vivo, PJ was shown to stimulate cholesterol efflux in apo E-deficient mice with advanced atherosclerosis [62] whereas no change was observed in an in-vitro assay using macrophages cells line [70]. Nevertheless, in a recent study Zhao et al., found that pomegranate polyphenols stimulate cholesterol efflux to apo-AI by augmenting ABCA1 and LXRα protein expression, which is in agreement with the in-vivo results obtained by Liu et al. [71] and Kaplan et al. [62].

4.2. Anti-Inflammatory and Anticancer Properties

Inflammation is a protective biological response that includes blood vessels, immunological cells, and inflammatory mediators [79]. Inflammatory diseases such as arthritis, asthma, allergic rhinitis and eczema are treated with conventional anti-inflammatory drugs to minimize damage and improve patient's quality of life. However, their prolonged use cause a range of adverse effects, including stomach upset and bleeding as well as serious cardiovascular events [80] which may sometimes be lethal , in addition to the suppression of the immune system, especially when administered chronically [81]. The numerous risks associated with anti-inflammatory drugs give rise to using natural compounds as alternative therapies. In this context, it is important to develop novel and organic anti-inflammatory agents with minimal adverse effect. According to recent reports, polyphenolic compounds of pomegranate possess a wide range of physiological activities that may contribute to their beneficial effects against inflammation-related diseases. Studies have shown that *P. granatum,* which is rich in polyphenol, exert anti-inflammatory, antioxidant and anticarcinogenic activity [82–84]. Extract of *P. granatum* has been shown to protect human skin fibroblast from cell death following UV exposure, which was related to reduced activation of the pro-inflammatory transcription factor nuclear factor-kappa B (NF-*κ*B) [85].

The effect and action mechanism of an ethanol extract from pomegranate on inflammation *in vivo* were investigated [86], the study indicated that pomegranate extract has been shown to inhibit the TLRs/NF-*κ*B signalling pathway, and down-regulated the production of TNF-*α*, IL-1*β*, IL-8, ICAM1, and VCAM1. The

treatment exerted an anti-inflammatory effect and resulted in the decreased mortality rate against the avian pathogenic *Escherichia coli* (APEC) [86]. In parallel, Park *et al*. [87] found that pomegranate peel extract (PPE) at 10-100 µg/ml, inhibit the production of ROS and the expression of TNF-*α*, IL1, MCP-1, and ICAM-1, but not VCAM-1, in THP-1 cells stimulated by PM10 (100µg/ml). Pomegranate peel extracts constituents, punicalagin and ellagic acid, attenuated the inflammatory cytokine secretion and cell adhesion of monocytic cells stimulated with airborne dust. In addition, Jianjun *et al*. [88] demonstrated that pomegranate flower extract is able to inhibit the production of NO, PGE2, and pro-inflammatory cytokines (TNF- *α*, IL-6, IL-1b), as well as the protein expression of iNOS and COX2 in LPS-stimulated RAW264.7 macrophages. Moreover, pomegranate flower extract treatment significantly inhibited LPS induced NF-*κ*B activation through blocking nuclear translocation of NF-*κ*B and I*κ*B*α* degradation and also inhibited the phosphorylation of MAPKs [88]. These results may be supported by those obtained from Marques et al. [89], which demonstrated that pre-treatment with hydroalcoholic extract prepared from *P. granatum* leaves (HEP) reduced TNF-α mRNA and protein levels in LPS-injected rats. A similar study carried out by Bachoual *et al*. [90], showed that an aqueous extract of *P. granatum* peel inhibits neutrophil-mediated myeloperoxidase activity and attenuates LPS-induced lung inflammation in mice. These results are in agreement with those reported by Mo et al., which demonstrated that pomegranate rind extract diminishes myeloperoxidase activity (a marker for polymorphonuclear leukocyte infiltration) in a mouse model of croton oil-induced ear oedema, suggesting this extract may represent a promising phytomedicine for the treatment of inflammatory diseases [91].

Several studies have confirmed the antiatherogenic effects of pomegranate on the prevention and amelioration of atherosclerosis and other CVD symptoms. de Nigris *et al*. [92] reported that supplementation of an atherogenic diet with pomegranate juice and pomegranate fruit extract can exert beneficial effects on vascular function and inflammation in obese Zucker rats. The results indicated that pomegranate significantly decreased the expression of vascular inflammation markers, thrombospondin (TSP), and transforming growth factor β-1(TGFβ-1) and increased endothelial NO synthase (eNOS) levels in a rat model of metabolic syndrome.

Additionally, it has been shown that administration of concentrated pomegranate juice for 4 weeks, in patients with type 2 diabetes, caused a significant reduction in serum IL-6, but tumor necrosis factor-α (TNF-α) and high sensitivity C-reactive protein (hs-CRP) remained unchanged [93]. Circulating pro-inflammatory cytokines in patients undergoing haemodialysis is slightly reduced by the consumption of pomegranate juice. The study showed that one year of pomegranate juice intake reduced polymorphonuclear priming (PMNL), oxidative damage, and inflammation; significantly lowered the incidence of hospitalization due to infections; and attenuated the atherosclerotic process in haemodialysis patients [94]. In addition, Labsi *et al*. [95] showed that after treatment of cystic echinococcosis infected mice with pomegranate aqueous extract, a significant decrease in nitric oxide, TNF-*α*and NF-kB expression was observed in liver tissue of treated mice.

Several studies assessed the efficacy of pomegranate fruit as an antiproliferative agent in animal models of prostate hyperplasia and carcinoma. Malik and Mukhtar [96] demonstrated that pomegranate fruit extract(PFE) resulted in inhibition of cell growth followed by apoptosis of highly aggressive human prostate carcinoma PC3 cells, accompanied by a reduction in serum prostate-specific antigen (PSA) levels. The decreasing serum PSA levels have also been confirmed in two studies in humans [97,98]. In addition, previous studies have demonstrated a role for pomegranate juice in the inhibition of proliferation and induction of apoptosis in colon cancer cell lines. Studies have shown a correlation between enhanced COX-2 expression and an increase in cell proliferation. Adams *et al*. [99] have reported the anti-inflammatory effects of pomegranate juice in human colon cancer cell line. The pre-treatment with PJ decreased COX-2 expression in HT-29 cells in a dose-dependent manner. At a concentration of 50mg/L, PJ suppressed TNF*α*-induced COX-2 protein expression by 79%.Therefore; they hypothesized that the modulation of COX-2 expression by PJ may be an important mechanism involved in its antiproliferative properties [99]. Conversely, pomegranate intake has no effect on the plasma levels of CRP or tumour necrosis factor α (TNF-α), except in patients with metabolic syndrome [100] or those undergoing dialysis [94].

Previous studies have demonstrated that dietary supplementation of 4% pomegranate extract with a standard chow diet inhibited neuro-inflammation in a transgenic mouse model of Alzheimer's disease (AD). A delay in the formation of senile plaques and the loss of synaptic proteins was also observed [101,102].

Conversely, treatment with pomegranate juice did not protect neuronal degeneration in a separate study that used a rat model of AD but instead exacerbated neuronal cell death and inflammation [103].

CONCLUSION

Punica granatum is an interesting source of phenolic compounds because of their presence in different parts of the fruit. Pomegranate constituents exhibit a broad range of bioactivities, such as anticarcinogenic, antioxidant, anti-inflammatory and anti-atherosclerotic activities. On the basis of these studies results, pomegranate may alleviate feature of the cardiovascular via antioxidant activity. Such observations are supported by short and long-term interventional studies in human subjects and animal models. However, small clinical trials have furnished some conflicting observations regarding the effect of the pomegranate fruit on the cardiovascular and metabolic diseases, pointing out the continuing need for additional human studies involving pomegranate dietary supplementation.

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