International Journal of Preventive Cardiology
Volume 1, Issue 1 - 2021, Pg. No. 19-28
Peer Reviewed & Open Access Journal

Review Article

Medicinal Properties of Antioxidant Pomegranate in Cardiovascular Health

Valentina Stefanou, Spiros Papatheodorou, Despoina Vougiouklaki, Dionisios Antonopoulos, Vladimiros Lougovois, Ioannis Tsaknis, Dimitra Houhoula

Department of Food Science and Technology, Faculty of Food Sciences, University of West Attica, Athens, Greece.

I N F O

Corresponding Author:
Valentina Stefanou, Department of Food Science and Technology, Faculty of Food Sciences, University of West Attica, Athens, Greece.
E-mail Id:
stef12valentin@gmail.com
Orcid Id:
https://orcid.org/0000-0003-2856-4206
How to cite this article:
Stefanou V, Papatheodorou S, Vougiouklaki D, Antonopoulos D, Lougovois V, Tsaknis I et al. Medicinal Properties of Antioxidant Pomegranate in Cardiovascular Health. *Int J Preven Cardio* 2021; 1(1): 19-28.

Date of Submission: 2020-09-26
Date of Acceptance: 2021-01-02

A B S T R A C T

Pomegranate is a plant that contains in its fruit, juice, peel, seeds, flowers, bark and roots high concentration of several phytochemicals as polyphenols, tannins, ellagitannins, gallotannins, flavanols, flavones, flavanones, pro-anthocyanidins, anthocyanins, organic acids, alkaloids and others. Most of these compounds possess strong antioxidant properties. Research has shown that due to this antioxidant activity, pomegranate phytochemicals as mixture in the juice, in the plant-part extracts and as isolated compounds may offer many benefits to cardiovascular health. The oxidation of Low-Density Lipoprotein (LDL) is the main cause of heart diseases. Pomegranate improves the antioxidant status and decreases the oxidative stress. It reduces serum total cholesterol, triglycerides, LDL levels, increases High Density Lipoprotein (HDL), protects against atherosclerosis and acts as antihypertensive. It is found to increase the activity of paraoxonase-1 and paraoxonase-2, serum and tissue enzyme respectively that protect against atherosclerosis. Besides it reduces cardiac fibrosis in diabetic patients, improves the cardiovascular health of aged people and reduces body weight. It is reversing the biochemical changes due to diabetes and the proatherogenic effects due to perturbed shear stress. It is found to affect the values of biochemical parameters as total cholesterol, triglycerides, LDL, HDL only when they are not normal showing a tendency to the normal, healthy condition than simply changing values even towards the desired direction. In the safety tests that were carried out no side effects were observed.

Keywords: Pomegranate, Phytochemicals, Antioxidant, Cardiovascular, Cholesterol, HDL, LDL, Antihypertensive, Antiatherogenic, Triglycerides

Introduction

Punica Granatum L. (pomegranate) is an ancient plant growing in tropical and subtropical climate.[1] It contains several categories of bioactive compounds and since ancient times, has been used in traditional medicine to lower blood lipids, treat fevers, malaria, chronic debility, wounds, mouth ulcers, gastroenterological problems, asthma, allergies, diabetes and parasitic infections. It's also referred to prevent conception and as aphrodisiac. Different plant parts containing different compounds, were used to treat different health problems.[2,3,4,5,6,7,8]

Scientific researches confirmed the high medicinal activity of the pomegranate constituents as mixture as they exist in its parts or isolated compounds against several diseases. It is found that it possesses strong antioxidant, cardioprotective, antihypertensive, antiatherogenic, anti-inflammatory, antimicrobial, anticancer, antitumor, antidiabetic, antiallergic properties, strengthens the immune system and improves memory.[9]

Phytochemicals in Pomegranate Plant

All pomegranate plant parts contain in high concentrations, several bioactive compounds that are called phytochemicals. In each plant part the compounds and their concentration differ, making each part more effective for specific diseases and health conditions.

Peel is rich in polyphenolic compounds, tannins, ellagitannins, gallotannins especially punicallin and punicalagin, flavonoids as flavones, flavanols, flavanones, proanthocyanidins. There are also complex polysaccharides and minerals as sodium, potassium, calcium and magnesium.[10-14] Pomegranate juice contains polyphenols, tannins, ellagitannins and flavonoids that possess strong antioxidant properties. It contains simple triterpenoids, phytosterols, organic acids as citric, ascorbic, malic and fumaric acid and amino acids as proline, valine and methionine. Main ellagitannins are punicalin and punicalagin. Most important flavonoids in the juice are flavanols, flavan-3-ols and anthocyanins.[14] Alkaloids are found in high concentration in bark and roots especially piperidine alkaloids, very effective against intestinal worms and also there are the antioxidant ellagitannins punicalin and punicalagin.[14,15] In the seed there are conjugated fatty acids as punicic acid, non-conjugated fatty acids as palmitic, linolenic and oleanolic acid, sterols, sex steroids and phenyl aliphatic glucosides.[16,10] In the pomegranate leaves are contained polyphenolic compounds, flavonoids, tannins, ellagic acids, esters ellagic acids with glucose and also piperidine alkaloids.[10,11,17] Phytochemicals that exist in flowers are triterpenoids as asiatic acid and maslinic acid, and also there are gallic and ursolic acid.[10,11] The phytochemicals' concentration in the plant parts vary due to the plant variety, ripening stage, climate, cultivar and storage conditions.[16]

Antioxidant Activity

Pharmacokinetic studies showed that the flavonoids cyanidin, pelargonidin, luteolin, luteolin7-O-glucoside, kaempferol, kaempferol 3-O-glucoside, prodelphinidin which are found in the peel have antioxidant properties. Catechol, cyaniding-3-O-glucoside, cyaniding-3,5-di-O-glucoside, procyanidin andpelargonidin-3-O-glucoside in the juice, also have antioxidant properties. Other flavonoids with antioxidant properties are apigenin in the leaves, catechin in the leaves and in the peel, quercetin in juice and peel and quercetin-3,4-dimethyl ether-7-O-α-L-arabinofuranosyl (1à6)-β-D-glucopyranoside in the bark. Tannins that are found to have antioxidant properties are brevifolin which is contained in the leaves, casuarinin in the peel, and gallic acid which is contained in the juice, flowers, leaves and peel. Besides, 3,3′-di-O-methyl ellagic acid and 3,3′,4′tri-O-methylellagic acid both found in the seed show also antioxidant properties. Pedunculagin found in peel, punigluconin found in bark and punicalagin and punicalin both found in bark, leaves, peel and roots are showing antioxidant properties too. Alkaloids that show antioxidant properties are serotonin and melatonin which are found in the juice.[10] Ellagic acid and ellagitannins show very high antioxidant activity.[18]

Due to high concentration in phenolic compounds, pomegranate has excellent antioxidant activity.[19] It is found that pomegranate promotes health via inhibition of free radical effect and also via modulation of activity of enzymes linked with development and progression of diseases.[20,21] Free radicals guide cholesterol in an oxidation process in arteries that leads to atherosclerosis which is the hardening of arteries due to atheromatic plaque and leads to heart diseases.[22,23]

Research showed that both pomegranate peel extract and pulp extract in a mixture of ethanol, methanol and acetone have antioxidant properties. The peel extract is found to be more potent antioxidant than the pulp extract as it shows higher preventive capacity against superoxide anion, hydroxyl and peroxyl radicals, inhibiting more efficiently the CuSO4 -induced Low-Density Lipoprotein (LDL) oxidation.[24] Cold pressed pomegranate seeds and fermented juice have antioxidant properties and inhibit cyclooxygenases and lipoxygenases decreasing prostaglandin and leukotriene formation.[25]

At an in vitro research of antioxidant activity of pomegranate beverages have been found that the 100% of the beverages shown very strong antioxidant properties, inhibiting by up to 95% LDL oxidation. The activity of serum paraoxonase-1 (PON 1), an HDL associated esterase that protects from lipid peroxidation, has been increased up to 51% and the serum lipid peroxidation has been inhibited up to 38%.[26,11]

Cardiovascular Health

Pharmacokinetic studies showed that the flavonoids kaempferol-3-O-rhamnoglycoside which exists in the peel and rutin which exists in peel and juice are showing antihypertensive properties. Brevifolin is a tannin that is showing hypolipidemic properties. The tannins punicalagin found in the bark, leaves, peel and roots and corrilagin found in leaves and peel are showing antihypertensive activity.[10]

Researches show that pomegranate juice, containing polyphenols in high concentration, has very strong

antiatherogenic, anti-inflammatory and antihypertensive properties and thus it protects against cardiovascular diseases.[22,27] The most important factor for atherosclerosis is the high concentration of the Low-Density Lipoprotein (LDL) in the plasma. Besides, LDL modifications as aggregation, oxidation and retention are related to atherosclerosis and prevention of modifications prevents atherosclerosis.[15]

Pomegranate extracts, rich in antioxidant agents such as gallic, oleanolic and ursolic acids, reduce LDL and increase HDL level and thus they can prevent cardiovascular diseases.[28]

In a research, pomegranate juice has been administrated to mice genetically predisposed to develop heart diseases and to humans. The results showed that the oxidation of LDL after administration was reduced up to 90%. Besides, the level of the LDL was reduced and increased the level of High-Density Lipoprotein (HDL) by 20% in the humans.[22]

Paraoxonase 1 (PON-1) is a serum enzyme that is associated with HDL. It prevents LDL oxidation and is breaking down harmful lipids existing in macrophages, lipoproteins and atherosclerotic plaques. Paraoxonase-2 (PON-2) exists in the tissues but not in the serum and shows antioxidant activity at the cellular, not humoral level. Both PON-1 and PON-2 protect against atherosclerosis. The antioxidants anthocyanins, tannins and their mixture as it exists in pomegranate have good antiatherogenic properties as they are found to increase the activity of PON-1.[29,30,31]

Hypercholesterolemic, diabetic and hypertensive patients, having weak antioxidative status, they have increased oxidative stress, and this means high risk for atherosclerosis. The pomegranate polyphenols increase the activity of PON-1 and PON-2 and thus decrease oxidative stress and atherosclerosis in cardiovascular patients.[31]

Research in humans and mice showed that consuming pomegranate juice decreases oxidative stress and atherogenic modifications to LDL. The pomegranate administration in humans resulted in significant reduction of LDL and 20% increase in the serum paraoxonase. Juice administration in mice resulted in up to 90% decrease of the LDL oxidation by peritoneal macrophages. This effect was linked to reduced cellular lipid peroxidation and superoxide release. Both human and mice had decrease in the size of atherosclerotic lesions.[25]

Pomegranate juice consumption for two weeks, decreased the aggregation and retention of LDL susceptibility. The activity of paraoxonase has been increased by 20% in the humans.[15] Pomegranate juice consumption by humans for 14 weeks and by E0 mice for 2 weeks resulted in LDL decrease and in 20% increase of paraoxonase 1 in humans. In the mice was observed an 90% decrease of LDL oxidation by peritoneal macrophages. In the mice there was 20% decrease of the oxidized LDL and native LDL uptake. There was also a 44% decrease of the atherosclerotic lesions of the mice. Besides lower number of foam cells has been found in the pomegranate mice group, compared with the control group.[32]

It is also found that the pomegranate juice causes significant decrease of the arterial plaque's size in humans and in mice. 19 patients aged 65-75 years with severe carotid artery stenosis (70%-90% occlusion) were administrated by 50 ml per day of concentrated pomegranate juice. After one year the carotid artery thickness has been decreased by 35% and in the patients administrated with placebo there was increase of the main artery thickness. Was found also that the mice's arterial plaque thickness reduced by 44%. Has been found that the systolic blood pressure of hypertensive patients can remarkably lower after 2 weeks administration with pomegranate juice. Patients with cardiovascular diseases had big improvement in several physiological measurements after consuming pomegranate juice.[22]

Administration of pomegranate seed oils (88% polyunsaturated fatty acids, 905.5μg/100 g total tocopherols), defatted pomegranate seeds (14.8 mg/g total phenolics, 98.2% scavenging activity) and a mixture of both on atherogenic rats for 1 month and comparation with LDL, total cholesterol, risk ratio, lipid peroxidation and atherogenic index results of control group showed that these pomegranate fractions have high protecting activity against atherosclerosis.[33]

In research, female hyperlipidemic mice were administrated for 30 days with pomegranate juice in order to evaluate its effect on the atherogenic index, lipid profile and lipoproteins. There were 4 groups of 6 mice each, and the group A mice were administrated with 0.2 ml distillated water, group B mice were administrated with high cholesterol diet, group C administrated as group B with high cholesterol diet but also with 0.2 ml pomegranate juice and group D administrated only with 0.2 ml pomegranate juice. Comparing the A and C groups, it was found that the high cholesterol diet increased remarkably the atherogenic index, total cholesterol, triglycerides, LDL and VLDL (very low-density lipoprotein produced in liver and supplies body tissues with triglycerides) while there was significant decrease of HDL. Comparing the groups C and D was found that the pomegranate administration without fat diet resulted in remarkable decrease of atherogenic index, total cholesterol and LDL in the D group. Besides, comparing C and D groups was observed significant increase in D group of the triglycerides, LDL and VLDL. There were no remarkable differences among A and B groups in VLDL levels. There was a remarkable reduction in atherogenic index in groups B and D compared with C group, but not significant difference

compared with control group A. There was a big decrease in VLDL in group B compared with C.[34]

Pomegranate juice showed in both mouse models and humans, very high antioxidant, anti-hypertensive, anti-atherosclerotic and anti-inflammatory activity. Has been found that pomegranate juice prevents the activity of the angiotensin-converting enzyme which is contained in the serum and this way the systolic blood pressure is reduced.[35] Angiotensin II increases the blood pressure of diabetic Wistar rats, which with a 4 weeks administration of 100mg/Kg pomegranate juice had less mean arterial blood pressure.[36]

In research hypercholesterolemic guinea pigs were administrated with methanolic pomegranate peel extract for 30 days in order to evaluate their activity on cardiac and liver status. There were 6 groups of 10 pigs each: The control group, a group where pigs were treated with pomegranate extract, a group which was treated with hypercholesterolemic diet and the group where fed with fat diet but were treated with pomegranate extract too. The fat diet group showed big increase of cholesterol and triglycerides in comparation with the control group. The pomegranate administration resulted in remarkable reduction in in cholesterol and triglycerides comparing with the fat diet group. The fat diet and in parallel pomegranate administrated group showed decrease in cholesterol and triglycerides compared with the just fat diet group. The group with the fat diet had remarkable increase of hepatic cholesterol content and catalase activity compared to the control group. The pomegranate administration decreased the hepatic cholesterol and catalase activity compared to control group.[37]

Immune deficient mice were administrated with pomegranate juice and there was remarkable reduce in atherosclerotic lesion arias. Lipid peroxidation and systolic blood pressure were reduced with pomegranate juice consumption by type 2 diabetic patients.[27]

Hemodialysis patients were administrated immediately after dialysis session for 8 weeks with 100 ml pomegranate juice. It was found that in the pomegranate group the total antioxidant capacity has been increased and in controls reduced. Triglycerides were reduced and HDL was increased in pomegranate administered group in contrast to the control group where triglycerides increased, and HDL reduced. LDL did not change with the administration. There was remarkable decrease in both systolic and diastolic blood pressure in pomegranate group. The lipid peroxidation marker malonaldehyde and inflammatory marker interleukin-6 were reduced in pomegranate treated patients and increased in control groups.[38]

Accumulation of macrophage cholesterol and formation of foam cell indicate early atherogenesis that pomegranate can inhibit as researches show. In research, in order to find by which mechanisms the accumulation of cholesterol is reduced, after pomegranate juice preincubation of macrophages J774.A1, the cholesterol influx (oxidized LDL (ox-LDL) cellular degradation), cholesterol efflux and also cholesterol biosynthesis were evaluated and was found that with the use of pomegranate juice there was a 40% decrease in ox-LDL degradation. The macrophage cholesterol efflux and macrophage native LDL degradation were not affected by pomegranate juice preincubation. With the pomegranate juice use has been noticed a 50% inhibition in macrophage cholesterol biosynthesis which was found that in the biosynthetic pathway was not mediated at the 3-hydroxy-3-methylglutaryl coenzyme A reductase level. It means that the cellular accumulation of cholesterol and the foam cell formation are decreased with the pomegranate juice because of suppression of the Ox-LDL degradation and of the biosynthesis of cholesterol in macrophages.[39]

In yet another research, 10 atherosclerotic patients with carotid artery stenosis were administrated with pomegranate juice for 1 up to 3 years. After one year was found that the pomegranate juice consumption resulted in up to 30% decrease of the common carotid intima media thickness. In the group that didn't use pomegranate juice it increased by 9%. The total antioxidant status increased by 130%. The antibodies against oxidized LDL reduced by 19%. The serum basal oxidative state decreased by 90%. The activity of paraoxonase 1 has been increased by 83%. The LDL susceptibility to copper ion induced oxidation decreased by 59%. Systolic blood pressure was reduced by 21% in one year, yet continuing consumption for 2 more years caused no further decrease.[40]

In a research, juice extracts from two pomegranate varieties were administered to evaluate the impact on LDL levels when compared with lovastatin, a cholesterol lowering medicine. Three groups of 20 hypercholesterolemic patients were administrated with 1) tabrizy pomegranate juice, 2) black pomegranate variety juice and 3) lovastatin and the plasma LDL levels were measured before and after consumption. In all three groups there was remarkable decrease in LDL levels and the pomegranate groups 1 and 2 showed similar decrease with the medicine group so the treatment with the pomegranate was as effective as the medicine treatment in the plasma LDL lowering.[41]

Lipid peroxidation leads to atherosclerosis, macrophage cholesterol accumulation and foam cell formation so it is important to be inhibited. Mice with advanced atherosclerosis were administrated with pomegranate juice for two months and it was found that the serum paraoxonase's activity that protects against lipid peroxidation

was remarkably increased in comparation with control group. The oxidized LDL was decreased by 31%. Mice peritoneal macrophage uptake and lipid peroxide content were decreased compared with control group. Macrophage cholesterol efflux reduced by 39%.[42]

Atherosclerosis is more easily developed in the exposed to disturbed flow arterial segments. The pomegranate polyphenols decrease the activation of the oxidation sensitive responsive genes ELK-1 and p-CREB, decrease the oxidative stress and atherogenesis caused by disturbed shear stress to hypercholesterolemic mice and human cultured endothelial cell. Research showed that chronic administration with pomegranate fruit extract can reverse the proatherogenic effects that are induced because of perturbed shear stress.[43]

It is found that punicic acid, which exists in high concentration in the pomegranate seed oil has antiatherogenic activity. Administration of 800 mg per day to 51 hyperlipidemic patients for 4 weeks resulted in a very big decrease of triglycerides and in decrease of the ratio triglycerides: HDL by 2.75 mmol/L and 5.7 mmol/L respectively. The concentration of glucose and of LDL-C did not change with the use of pomegranate seed oil.[15]

Obese Zucker rats were administrated with pomegranate juice or fruit extract or seed oil and was found that both juice and extract caused remarkable decrease of the expression of thrombospondin and cytokine, vascular inflammation markers. The seed oil reduced only thrombospondin expression. Besides, plasma nitrite and nitrate were with both juice and extract, increased.[44]

Experiments have shown that 1% pomegranate seed oil, a good source of punicic acid with high fat diet for 12 weeks managed to reduce the body weight by 4% and the body fat mass by 3.1% in comparation with mice which were fed in same high fat diet but without the seed oil.[45]

Hyperlipidemic high fat diet ICR mice with obesity were administrated with 400 or 800 mh.kg/day of pomegranate leaf extract for 5 weeks. The results showed that there was remarkable reduction in the body weight, triglycerides, energy intake, Total Cholesterol (TC) and TC/HDL-C ratio. There was also remarkable attenuation of the triglycerides' level raising and the absorption of intestinal fat was inhibited. The pomegranate leaf extract reduced the appetite in obese high diet fed mice but there was no effect on the normal diet mice.[46] and this is important to be mentioned as it seems that the leaf extract acts more as a regulator that affects only the pathogenic but not the natural case.

Pomegranate juice has protective effects against reperfusion injury and myocardial ischemia. Patients with unstable angina or myocardial infraction were administrated daily in addition with conventional medicines with 22o ml pomegranate juice, for 5 days. Results showed remarkable decrease in the duration, intensity and occurrence of angina. Besides, the serum troponin and malondialdehyde levels were remarkably reduced.[47] Serum troponin is cardiac regulator protein and high levels in serum could mean cardiac muscle disease or chronic diseases. It is used to diagnose muscle infraction.[48] Malondialdehyde is marker of lipid peroxidation and of oxidative stress, as increased free radicals cause overproduction of it.[49]

Research showed that the polysaccharide inulin and pomegranate extract can improve metabolic changes which are caused by high fat diet. Administration on C57BL/6J mice with i) pomegranate extract, ii) inulin, iii) both inulin and extract resulted in determination of the lipid metabolism, hepatic gene expression of key regulators of cholesterol and levels of serum/hepatic cholesterol and triglycerides. Administrations of alone inulin and pomegranate extract reduced by different mechanisms the serum and hepatic cholesterol. The extract administration reduced liver triglyceride. Inulin and inulin-extract combination didn't reduce. Combination of extract and inulin lead to significantly lesser serum and hepatic cholesterol in comparation with the individual administrations.[50]

In yet another research, 22 hyperlipidemic and type-2 diabetic patients were administrated with 40 g concentrated pomegranate juice daily for 8 weeks. It was found that there was remarkable decrease in total cholesterol, LDL-C levels and TC: HDL-C ratio. The LDL and serum triacylglycerol were not much affected.[51].

Endothelin-1 (ET)-1 is a blood vessel narrowing peptide that is involved in cardiac fibrosis. Cardiac fibrosis is a disease where the heart valves get abnormal thickened. In research has been found that extracts from the pomegranate flower suppress the signaling of endothelin-1 and helps to inhibit heart disease and also metabolic syndrome and type -2 diabetes.[22]

Nuclear factor kappa B (NF-κB) is a transcription factor that controls inflammation and is linked to cardiovascular health influencing ischemic preconditioning, myocardial ischemia and reperfusion injury, atherosclerosis, heart hypertrophy, vein graft disease and heart failure. Depending on the physiological and cellular context, it can prevent injuries of cardiovascular tissues or lead to pathogenesis. Incorrect regulation of NF-κB is connected with inflammatory and other diseases. Research showed that pomegranate peel polyphenols suppress the activation of TLR4/NF-κB pathway and this way the inflammation in lipopolysaccharide induced macrophages is inhibited.[52]

The cardiac function in diabetic patients is infected by the increased fibrosis. Endothelin and NF-κB both, interacting

each other regulate the fibroblast growth. Administration of 500 mg/Kg per day of flower extract in Zucker diabetic fatty rats reduced cardiac fibrosis. The overexpressed cardiac fibronectin and collagen I and II messenger RNAs have been inhibited and were reduced the upregulated cardiac m-RNA expression of ET-1 which is a fibroblast growth regulator. There was modulation of cardiac ET-1 and NF-κB signaling and thus cardiac fibrosis was eliminated. There was also improvement in hyperlipidemia, hyperglycemia and in the fatty heart condition of type-2 diabetic rats.[53]

Pomegranate juice extract administration on diabetic rats at dosages of 100 mg/kg and 300 mg/kg for 4 weeks reversed biochemical changes that were caused by diabetes and it prevented the tubular degenerative changes that are created by diabetes. Besides the mean arterial blood pressure of the rats was lowered and is suggested that this happens because the oxidative stress that is caused because of diabetes is reduced by the antioxidant pomegranate juice extract. Besides, is reduced the activity of angiotensin converting enzyme, which converts angiotensin I to angiotensin II that is involved in cardiovascular pathogenesis on diabetic patients and rises the blood pressure.[36]

Patients with type-2 diabetes were administrated with 2 capsules/ day, of 753mg pomegranate polyphenols each and the results showed that there was remarkable decrease in lipid peroxidation and that there was no decrease in healthy controls.[54]

Pomegranate flower extract has been orally administrated in Zucker diabetic fatty rats in dosage of 500 mg/kg and the results showed that there was improvement in the abnormal cardiac lipid metabolism in the rats. This happens due to PPAR-α activation and decrease of the circulating lipid. The circulating lipid cardiac uptake was inhibited.[55]

The main cause of diabetes complication is oxidative stress. Research showed that the antioxidant pomegranate seed oil has strong protecting effect against cardiovascular diabetes complications. The pomegranate seed oil administration remarkably reversed histopathological abnormality that was caused in rats with streptozotocin induced diabetes. Decrease of creatinine and urea levels was observed. There was also remarkable decrease in serum glucose, LDL, triglycerides, cholesterol in seed oil rats in contrast with the streptozotocin administrated rats that became diabetic and all those values were increased.[56]

Pomegranate juice extract administration on diabetic rats at dosages of 100 mg/kg and 300 mg/kg for 4 weeks reversed biochemical changes that were caused by diabetes and it prevented the tubular degenerative changes that are created by diabetes. Besides the mean arterial blood pressure of the rats was lowered and is suggested that this happens because the oxidative stress that is caused because of diabetes is reduced by the antioxidant pomegranate juice extract. Besides, is reduced the activity of angiotensin converting enzyme, which converts angiotensin I to angiotensin II that is involved in cardiovascular pathogenesis on diabetic patients and rises the blood pressure.[36]

Research on high fat diet diabetic rats showed that pomegranate flowers could be useful in therapy or prevention of chronic diseases where there is bad antioxidant status, atherogenesis and abnormal glucose metabolism. In the research pomegranate flower aqueous extract has been orally administrated at dosages of 250 and 500 mg/ kg for 21 days and was observed significant decrease in triglycerides, total cholesterol, LDL-C, VLDL-C, tissue peroxidation level and fibrinogen (high levels of it indicate systemic inflammation, tissue injury or other issues). Besides there was increase of HDL-C and glutathione (important antioxidant tripeptide), compared with the diabetic control group.[57]

Chronic use of the opioid analgesic tramadol creates oxidative stress toxicity and testicular damage in rats. Tramadol and pomegranate seed extract with high total phenolics, flavonoids and DPPH scavenging activity were administrated to male rats for 3 weeks and results were compared with only tramadol administrated group. In tramadol group were several structural changes as intercellular spaces, blood vessels hemorrhage, interstitial vacuoles but in tramadol-pomegranate seed extract administrated group were not observed any of these structural changes.[58]

There are several health problems associated with aging. In a study, the effect of pomegranate juice has been evaluated on biochemical parameters on healthy active aged men. The men were administrated with 250 ml of pomegranate juice twice a day for 15 days. Results showed that there was remarkable difference between biochemical parameters of these men and placebo administrated men. Specifically, it was found that pomegranate juice significantly decreased hematological and muscle damage parameters, creatinine, systolic blood pressure, and C-reactive protein. Besides it was found that pomegranate juice consumption increased platelets blood levels. The research showed strong anti-inflammatory properties and that it probably could be used for thrombocytopenia disease treatment.[59]

In menopause, estrogen levels decrease, and this causes endothelial disfunction and cardiovascular disease. In a research, hydralcoholic pomegranate extract was by gavage administrated in rats at dosage of 250 mg/kg for a month. Results showed LDL and total cholesterol decrease. Cardiovascular parameters were improved, and endothelium-dependent coronary relaxation was enhanced.[60]

In a research on how pomegranate juice affects healthy

humans was found the levels of hematocrit, hemoglobin and red blood cell count were raised on the health humans there was no effect on cholesterol, HDL, LDL, triglycerides and complete blood count.[61]

Pomegranate Safety

Pomegranate consumption has no side effects, nor the pomegranate extracts used in folk medicine. Administration of 1420 mg/day fruit extract tablets in humans did not cause any side effects.[23] Research on the safety of whole fruit hydralcoholic extracts used in Cuban traditional medicine showed that it is safe in used dosage and that the LD_{50} in OF-1 mice is 731 mg/kg with confidence limits 565-945 mg/kg.[62] Four-week administration of 710 mg or 1420 mg of ellagitannin enriched polyphenol extract in overweight individual found to be safe.[63] The LD_{50} of ethanolic seed extract and pericarp extract administration in mice were 5000 mg/kg and 2000 mg/kg respectively. No side effects were observed in oral administration of methanolic peel extract (500 mg/kg/day) in rats for 15 days. 7 mg/kg lyophilized ethanolic fruit extract administration in rats for 35 days did not cause side effects except creatinine value increase but without any kidney damage. Administration of hydralcoholic fruit extract in male mice at dosage higher than 70 mg/kg bw resulted in abnormal sperm creation. Administration of pomegranate seed extract (1g/kg in 0.2 ml distilled water) or juice extract (3.3ml/kg in 0.2 ml distilled water) or mixture of both in female mice for 18 days did not cause any side effects in fetuses.[64]

Discussion

Pomegranate is rich in several phytochemicals with strong antioxidant properties and it is found that the pomegranate's cardioprotective effect is due to this antioxidant activity. Pomegranate isolated phytochemicals and also as mixture in juice and extracts of pomegranate fractals where they show synergic action reduce total cholesterol, LDL, triglycerides, increase HDL and show remarkable antihypertensive and antiatherogenic properties and even are reversing proatherogenic effects due to perturbed stress. Reversing, means not allowing the disease to develop, means prevention. It also improves the cardiovascular health of diabetic and of hemodialysis patients, women under menopause and elder men. It is found to reverse biochemical changes due to diabetes. Researches showed that pomegranate improved the values of biochemical parameters as LDL, HDL, total cholesterol, triglycerides, in patients but did not affect in the healthy human's research or in the healthy controls. This is very important information as pomegranate seems to act more as a regulator, affecting parameters as much as needed, if needed (and as much as its possible too, depending on each case), in order to return or tend to the normal healthy condition and it's not simply affecting the parameters towards the desirable direction that could probably cause problems if the tendency was not towards normality but towards limiting a value even if it would this way move away from normality. Further clinical tests would give more information on this tendency and the biochemical paths the pomegranate constituents are involved to achieve it.

Conclusion

The beneficial effect of the antioxidant pomegranate on biochemical parameter values combined with the regulation activity it shows, as it does not affect biochemical parameters if they are normal, the ability to reverse early pathogenic changes and the fact that it has no side effects makes it a promising alternative treating agent in cardiovascular health issues.

Sources of Funding: No sources of funding

Conflicts of Interest: None

References

1. Fadavi A, Barzegar M, Azizi MH, Bayat M. Note. Physicochemical Composition of Ten Pomegranate Cultivars (Punica granatum L.) Grown in Iran. *Food Science and Technology International* 2005; 11(2): 113-119.
2. Dan Tang, Liu Liu, Dildar Ajiakber, Jianping Ye, Jianjun Xu Xuelei Xin, Haji Akber Aisa. Anti-diabetic Effect of *Punica granatum* Flower Polyphenols Extract in Type 2 Diabetic Rats: Activation of Akt/GSK-3β and Inhibition of IRE1α-XBP1 Pathways. *Frontiers in Endocrinology* 2018; 9: 1-11.
3. Sunil N, Surekha B, Vipul D, Anuja P. Effects of Punica granatum on milk-induced leukocytosis and eosinophilia in mice. *Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas* 2011; 10(3): 222-227.
4. Das S, Barman S. Antidiabetic and antihyperlipidemic effects of ethanolic extract of leaves of Punica granatum in alloxan-induced non-insulin-dependent diabetes mellitus albino rats. *Indian Journal of Pharmacology* 2012; 44(2): 219-224.
5. Jang-Gi Choi, Ok-Hwa Kang, Young-Seob Lee, Hee-Sung Chae, You-Chang Oh, Obiang-Obounou Brice et al. In Vitro and In Vivo Antibacterial Activity of Punica granatum Peel Ethanol Extract against Salmonella. *Evidence-Based Complementary and Alternative Medicine* 2011; article ID 29058; 1-8.
6. King H, Riddle JM. Eve's herbs: a history of contraception and abortion in the West. Cambridge, Mass., Harvard University Press, 1997, pp. vii, 341, £26.50 (0-674-27024-X). *Medical History* 42(03): 412-414.
7. Langley P. Why a pomegranate? *BMJ* 321(7269) 2000; 1153-1154.
8. Tristão Banhos Delgado N, do Nascimento Rouver W, Santos RL. Protective effects of pomegranate in

endothelial dysfunction. *Current Pharmaceutical Design 26* (April 2020).
9. Kumari A, Dora J, Kumar A, Kumar A. Pomegranate (*Punica granatum)*-Overview. *International Journal of pharmakeutical and Chemical Sciences* 2012; 1(4): 1218-1222.
10. Wang RE, Yi Ding, Liu R, Yiang L, Du L. Pomegranate: Constituents, Bioactivities and Pharmakikinetics. Global Science Books; *Fruit, Vegetable and Cereal Science and Biotechnology* 2020; 4(2): 77-87.
11. Rahimi HR, Arastoo M, Ostad SN. A Comprehensive Review of PunicaGranatum (Pomegranate) Properties in Toxicological, Pharmacological, Cellular and Molecular Biology Researches. *Iranian Journal of Pharmaceutical Research* 2012; 11(2): 385-400.
12. Jurenka J. Therapeutic Applications of Pomegranate (PunicaGranatum L): A Review. *Alternative Medicine Review* 2008; 13(2): 128-144.
13. Sharma P, McClees SF, Afaq F. Pomegranate for Prevention and Treatment of Cancer: An Update. *Molecules* 2017; 22(1): 1-18.
14. Vučića V, Grabežb M. Armen Trchounianc and Aleksandra Arsića; Composition and Potential Health Benefits of Pomegranate: A Review. *Current Pharmaceutical Design* 2019; 25(16): 1817-1827.
15. Asgary, Sedigheh, Javanmard, Haghjoo S, Zarfeshany, Aida. Potent health effects of pomegranate. *Advanced Biomedical Research* 2014; 3(1): 1-8.
16. Boroushaki MT, Mollazadeh H, Afshari AR. Pomegranate seed oil: A comprehensive review on its therapeutic effects. *International Journal of Pharmaceutical Sciences and Research* 2016; 7(2): 430-442.
17. Trabelsi A, El Kaibi MA, ¨ımen Abbassi A, Horchani A, Chekir-Ghedira L, Ghedira K. Phytochemical Study and Antibacterial and Antibiotic Modulation Activity of Punica granatum (Pomegranate) Leaves. *Hindawi* 2020; 7.
18. Seeram NP, Lee R, Heber D. Bioavailability of ellagic acid in human plasma after consumption of ellagitannins of pomegranate (Punicagranatum. L.) juice. *Clinica Chimica Acta* 2004; 348(1-2): 63-68.
19. Salgado JM, Baroni Ferreira TR, de Oliveira Biazotto F, dos Santos Dias CT. Increased Antioxidant Content in Juice Enriched with Dried Extract of Pomegranate (Punica granatum) Pee"l. *Plant Foods Hum Nutr* 2012; 67(1): 39-43.
20. Basu A, Penugonda K. Pomegranate juice: A heart-healthy fruit juice. *Nutrition Reviews* 2009; 67(1): 49-56.
21. Seerama NP, Adamsa LS, Henninga SM, Niua Y, Zhangb Y, Nairb MG. *In vitro* antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. *Journal of Nutritional Biochemistry* 2005; 16(6): 360-367.
22. Ahmad R. Pomegranate - A Super Antioxidant. *International Journal of Biochemistry & Physiology* 2017; 2(1): 1-3.
23. Chandulal D, Maya I, Jayshri W. Pomegranate: Natural remedy for treating periodontal disease. *International Journal of Advanced Education and Research 2016;* 1(8): 27-31.
24. Yunfeng Li, Changjiang Guo, Jijun Yang, Jingyu Wei, Jing Xu, Shuang Cheng. Evaluation of antioxidant properties of pomegranate peel extract in comparison with pomegranate pulp extract. *Food Chemistry* 2006; 96(2): 254-260.
25. Aviram M, Dornfeld L, Rosenblat M, Volkova N, Kaplan M, Coleman R et al. Pomegranate juice consumption reduces oxidative stress,atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *American Journal of Clinical Nutrition* 2000; 71(5): 1062-1076.
26. Stockton A. The effect of pomegranate on anthropometric, biochemical, cognitive and safety indicators of risk factor for non-communicable diseases. (PhD diss, Queen Margeret University. 2019; 62.
27. Basu A, Penugonda K. Pomegranate juice: a heart-healthy fruit juice. *Nutrition Review* 2009; 6(1): 49-56.
28. Katz SR, Newman RA, Lansky EP. Punica granatum: Heuristic Treatment for Diabetes Mellitus. *Journal of Medicinal Food* 2007; 10(2): 213-217.
29. Michael Aviram D, Rosenblat M. Pomegranate for Your Cardiovascular Health. *Rambam Maimonides Medical Journal* 2013; 4(2): 12, e0013.
30. Vekic J, Kotur-Stevuljevic J, Aleksandra Zeljkovic, Stefanovic A, Jelic-Ivanovic Z, Spasicand S. Serum Paraoxonase (PON1) and its Interactions with HDL: Relationship between PON1 and Oxidative Stress. *The HDL Handbook* 2010; 77-98.
31. Aviram M, Rosenblat M. Pomegranate Protection against Cardiovascular Diseases. *Evidence-Based Complementary and Alternative Medicine* 2012: 382763: 98-104.
32. Aviram M, Dornfeld L, Rosenblat M, Volkova N, Kaplan M, Coleman R et al. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *The American Journal of Clinical Nutrition* 2000; 71(5): 1062-1076.
33. Elbandy MA, Ashoush IS. Phytochemicals in Pomegranate Seeds and Their Effect as Hypolipidemic Agent in Hypercholesterolemic Rats. *World Journal of Dairy & Food Sciences* 2012; 7(1): 85-92.

34. Al-Fartosi KG, Tuama RJ, Roomi AB, Hasim SH. Effect of pomegranate (PunicaGranatum L) juice on lipid profile of hyperlipidemic female mice. *International Journal of Research in Applied,Natural and Social Sciences* 2015; 3(10): 2347-4580.
35. CB Stowe. The effects of pomegranate juice consumption on blood pressure and cardiovascular health. *Complementary Therapies in Clinical Practice* 2011; 17(2): 113-115.
36. Mohan M, Waghulde H, Kasture S. Effect of pomegranate juice on Angiotensin II-induced hypertension in diabetic wistar rats". *Phytotherapy Research* 2009; 24(2): 196-203.
37. Hasona NA, Ahmed MQ, Alghassab TA, Alghassab MA, Alghabban AA. Antihyperlipidemic effect of pomegranate peel and Iranian fenugreek extracts on cholesterol-rich diet-induced hypercholesterolemia in guinea pigs. *Merit Research Journals* 2016; 4(4) 196-203.
38. Barati Boldaji R, Esmaeilinezhad Z, Sagheb MM, Akhlaghi M. Pomegranate juice improves the cardiometabolic risk factors, biomarkers of oxidative stress and inflammation in hemodialysis patients: A randomized crossover trial. *Journal of the Science of Food and Agriculture* 2019; 100(2): 846-854.
39. Fuhrman B, Volkova N, Aviram M. Pomegranate juice inhibits oxidized LDL uptake and cholesterol biosynthesis in macrophages. *The Journal of Nutritional Biochemistry* 2005; 16(9): 570-576.
40. Aviram M, Rosenblat M, Gaitini D, Nitecki S, Hoffman A, Dornfeld L et al. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. *Clinical Nutrition* 2004; 23(3): 423-433.
41. Anoosha E, Mojtabaa E, Fatemeha S. Study the effect of juice of two variety of pomegranate ondecreasing plasma LDL cholesterol. *Procedia Social and Behavioral Sciences* 2010; 2(2): 620-623.
42. Kaplan M, Hayek T, Raz A, Coleman R, Dornfeld L, Vaya J, Aviram M. Pomegranate Juice Supplementation to Atherosclerotic Mice Reduces Macrophage Lipid Peroxidation, Cellular Cholesterol Accumulation and Development of Atherosclerosis. *The Journal of Nutrition* 2001; 131(8): 2082-2089.
43. De Nigris F, Williams-Ignarro S, Sica V, Lerman LO, D'Armiento FP, Byrns RE et al. Effects of a pomegranate fruit extract rich in punicalagin on oxidation-sensitive genes and eNOS activity at sites of perturbed shear stress and atherogenesis. *Cardiovasc Res* 2007; 73(2): 414-423.
44. de Nigris F, Luisa Balestrieri M, Williams-Ignarro S, D'Armiento FP, Fiorito C, Ignarro LJ et al. The influence of pomegranate fruit extract in comparison to regular pomegranate juice and seed oil on nitric oxide and arterial function in obese Zucker rats. *NitricOxide* 2007; 17(1): 50-54.
45. Vroegrijk Irene OCM, Janna A vD, Sjoerd vdB, Irene W, Hiskias K, Luisa Gambelli et al. Pomegranate seed oil, a rich source of punicic acid, prevents diet-induced obesity and insulin resistance in mice. *Food and Chemical Toxicology* 2011; 49(6): 1426-1430.
46. Lei F, Zhang XN, Wang W, Xing DM, Xie WD, Su H et al. Evidence of anti-obesity effects of the pomegranate leaf extract in high-fat diet induced obese mice. *Int J Obes (Lond)* 2007; 31(6): 1023-1029.
47. Razani Z, Dastani M, Kazerani HR. Cardioprotective Effects of Pomegranate (Punica granatum) Juice in Patients with Ischemic Heart Disease. *Phytotherapy Researc* 2017; 31(11): 1731-1738.
48. Sharma S. Cardiac troponins. *Journal of Clinical Pathology* 2004; 57(10): 1025-1026.
49. Park KC, Gaze DC, Collinson PO, Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovascular Research* 2017; 113(14): 1708-1718.
50. Yang J, Zhang S, Henning SM, Lee R, Hsu M, Grojean E, et al. Cholesterol-lowering effects of dietary pomegranate extract and inulin in mice fed an obesogenic diet. *Journal of Nutritional Biochemistry* 2018; 52: 62-69.
51. Esmaillzadeh A, Tahbaz F, Gaieni I, Alavi-Majd H, Azadbakht L. Cholesterol-Lowering Effect of Concentrated Pomegranate Juice Consumption in Type II Diabetic Patients with Hyperlipidemia. *International Journal for Vitamin and Nutrition Research* 2006; 76(3): 147-151.
52. van der Heiden K, Cuhlmann S, Luong LA, Zakkar M, Evans PC. Role of nuclear factor κB in cardiovascular health and disease. *Clinical Science* 2010; 118(10): 593-605.
53. Huang THW, Yang Q, Harada M, Li GQ, Yamahara J, Roufogalis BD. Pomegranate Flower Extract Diminishes Cardiac Fibrosis in Zucker Diabetic Fatty Rats. *Journal of Cardiovascular Pharmacology* 2005; 46(6): 856-862.
54. Basu A, Newman ED, Bryant AL, Lyons TJ, Betts NM. Pomegranate Polyphenols Lower Lipid Peroxidation in Adults with Type 2 Diabetes but Have No Effects in Healthy Volunteers: A Pilot Study. *Journal of Nutrition and Metabolism* 2013: 708381: 7.
55. Huang THW, Peng G, Kota BP, Li GQ, Jamahara Y, Roufogalis BD et al. Pomegranate flower improves cardiac lipid metabolism in a diabetic rat model: role of lowering circulating lipids. *British Journal of Pharmacology* 2005; 145(6): 767-774.
56. Mollazadeh H, Sadeghnia HR, Hoseini A, Farzadnia M, Boroushaki MT. Effects of pomegranate seed

oil on oxidative stress markers, serum biochemical parameters and pathological findings in kidney and heart of streptozotocin-induced diabetic rats. *Renal Failure* 2016; 38(8): 1256-1266.
57. Bagri P, Ali M, Aeri V, Bhowmik M, Sultana S. Antidiabetic effect of Punica granatum flowers: Effect on hyperlipidemia, pancreatic cells lipid peroxidation and antioxidant enzymes in experimental diabetes. *Food and Chemical Toxicology* 2009; 47(1): 50-54.
58. Minisy FM, Shawki HH, El Omri A, Massoud AA, Omara EA, Metwally FG et al. Pomegranate Seeds Extract Possesses a Protective Effect against Tramadol-Induced Testicular Toxicity in Experimental Rats. *Biomed Research International* 2020; 2732958: 12.
59. Achraf A, Hamdi C, Turki M, Abdelkarim O, Ayadi F, Hoekelmann A et al. Natural pomegranate juice reduces inflammation, muscle damage and increase platelets blood levels in active healthy Tunisian aged men *Alexandria Journal of Medicine* 2018; 54(1): 45-48.
60. Delgado NTB, Rouver W do N, Freitas-Lima LC, de Paula TDC, Duarte A et al. Pomegranate Extract Enhances Endothelium-Dependent Coronary Relaxation in Isolated Perfused Hearts from Spontaneously Hypertensive Ovariectomized Rats. *Frontiers in Pharmacology*, 2017; 7(522): 1-12.
61. Barati Boldaji R, Esmaeilinezhad Z, Sagheb MM, Akhlaghi M. Pomegranate juice improves the cardiometabolic risk factors, biomarkers of oxidative stress and inflammation in hemodialysis patients: A randomized crossover trial. *Journal of the Science of Food and Agriculture* 2020; 100(2): 846-854.
62. Vidal A, Fallarero A, Peña BR, Medina ME, Gra B, Rivera F et al. Studies on the toxicity of Punica granatum L. (Punicaceae) whole fruit extracts. *Journal of Ethnopharmacology* 2003; 89(2-3): 295-300.
63. Basu A, Penugonda K. Pomegranate juice: a heart-healthy fruit juice. *Nutrition Reviews* 2009; 67(1): 49-56.
64. Bergfeld WF, Belsito DV, Klaassen CD, Liebler DC, Marks JG, Shank RC et al. Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics. *Cosmetic Ingredient Review* 2019: 19.