e-ISSN:2321-6182
p-ISSN:2347-2332

Research & Reviews: Journal of Pharmacognosy and Phytochemistry

Pomegranate (*Punica granatum* l.) in Cardio Metabolic Syndromes

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Research Article

Received date: 23/11/2001
Accepted date: 09/12/2021
Published date: 16/12/2021

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Keywords: Pomegranate, Cardio metabolic Syndromes, Diabetes, Obesity, Atherosclerosis, Hypertension.

ABSTRACT

Background: Scientific interest in pomegranate is escalating in recent year due to its use in the treatment of diarrhea, parasitic infection, diabetes mellitus, cancer Dermatological disorders, neurodegenerative, and Depressive Disorders, hemodialysis respiratory diseases, prostate cancer, hepatocellular carcinoma, prostatic hyperplasia, rheumatoid arthritis, inflammatory bowel disease, cardiovascular disorders, and obesity have been ascribed to various diversified phytochemical constituents present in juice, peel flower, seed, and leaf.

Objectives: The current review expedites the role of polyphenolic compounds and their mechanism involved in combating cardiometabolic syndromes and various pathological biomarkers involving preclinical and clinical studies and future perspective of pomegranate as a therapeutic and pharmacological agent in cardiometabolic syndrome.

Methodology: The present review summarizes the data and literature taken from previously done studies from research gate, science direct, PubMed, PubMed Central, Medline, and some other scientific databases emphasizing the role of Punica granatum and besides its pharmacological, therapeutic perspective in cardiometabolic syndrome. The results obtained through this database were assembled, composed, critically elucidated and presented in explanatory and tabular form.

Results: anti-obesity constituents from juice (urolithin A, EA, punicalagin,) seed (linoleic acid punicic acid) leaf (punicalin, EA) inhibited DPD-4, TGs deposition mainly via PPAR-γ, GLUT4, FABP4 NF-β expressions. The preclinical and clinical study showed leaf, and PV (AMPK phosphorylation) exerted anti-obesity effects. Antidiabetic constituents from flower (oleanolic acid, ursolic acid, gallic acid,) presented antidiabetic activity via PPAR-γ and PPAR-expression activation and improvement in sensitivity of insulin, Tricetin showed significant α- glucosidase inhibition properties. Peel and leaf showed a significant reduction in TGs, Blood glucose, TC, LDL-c alone and combined with anti-diabetic drugs. The pancreatic restoration was seen with juice in preclinical and clinical studies. JP reduced oxidative stress at lower doses, and inflammation at higher doses. Insulin resistance and fasting blood glucose was reduced. SICAM-1 and VCAM-1 did not alter. anti-atherosclerotic, anti-hyperlipidemic and antidyslipidemic constituents from juice e.g. urolithin A and D were more effective than punicalagin and ellagic acid, urolithin reduced THP-1, ICAMP-1, MCP-1, TNF-α, IL-6 and increased in PPAR- γ and anthocyanins inhibits xanthine oxidase and chelate metal ion, TNF-α, NF-κβ Arachidonic acid pathway, enhance Nrf2 expression. Leaf extract (pyrogallic acid, tannic acid, and ellagic acid) decreased intestinal, pancreatic lipases and inhibited absorption of lipids. Punicalagin and gallic acid from juice and peel of pomegranate enhanced PPAR- γ, AP-1, PON-2 eNOS expression, and NO production. PJ in pre-clinical studies decreased lipid oxidation, uptake by macrophages, triglycerides, total cholesterol, LDL-c VLDL-c, atherosclerotic

e-ISSN:2321-6182
p-ISSN:2347-2332

size, and foam cell and increased HDL-c. Upregulation of FN-1, BdKrB1 and at/K/ eNOS pathway and downregulation of MCP-1, IL-1β, and TNF-α In Clinical studies, PJ reduced IMT and SBP. Peel significantly decreased TGs, TC and TC. Antihypertensive constituents (Quercetin, naringin, and naritutins) in seed, peel, and juice enhanced EDHF. Preclinical PJ and peel increased eNOS, NO and reduced TGβ-1, MABP, ACE, Angiotensin II. PJ increased drastically SOD, CAT, and GHS. Seed significantly decreased TSP-1. In clinical trials PJ drastically decreased SBP DBP (at a higher dose). While Peel significantly decreased hsCRP, SBP, LDL-c, TGs, and TCs at higher doses and longer duration compared to juice. In-vitro pre-clinical and clinical studies reduced drastically LDH, CK, troponin1 and increased antioxidant status in (MI) myocardial ischemia and reperfusion MI/R

Conclusion: Constituents from leaf, juice, peel, seed exert protection against obesity, diabetes, hyperlipidemias, dyslipidemias, atherosclerosis, hypertension myocardial infarction (MI) myocardial ischemia and reperfusion MI/R. Studies from marine and human subjects disclosed that Pomegranate leaf, and vinegar has many promising effects against obesity these areas needed further clinical interrogations to reveal other hidden perspectives of it. According to preclinical in-vitro and in-vivo all parts possessed anti-diabetic properties but peel and leaf exerted significant antidiabetic properties. Juice produced restoration properties in the pancreas of Langerhans in preclinical and clinical studies. But clinical data is not sufficient to conclude it. Pomegranate juice and peel have many promising effects against atherosclerosis, hyperlipidemia, dyslipidemia, and hypertension. Juice at higher doses is significant against DBP and SBP but lipid profile wasn't affected much at a higher dose and longer duration of action compared to peel which covers lipid profile in a better way at higher doses and longer duration of action. BP and ACE reduction and its relation with pomegranate juice are still in question. PJ gives protective shreds of evidence in myocardial infarction (MI) myocardial ischemia and reperfusion MI/R but some biomarkers could cover better results by the peel.

Future Perspective: Pomegranate covers the wider range of satiety in cardiometabolic syndromes. If pomegranate juice and peel are combined together it could be proven as an unprecedented exemplary juice for combating Cardiometabolic syndromes

INTRODUCTION

Pomegranate is an ancient paradise nutrient-dense fruit and it's native to central Asia, neutralized and cultivated in throughout Iran, India, Mediterranean countries, the drier parts of Southeast Asia, Malaysia, the East Indies, and tropical Africa [1]. Its utilization had been mentioned in various cultures like Islam, Christianity, and Judaism, Zoroastrianism [2]. It used to denote a symbol of reincarnation [3,4]. Its use is intensely submerged in human history. Biochemical profile of pomegranate fruits detains diverse sort of constituents in its different parts such as juice, peel, seeds, flower, and Leaves [5]. Pomegranate juice is rich in phytochemicals like polyphenols tannins, vitamins (B, C), coenzyme Q10, and lipolic acid. Most important anti-oxidants are anthocyanins and ellagic acids. Anthocyanins such as cyanidin 3, 5-diglucoside, Delphinidin 3-glucoside, Cyanidin 3- glucoside are present in juice of pomegranate responsible for the colour of pomegranate [6-8]. About 50% to 60% of the fruit is peel which is rich in a variety of phytochemicals like phenolics, flavonoids ellagitannins, anthocyanins, and proanthocyanidin, minerals and polysaccharides. Ellagitannins are major components present in the peel e.g. punicalagin and punicalin. Punicalagin is present in abundant quantity in a peel. Punicalagin concentration in different varieties from Pakistan (badana, desi, Kandhari) and Chinese were reported to be highest. But its concentration varies according to the cultivation conditions. Punicalagin and punicalin have ability to hydrolase into ellagic acid which is responsible for the highest antioxidant activity of peel. Gallic acid is the main phenolic constituent present in peel. kaempferol-3-O-glucoside is most important flavonoid present in peel [9]. Peel represents highest antioxidant activity compared to other fruits. Antioxidating property is responsible for the anti-inflammatory, anti-atherosclerotic property and hypolipidemic properties [10,11]. Pomegranate flower is also rich in Triterpenoids such as oleanolic acid, gallic acid and ursolic acid. Other volatile components e.g. monoterpenes, monoterpenoids, as well as straight chain hydrocarbons monoterpenes also present in flower. Alpha terpinene and alpha-terpineol are considered as a most important ingredient of flower [12,13]. Pomegranate seed comprises almost 3% of fruit weight. Seed is rich in phytochemicals including lipids and its oils (which constitute 12–20% of total seed weight) like punicic acid, oleic acid, stearic acid, catalpic, gadoleic, arachidic, behenic, and palmitic acids α and β-eleostearic [14]. Higher concentration of fatty acids like linoleic, linolenic acid, caproic acid, capric acid, myristic acid is also

reported [15]. Hydrolysable tannins, flavonoids and phenolic acids are present in seed oil. Among all punicic acid covers 70 -76% of seed oil. Other constituents which are present in minor quantities are sterols, steroids, cerebrosides, proteins vitamins and minerals [16]. From ancient times, pomegranate was used in the treatment of diarrhea [17], parasitic infections [18], and diabetes mellitus [19]. In Recent years its cardioprotective action has been extensively studied [20,21]. The present study aimed to review the protective role of pomegranate in Cardiometabolic Syndromes (CMTs). CMTs is considered single affliction by the American Society of Endocrinology, National Cholesterol Education Program (NCEP), and World Health Organization. CMTs is metabolic abnormality exemplify by insulin resistance, deteriorated glucose tolerance, atherogenic dyslipidemias, hypertension and obesity [22]. The integrands of this syndrome are alone vigorous perils for cardiovascular mortality and morbidity [23]. People with this syndrome are more prone to have a heart attack, stroke and die from coronary heart disease [24]. The intersections between CMTs and CVD are endothelial rupturing. This leads to deposition of low-density lipoprotein cholesterol (LDL-c), in the muscle cell of arterial wall monocytes are recruited, migrated, and proliferated which is foremost towards the beginning and succession of atherosclerosis [25].

Pomegranate Protective Role against Obesity

The biochemical constituents from peel, seeds, leaf, and flower have been well studied and their favorable consequences in obesity are associated with the availability of anthocyanins, tannins, and considerably elevated amounts of antioxidants, as well as flavonoids and polyphenols [26]. Pomegranate juice constituents such as ellagic acid, urolithin A and punicalagin have a significant role in the prevention of metabolic associated complications such as obesity, diabetes. The protective effects were seen due to inhibition of enzymes like α-glucosidase, lipase, and dipeptidyl peptidase-4 as well changing gene expressions of Adiponectin, PPAR-γ, GLUT4, and FABP4 in adipocytes and urolithin displays more prominent action as it reduces TGs deposition. This molecular mechanism in this study confirmed pomegranate beneficial effects in metabolic disorder related to diabetes and obesity [27]. Pomegranate seed oil contains fatty acids including linoleic acid, punicic acid, catalpic acid, and stearic acid activate PPAR-γ in both epithelial cells and macrophages. Thus, produce profound anti-obesity and lipid-lowering effect [28]. Leaf extract of pomegranate also possessed anti-obesity effects as its constituent ellagic acid inhibits pancreatic lipase activity by reducing appetite [29]. The detailed mechanism of punicalin and Punicalagin has been well defined in the study. These effects are produced by increasing the production of short chain fatty acids enhancing the bacterial growth then activate (PPAR-γ), which blocks the transcription of pro-inflammatory molecules by NF-κB, results in anti-inflammatory effects Constituents from juice (urolithin A, EA, punicalagin) seed (linoleic acid punicic acid) leaf (punicalin, EA) mainly exert their anti-obesity effects by decreasing energy intake, intestinal absorption of fats, inflammatory response and oxidative stress mainly *via* PPAR-γ expression at various sites.

Preclinical Studies

A study was done on pomegranate leaf extract (400 and 800 mg/kg/day) for the period of 5 weeks in obesity induce ICR mice given with high-fat diet revealed that pomegranate leaf extract showed a significant reduction in body weight, energy intake, the serum level of Triglycerides, total cholesterol appetite and glucose level. Intestinal fat absorption and elevated serum triglycerides were significantly reduced. More prudent results were seen at a dose of 800 mg /kg /day. Another study conducted in male C57BL/6J mice given with high feed diet (1 g/100 g of body weight) to induce obesity and insulin with 1% of pomegranate for the period of 12 weeks. Obesity and insulin resistance were induced. Pomegranate seed oil concluded to be beneficial in lowering body weight and body mass 50% and 50% respectively. It has pronounced effects on peripheral insulin sensitivity but did not produce effects on liver insulin sensitivity as well as energy expenditure. Pomegranate flower extract (500 mg/kg *p.o*) consumed by Zucker diabetic fatty rats for the period of 6 weeks produces protective effects against diabetes and obesity with is related to the fatty liver by enhancing expression of peroxisome proliferator-activated receptor (PPAR)-alpha, -CoA oxidase (ACO), carnitine palmitoyltransferase-1 and reduces stearoyl-CoA desaturase-1. But pomegranate flower extract showed negligible effects on expressions related to synthesis, hydrolysis as well as uptake of fatty acids and triglycerides [30]. Pomegranate juice (300 µL containing 0.35 mmol total polyphenols) in mice model which were fed with high-fat diet (which contains cholesterol 1.25%, sodium cholate 0.5%, saturated fat 5% weight /weight) produces supportive effects against obesity in reducing body weight cholesterol as well as triglycerides level. Higher expression of PON1 is responsible for it. The level of triacylglycerol did not consistently decrease [31]. Preclinical studies also confirmed anti-obesity properties from all parts (Leaf, seed, flower, juice) of pomegranate. But leaf extract (800 mg/kg) produced significant effects in impeding obesity mainly by improving the lipid profile. Flower of pomegranate resists obesity related to diabetes (Table 1).

Clinical Studies

A double-blind, randomized, and placebo-controlled trial seventy-eight overweight women were given pomegranate vinegar (1.5 g acetic acid and 700 µg ellagic acid/200 mL/day) for the period of 8 weeks. It caused a reduction in adipose and potentiates AMPK phosphorylation in adipose tissues compared with control group. Pomegranate is a potential AMPK activator and it tends to exert its beneficial effects by suppressing sterol regulatory element binding protein-1c (SREBP-1c) and acetyl coenzyme carboxylase (ACC) (downstream gene expression) in adipocytes tissues [32]. In a randomized double-blind placebo-controlled clinical trial 120 ml of pomegranate juice were given to 20 obese adult subjects for the period of 1 month. Administration of pomegranate for the period of 1 month did not significantly modify insulin secretion as well as the sensitivity of insulin in obese subjects. But the natural tendency to gain weight and adiposity was terminated [33]. In a clinical evaluation study was done to assess the antioxidant properties of pomegranate in obese subjects. Pomegranate rich in ellagitannins extract 1000 mg (610 mg of Gallic acid equivalent) was consumed by 22 obese subjects for the period of 4 weeks. Pomegranate protective effects were seen with

Table 1. Cardio Metabolic Protective Effects of Pomegranate Derived Phytochemicals and their Metabolites.

Cardio metabolic Protective Ingredient	Possible Mechanism	References
Ellagic acid, Urolithin A and Punicalagin	Inhibited α-glucosidase,lipase, dipeptidyl peptidase-4 ,TG deposition, changes gene expression of Adiponectin, PPAR-γ, GLUT4 and FABP4	[1] Obesity
linoleic acid, Punicic acid, Catalpic acid, and Stearic acid	Pomegranate seed oil can activate (PPAR-γ) in epithelial cells and macrophages.	[2] Obesity
Punicalin and Punicalagin	activates (PPAR-γ) which blocks NF-κB	[3] Obesity
Oleanolic, Ursolic, and Gallic acids	Activates (PPAR-γ) Increases NO production	[1]antidiabetic
Punicic acid, Punicalagin and ellagic, gallic, oleanolic, ursolic, and uallic acids	reduces the fasting blood glucose and oxidative stress PON1 stabilization, increased PON1 association with HDL	[4] antidiabetic
Gallic acid	Enhancement of Cardiac (PPAR-γ) mRNA and (GLUT)-4	[5]Antidiabetic
4′-O-β-glucopyranoside ellagitannins and flavones tricetin, luteolin, ellagic acid and granatin B	suppression of α-glucosidase, α-amylase, and lipase activities	[6] antidiabetic
Ellagic acid	Promotion of occludin,claudin 4and nuclear factor erythroid 2-related factor 2 expressions. Inhibits (TNF-α), IL-1β, NF-κB, 3-heneficydroxy-3 methyl glutaryl CoA reductase.	[1,2,6] hyperlipidemia and dyslipidemias
Punicic acid	Inhibits (TNF-α)	[3] hyperlipidemia and dyslipidemias
Gallic acid, Pyrogallic acid and Tannic acid	Reduces pancreatic lipase activity	[6] hyperlipidemia and dyslipidemias
Punicalagin	Enhance NO production	[4] AC
Punicalagin and Phytosterol β-sitosterol	Up regulation of PON-2 Increases glutathione level	[7] AC
Ellagic acid, gallic acid; punicalagin and punicalin	Repress AGEs	[8]AC
Ellagic acid	Inhibits LOX-1 up regulation,ROS,RNS, prevents eNOs down regulation	[9]AC
Punicalagin and gallic acid	Increase PON-2, PPAR-γ,AP-1	[10]AC
Urothins	decrease THP-1 derived macrophages, VCAM-1,IL-6,ICAM-1,MCD-1,TNF-α,endothelin-1 increase PPAR-γ mRNA down regulation of ERK1/2	[11, 12]AC
ATs	Quench free radicals, Decrease Xanthine oxidase Enhance Nrf-2 REPRESS Arachidonic acid, TNF-α, NF-κB	[13]AC

a significant reduction in plasma thiobarbituric acid reactive substances (elevated serum TBARS level is a strong predictor of cardiovascular events irrespective of other inflammatory biomarkers). Other biomarkers e.g. C- peptide, paraoxonase-1, liver enzymes (AST, ALT), creatine, liver, insulin, and glucose showed no significant statistical variation to be counted [34].

It is concluded from the clinical study done PJ is effective in obesity associated with cardiovascular complications in obese subjects. The natural tendency to weight gain and adiposity was terminated without affecting the other biomarkers (Table 2). Pomegranate vinegar extract is an excellent AMPK activator for obesity this area needs further investigation.

Pomegranate Protective Role in Diabetes

Pomegranate plants parts have been used since long for the treatment of various disorders. In Unani and Ayurvedic medicine only the flower has been used for the treatment of diabetes. In various other studies pomegranate juice, peel and seeds also possess antidiabetic properties. Pomegranate produces its hypoglycemic effects *via* various mechanisms by activating peroxisome proliferator-activated receptor-γ binding and nitric oxide production. Pomegranate flower contains compounds like oleanolic, ursolic, and gallic acids are mainly responsible for its antidiabetic effects [35]. Pomegranate flower is thought to activate PPAR-α and PPAR-γ family. PPAR is a transcription factor which is a subfamily of the nuclear receptor. PPAR regulates fatty acids uptake its storage and oxidation. It has a role in the homeostasis of glucose. Synthetic PPAR-α and PPAR-γ are widely used as anti dyslipidaemic and anti-hyperglycemic agents. So, pomegranate flower has potential dual PPAR-α and PPAR-γ activation properties. It is beneficial in diabetes as well as diabetic complication like dyslipidemias [36]. In other study done on pomegranate flower claims, it improves the sensitivity of insulin receptors by activating Peroxisome proliferator-activated receptor (PPAR)-γ. This action mainly produced through the enhancement of Cardiac PPAR-γ mRNA expression further it restores the down-regulated cardiac glucose transporter (GLUT)-4 (the insulin-dependent isoform of GLUTs) mRNA. These effects are responsible for the anti-diabetic effects of pomegranate flower extract. A recent comparative study among glucoside tricetin 4′-O-β-glucopyranoside and four known ellagitannins and flavones tricetin, luteolin, ellagic acid, and granatin B from the flower of pomegranate concluded that tricetin possesses greater α-glucosidase inhibitory activity that was comparable to the anti-diabetic drug acarbose. The mechanism responsible claims that the greater number of hydroxyl groups on the flavone molecule is responsible for the suppression of α-glucosidase, α-amylase, and lipase activities. It could be helpful in managing diabetes [37]. Pomegranate juice contains unique antioxidant polyphenols like tannins and anthocyanins in juice fraction could be beneficial to control conditions in type 2 diabetes

e-ISSN:2321-6182
p-ISSN:2347-2332

Table 2. Clinical studies showing Anti-Obesity Effects of Pomegranate.

Test substance	Study type/ subjects/ no of participants	Dose	Duration	Effects	References
PJ	Clinical study/obese (N=22)	1000 mg/day (610 mg of Gallic acid equivalent)	4 weeks	↓↓↓TBARS, ↕CRP,PON1,AST,ALT,creatinine,insulin glucose	[11]
PJ	Randomized double-blind placebo controlled clinical trial/ obese (N=20)	120 ml	1 month	↔insulin secretion and sensitivity ↓weight gain ↓adiposity	[10]
PVE	Double-blind, randomized, and placebo-controlled trial/overweight women (N=80)	1.5 g acetic acid and 700 µg ellagic acid/200 mL/day	8 weeks	↓↓↓Adipose and ↑AMPK phosphorylation, ↓↓ SREBP1c ↓↓ ACC	[12]

[38]. In a study, pomegranate juice consumption showed antidiabetic action by targeting an enzyme called Paraoxonase-1 (PON1). This enzyme prevents lipoprotein oxidation. It is thought that the level of this enzyme is reduced in a diabetic patient. Pomegranate juice consumption possesses its antioxidant action may be proven as a contributor in chaining lipid profile, lipoprotein oxidation, fasting blood sugar level PON1 activity [39]. Punicalagin and ellagic, gallic, oleanolic, ursolic, and uallic acids known compounds isolated from methanolic seeds and peel extracts have been identified as having anti-diabetic actions. Punicic acid from seeds of pomegranate significantly reduces the fasting blood glucose level [40].

Constituents (oleanolic acid, ursolic acid, gallic acid) from the flower of pomegranate possesses exceptional antidiabetic properties compared to juice, seed, and peel as it activates PPAR-γ and PPAR-α and improves the sensitivity of insulin. A tricetin new chemical entity identified in flower presented powerful α- glucosidase inhibitor properties.

Preclinical Studies

Diabetes mellitus (DM) is a metabolic disorder in which the carbohydrate and lipid metabolism is improperly regulated by insulin. A study performed in Wister rat induced streptozotocin diabetes. Pomegranate hydroalcoholic leaf extracts at different doses (100 mg/kg and 200 mg/kg) and peel extract (100 mg/kg, 200 mg/kg) was given up to 28 days. Fruit Peel extracts of pomegranate and glibenclamide together significantly lowered blood glucose level from 7th day to onward. But Glibenclamide and higher doses of fruits peel extract significantly lowered total cholesterol, triglycerides and prominently increased high-density lipoprotein HDLP. Leaves extract of pomegranate at lower and higher dose found to be effective in reducing blood glucose level from 7th and 21st day to onward respectively. Results confirmed the antidiabetic, hypolipidemic and antioxidant activity of pomegranate [41]. In another study performed in Wister rat induced streptozotocin diabetes (alloxan 150 mg/kg, intraperitoneally). Ethanolic leaves extract of Pomegranate (500 mg/kg/ *p.o*) and Glibenclamide (0.5 mg/kg/day/*p.o*) were administered in different groups of rats and compared with control groups. Pomegranate and Glibenclamide showed a significant reduction in blood glucose level in comparison to control. Significant reduction in intestinal absorption of glucose, triglycerides, total cholesterol, low-density lipoprotein and a significant increase in high-density lipoprotein (HDLP) was seen compared to control. Pomegranate is proven beneficial in diabetes according to this study [42]. The study was done on Alloxan induce (120 mg/kg for 2 consecutively for two days,) diabetes and hyperlipidemia in rats. Power of *Punica granatum* husk (1 kg/day for the period of 10 days) administration produced protective effects against diabetes and hyperlipidemias. Significant reduction in the concentration of glucose, triglycerides, cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol was seen and level of High-density lipoprotein (HDLP) cholesterol and hemoglobin content (during diabetes the elevated glucose reacts with hemoglobin to form glycosylated hemoglobin, so total hemoglobin is lower in diabetic rat) was raised [43]. Ethanolic extract of pomegranate seed and rind (200 mg/kg/day for the period of 2 weeks) was administered in alloxan induced (150 mg/kg body weight intraperitoneally) diabetic rats (24). Both extracts of pomegranates showed a significant reduction in rising blood glucose. The significant escalation in liver glycogen was also seen. Adrenaline-induced hyperglycemia was also drastically reduced. Level but rind showed better results than seeds in lowering blood glucose level [44]. A comparative study was done to establish the antidiabetogenic effect of glibenclamide (5 mg/kg) and pomegranate juice (1 ml/day) in streptozotocin and nicotinamide induced type 2 diabetes mellitus rats for up to 21 days. It showed prominent restoration effects in islets of Langerhans. It reduces plasma total cholesterol, triglycerides and inflammatory mediators which were found to be higher in diabetic rats. Findings confirm that active constituents in pomegranate juice responsible for its hypolipidemic and anti-inflammatory effects. These effects were confirmed by the histopathological, pharmacological and biochemical profile of pomegranate juice [45]. High level of low-density lipoprotein (LDL) is a risk factor for cardiovascular disease the esterase paraoxonase1 (PON1) prevents oxidation of LDL. Decreased levels of PON1 increase the incidence of cardiovascular disease. Pomegranate juice in a concentration of (12.5 mL/L of juice in water/ day for the period of 4 months) significantly enhances PON1 gene expression. When administered daily to streptozotocin-induced diabetic mice were given with high-fat diet. Pomegranate induces its antidiabetic effects by reducing in blood glucose level and body weight [46]. Alloxan (150 mg/kg *I.p*) induced in Rats model were treated with pomegranate juice (PJ) [3 mL/animal) and Tolbutamide (20 mg/kg, *p.o*), and their combination for 4 weeks. The results showed potential beneficial effects in combination as compared to

alone in diabetic complication. The pharmacokinetic and pharmacodynamics justifies the results. PJ increases BA and half-life of Tolbutamide responsible for these effects [47]. Alloxan (150 mg/kg *I.p*) induced in Rats model were treated with pomegranate juice (PJ) [3 mL/animal) nateglinide and (20 mg/kg, *p.o*) and combinations for 4 weeks. The results showed potential beneficial effects by in combination as compared to alone in diabetic complication [48].

From the comparative anti-diabetic study between pomegranate leaf, seeds and peel extracts revealed more beneficial effects of pomegranate leaf extract (Dose 100 to 500 mg /kg) alone and in combination with another antidiabetic drug. On the other hand, pomegranate juice alone (dose 1 mL to 12.5 ml/day) or in combination (PJ dose 3 ml/day) with Tolbutamide and nateglinide effective in reducing blood glucose level, restoration of islets of Langerhans and increasing BA and half-life of antidiabetic drugs which in turn improves diabetic complications (Table 3).

Clinical Studies

A single-blind, randomized clinical trial was done in 60 type 2 diabetic patients with oxidative stress (30 in the PJ-treated group and 30 in the control group). Consumption of Pomegranate Juice (200 ml of PJ / day for 6 weeks) decreased the amount of oxidized LDL and anti-oxidized LDL- antibody. Protective effects were seen due to a significant escalation in serum antioxidant capacity and arylesterase activity of paraoxonase compare to control group. Pomegranate supplementation has pronounced protective effects in decreasing oxidative stress in a patient with type 2 diabetes [49]. A randomized placebo-controlled clinical trial done on 44 diabetic patients randomly which were assigned into 2 groups as pomegranate juice consumption group and placebo-controlled. Pomegranate juice (250 mL/day) was given them for the period of 12 weeks produces potential beneficial effects in diabetic patients as it showed a significant reduction in Plasma sE-selectin concentration, NF-κB, and SIRT1 levels were found to be higher significantly as compared to placebo control group. There was no significant difference seen among plasma SICAM-1 and sVCAM-1 level [50]. In a randomized, placebo-controlled crossover study done on human subjects (twelve males and sixteen females) revealed protective effects of pomegranate juice (500 ml 1685 mg/l polyphenols/ day for the period of 4 weeks) in alleviating cardiovascular risk factors in obese and overweight subjects. Results showed a significant reduction in fasting plasma insulin as well as insulin resistance (homeostatic model assessment of insulin resistance) and reduction in systolic and diastolic blood pressure was also seen. The reduction in insulin resistance could be proven beneficial for a patient with non-insulin dependent diabetes, obesity and related metabolic syndromes [51]. From the clinical data, studies revealed the potential beneficial effects of PJ (200 ml to 250 mL /day for the period between 4 to 6 weeks) are effective against diabetes and diabetic complications (Table 4).

Protective Role of Pomegranate in Hyperlipidemias Dyslipidemias and Atherosclerosis

Escalated level of circulating low-density lipoprotein is the initial events in the progression and pathology of atherosclerosis. Polyphenolic anti-oxidant effects against atherosclerosis are well defined. Pomegranate leaves and fruit have proven notable hypolipidemic probably due to its antioxidant properties. So, the traditional use of pomegranate has been justified by this study [52]. Beyond its antioxidant action, another mechanism which corresponds to protective effects is *via* apolipoproteins (B-100 that

Table 3. Cardio-protective action against ischemia and reperfusion (I/R).

Part	Cardiometabolic protective	Possible mechanism	References
Leaf extract	Anti-obesity	Significant reduction in body weight, TG,TC, appetite and glucose in obesity induced ICR mice	
Seed oil	Anti-obesity	reduce body weight and body mass 50% and 50% respectively in male C57BL/6J mice	
Flower extract	Anti-obesity	Enhances PPAR-α, -CoA oxidase (ACO), carnitine palmitoyltransferase-1 and reduces stearoyl-CoA desaturase-1 by Zucker diabetic fatty rats	
Juice	Anti-obesity	reduce body weight TC,TG and enhance PON1 is in high fat fed mice model	
Leaf and peel extract	Anti-diabetic	Reduce blood glucose, TC,TG and increased HDLP in Wister rat induced streptozotocin diabetes	
Leaf extract	Anti-diabetic	Significant reduction in blood glucose, intestinal absorption of Glucose, TG, TC and LDL-c. Significant increase in HDLP was seen in Alloxan-induced non-insulin-dependent diabetes mellitus albino rats.	
Husk	Anti-diabetic	Decrease in Glucose, TG, TC, LDL-c, VLDL-c increase in (HDLP) cholesterol in Alloxan induce diabetic and hyperlipidemic rat.	
Seeds and rind	Anti-diabetic	reduce in rising blood glucose and hyperglycemia in Alloxan induced diabetic rat	
Juice	Anti-diabetic	Enhances PON1, reduce in blood glucose level and body weight in streptozotocin-induced diabetic mice were given with high-fat diet.	
Juice	Anti- hyperlipidemia and anti-dyslipidemias	Reduces elevated plasma TC and LDL-c in Hypercholesterolemic rats	
Juice	Anti- hypertensive	Reduces MBP, enhances superoxide dismutase (SOD), catalase (CAT), and glutathione reductase (GSH). Reduces angiotensin II and ACE activity in Angiotensin II induced diabetic model	
Juice and seed oil	Anti- hypertensive	Decreases thrombospondin cytokine TGFβ, TSP-1 expression. Significantly increases NO and NO synthase (eNOS) expression.	
Fruit extract	Anti-atherosclerotic	reducing oxidation of LDL by peritoneal macrophages, the uptake of oxidized LDL by peritoneal macrophages	
Juice	Anti-atherosclerotic	Decrease oxidative stress, IL-1β expression, TNF-α, Fn1, significant up regulation of Bdkrb1 expression reduced	

Table 4. Clinical studies showing Anti-Diabetic Effects of Pomegranate.

Test substance	Study type/ subjects/ no of participants	Dose	Duration	Outcomes	References
PJ	A single-blind, randomized /clinical type2 diabetic patient with oxidative stress (N= 60)	200 ml /day	6 weeks	↓↓oxLDL and Anti oxLDL-antibody ↑↑↑ anti-oxidants	[11]
PJ	Randomized placebo controlled clinical trial/ diabetic patients/ (N=44)	250 mL/day	12 weeks	↓↓↓E-selectin ↓↓↓NF-κB and ↑↑↑SIRT1 levels ↑↑↑SIRT1 levels	[12]
PJ	randomized, placebo-controlled crossover study/ obese and overweight subjects	250 mL/day	4 weeks	↓↓↓ FBI as well as insulin resistance.	[14]

covers LDL) [53, 54]. Pomegranate juice rich in anthocyanins and hydrolysable tannins is more effective in reducing serum oxidative stress as compared to peel extract which exerts its effects on decreasing the extent of ox-LDL uptake by macrophages [55]. Pomegranate juice and punicalagin induce plasma LDL removal and inhibit macrophage cholesterol synthesis and accumulation as a result LDL influx to macrophage are initiated and circulating blood cholesterol level is decremented [56,57]. Pomegranate juice consumption has been beneficial in reducing oxidation of LDLP-c as well as VLDL-c which could further abolish arterial plaques in human and animal studies [58]. Pomegranate juice rich in anti-oxidant punicalagin and Phytosterol β-sitosterol was shown to possess its cardioprotective effect. Its protective effects were believed to be due to its free radical scavenging properties, up-regulation of paraoxonase-2 (PON-2) and raising the level of glutathione [58]. The beneficial effects of polyphenols of pomegranate are confirmed *in-vivo* and *in-vitro*. These effects were produced by inhibiting the macrophage-mediated lipid peroxidation by reducing reactive oxygen and reactive nitrogen species to be accumulated in macrophages. On the other hand, enhances the paraoxonase activity and hydrolysis of lipids in atherosclerotic lesions. Thus, produces anti-atherosclerotic activity *via* anti-oxidation [59]. Polyphenolic compounds of pomegranate juice like punicalagin and gallic acid induce their anti-oxidative stimulatory effects on PON-2 expression in macrophages which further activates transcription factor PAPR-γ and AP-1 [60]. Polyphenols and tannins exert their beneficial effects in atherosclerosis and other related metabolic disorders. E.g. punicalagin has the ability to enhance NO production in endothelial cells in vessels *via* activation of eNOS (endothelial synthase). It acts as a potent vasodilator [61]. Gallic acid and pomegranate unique complexed sugars are capable of producing potential antiatherogenic effects [62]. Previous studies were done on pomegranate and its polyphenolic constituents from leaf extracts is proven beneficial against hyperlipidemias and dyslipidemias e.g. ellagic acids (metabolites of ellagitannins) by interfering with lipid metabolism inhibits absorption of lipids from small intestine [63] and reduces proinflammatory mediators TNF-α, IL-1β, IL-6, NFκB, an increase in nuclear factor erythroid 2-related factor 2 expression other beneficial effects of ellagic acid is *via* anti-lipid peroxidation by *via* 3-heneficydroxy-3 methyl glutaryl CoA reductase inhibition [64] other ingredients from leaf of pomegranates like gallic acid, pyrogallic acid, and tannic acid were beneficial in reducing pancreatic and intestinal lipase activity total cholesterol and triglycerides [65]. Punicic acid from pomegranate seed extract is beneficial against dyslipidemias by reducing TNF-α [66]. Pomegranate seed oil is a rich source of polyphenolic compounds especially methanolic seed extract contains conjugated linolenic acid is beneficial in hyperlipidemias [67]. Pomegranate juice also contains Urolithins (metabolites of ellagitannins which hydrolyzed to ellagic acid then convert to Urolithins it enters circulation after consumption). Urolithins decreases adhesion of THP-1 derived macrophages, (VCAM-1), (IL-6), expression of (ICAM-1), (MCP-1), (TNF-α), IL-6, endothelin-1, increased PPAR-γ mRNA expression as well as down-regulation of phosphorylation of ERK1/2 [68]. The antioxidant properties of Urolithins (A and D) are also important in combating CVS [69,70] and it was found to be more than Ellagic acid and Punicalagin [71]. Anthocyanins (ATs) are the color full polyphenolic pigments present in juice and peel of pomegranate and its anti-inflammatory and cardioprotective effects are due to its potent anti-oxidant actions [72]. ATs can quench free radical species as decrease the xanthine oxidase and chelate metal ion which is responsible for the oxidation of low-density lipoprotein (LDL) [73]. ATs enhance expression of nuclear factor –erythroid 2 related factor -2 (Nrf2) it's important in the regulation of antioxidant enzymes such as heme oxygenase-1(HO-1) [74]. ATs can repress signaling pathways and proinflammatory mediators and adhesion molecules like Arachidonic acid, TNF-α, and NF-κB respectively [75]. Phytochemicals from juice seeds leaves have exceptional properties against atherosclerosis and hyperlipidemias. Punicalagin, phytosterols-β, urolithins, gallic acid present in juice halts oxidative stress and inflammatory markers and enhances NO production and antioxidant status.

Preclinical Studies

Pomegranate extract was administered in mice model of coronary artery disease and atherosclerosis. The drastic reduction was seen in oxidative stress monocyte chemotactic protein-1 in coronary arteries on the other hand lipid profile was much improved by the reduction in lipid accumulation and filtration of monocytes. Imbalance in unesterified/esterified cholesterol ratio of very low-density lipoprotein was decreased. The atherosclerotic plaques in aortic sinus and coronary arteries were found to be reduced. The ECG abnormalities were also reduced by pomegranate extract. Pomegranate is protective in this case in several ways [76]. Pomegranate juice extract (was administered to pigs which were given high fat and cholesterol diet (20% saturated fat, 2% cholesterol, and 1% cholic acid) to check its favorable effects in hypercholesterolemic pigs. The diet-induced impairments in endothelial functions were reduced. Its beneficial effects were seen due to the activation of Akt/ endothelial nitric oxide-synthase (Akt/eNOS) pathway and decremented monocyte chemoattractant protein-1 expression (MCP-1). Vascular inflammation and oxidative stress were decremented by the LDL-c to be oxidized mainly *via* antioxidating properties [77]. Beneficial effects of pomegranate extract were seen in atherosclerotic mice model as prudent effects were seen in case of lipid profile. Not only Oxidation of low-density lipoprotein cholesterol LDL-c by peritoneal macrophages was drastically reduced but uptake of oxidized LDL by macrophages was also reduced. The size of atherosclerotic plaques and no of foam cells were drastically decremented compared to control group [78]. Pomegranate juice by its potent antioxidant properties protected against cardiovascular injury induced by

cigarette smoking (cigarette smoking exposure was done per day two sections for the period of 5 days). Cigarette smoking caused a drastic escalation in oxidative stress, IL-1β expression, TNF-α, Fn1 as well as significant up-regulation of Bdkrb1 expression was also assessed. Cardiac protective effects were seen by altering above parameters by pomegranate juice consumption mainly through its anti-oxidant effects and remediating cardiac hypertrophy induced by cigarette [79]. A study performed concluded that oral administration of *Punica granatum* juice at low and higher doses were given to Hypercholesterolemic rats (cholesterol powder 5.5 g/30 ml of Ghee at a dose of 1 ml/ kg of the body). After consumption of cholesterol powder the Total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-c) high-density lipoprotein cholesterol (HDL-c) was raised at day 7th. But all these parameters were reduced at day 14th and 21st. The most significant reduction was seen in aforementioned parameters after oral administration of *Punica granatum* juice at higher doses and statin drug (atorvastatin) at days 14 and 21. Pomegranate juice has potential hypolipidemic effects [80]. It is concluded from the preclinical studies that PJ could be helpful in combating the beginning and progression of atherosclerosis by targeting various biomarkers in hypercholesterolemic, Coronary artery atherosclerosis, Cigarette Smoking-Induced Cardiac Hypertrophy in murine models. (Table 5)

Clinical Studies

Pomegranate juice was consumed by patients with carotid artery stenosis for the period of 1-year and out of ten patients, 5 patients continued pomegranate consumption for further 3 years. The consumption of PJ for 1 year showed a drastic reduction in mean intima-media thickness (IMT), systolic blood pressure as well as serum lipid peroxidation. There were no significant changes observed in aforementioned parameters after 3 years of consumption of PJ except for lipid peroxidation which was further reduced there were no changes observed in serum glucose and lipid concentration. In an ex vivo study done on the human subject, 13 healthy nonsmokers male (20–35 y) were supplemented with 50 mL PJ/day (1.5 mmol total polyphenols) for the period of 2 weeks. Pomegranate protective effects were seen by decreasing the LDL ability to coagulate or aggregate and an increased serum paraoxonase activity was seen which was proven helpful in the reduction of lipid peroxidation. In the second study on 3 human subjects supplemented with an elevated dose of pomegranate juice (20–80 mL/day, equivalent to 0.54–2.16 mmol total polyphenols/day) for the period of 10 weeks. There was also no significant effect of increasing PJ doses on blood chemistry and plasma lipid and lipoprotein patterns in 3 studied subjects, except that plasma glucose, cholesterol, and triacylglycerol concentrations were found to be little higher after 1 week of supplementation with the highest PJ dose (80 mL/d) [81]. Pomegranate (500 mg) peel extract was given to 38 obese women with dyslipidemias daily for the period of 8 weeks. The results showed beneficial effects against dyslipidemias by reducing serum total cholesterol (TC) LDL-cholesterol (LDL-C), triglycerides (TG), Blood Pressure (systolic BP) as compared to control group. Consumption of pomegranate in diabetic patients with hyperlipidemia has also resulted in beneficial effects as its beneficial effects were in seen diabetic patients with hyperlipidemia (cholesterol and triglycerides level ≥ 200 mg/dL). The biomarkers assessed after the study showed beneficial effects in lowering total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), low-density lipoprotein cholesterol / high-density lipoprotein cholesterol (LDL-c/HDL-c), and total cholesterol / HDL-c. But no significant results were seen in altering serum triacylglycerol and HDL-c concentration. According to this study, pomegranate is beneficial in modifying heart-related risk factors associated with hyperlipidemic patients [82]. TNF-α is the pathological biomarker for dyslipidemias. A higher level is seen in dyslipidemic patients it might be considered as one of a potential target for dyslipidemia. In a study conducted to check pomegranate beneficial effects in dyslipidemic patients showed an insignificant reduction in serum TNF-α [83]. A meta-analysis from 12 RCTs did not show any potential effects of pomegranate on lipid profile. It wasn't shown any significant relation seen with duration of supplements and impact of pomegranate consumption on total cholesterol; high-density lipoprotein cholesterol [HDL-C] and no other significant

Table 5. Cardiometabolic Protective Effects of Pomegranate Derived Phytochemicals and their Metabolites.

Cardiometabolic Protective Ingredient	Possible Mechanism	References
Ellagic acid, Urolithin A and Punicalagin	Iinibited α-glucosidase,lipase, dipeptidyl peptidase-4 ,TG deposition, changes gene expression of Adiponectin, PPAR-γ, GLUT4 and FABP4	[5] Obesity
linoleic acid, Punicic acid, Catalpic acid, and Stearic acid	Pomegranate seed oil can activate (PPAR-γ) in epithelial cells and macrophages.	[8] Obesity
Punicalin and Punicalagin	activates (PPAR-γ) which blocks NF-κB	[9] Obesity
Oleanolic, Ursolic, and Gallic acids	Activates (PPAR-γ) Increases NO production	[15, 16] antidiabetic
Punicic acid, Punicalagin and ellagic, gallic, oleanolic, ursolic, and uallic acids	reduces the fasting blood glucose and oxidative stress PON1 stabilization, increased PON1 association with HDL	[17] antidiabetic
Gallic acid	Enhancement of Cardiac (PPAR-γ) mRNA and (GLUT)-4	[6] Antidiabetic
4′-O-β-glucopyranoside ellagitannins and flavones tricetin, luteolin, ellagic acid and granatin B	suppression of α-glucosidase, α-amylase, and lipase activities	[15] antidiabetic
Ellagic acid	Promotion of occludin, claudin 4and nuclear factor erythroid 2-related factor 2 expressions. Inhibits (TNF-α), IL-1β, NF-κB, 3-heneficydroxy-3 methyl glutaryl CoA reductase.	[1,2,6] hyperlipidemia and dyslipidemias
Punicic acid	Inhibits (TNF-α)	[3] hyperlipidemia and dyslipidemias
Gallic acid, Pyrogallic acid and Tannic acid	Reduces pancreatic lipase activity	[6] hyperlipidemia and dyslipidemias
Punicalagin	Enhance NO production	[4] Anti atherosclerotic
Punicalagin and Phytosterol β-sitosterol	Up regulation of PON-2 Increases glutathione level	[18] Anti atherosclerotic

changes were seen per day of consumption of pomegranate juice in plasma total cholesterol, LDL-C HDL-C as well as triglycerides [84]. Thus from the clinical studies discussed in this review revealed PJ (50 ml /day) is effective in patients of carotid artery stenosis, healthy nonsmokers, Diabetic patients with hyperlipidemia for the period between 2 weeks to 1 year. On another side in Dyslipidemia with diabetes PPE was found to be more effective. PSO didn't produce satisfactory results in this domain (Table 6).

Pomegranate in Hypertension

Hypertension/ high blood pressure is the most prevalent risk factor for cardiovascular disease and alone consider as the major contributor to cardiovascular disease worldwide. Failure in endothelial function and increased arterial stiffness are the major pathophysiology associated with hypertension. Lifestyle modification can be beneficial along with medications. Pomegranate juice consumption is proven as a good remedy for the management of hypertension *via* reducing systolic blood pressure inhibits ACE activity. Mainly these effects are produced through pomegranate juice rich in tannins produces anti-atherosclerotic activity anti-aging effects and potent anti-oxidative properties [85]. As discussed previously the protective effects of hydrolysable tannins (ellagitannins and gallotannins) derivatives urolithins, other substances were also proven to produce beneficial due to polyphenolic compounds mainly anthocyanins (exhibits anti-inflammatory activity), flavonoids (naringin along with naritutins) have anti-hypertensive activities [86]. Quercetin is present in fruit; seeds juice and peel of pomegranate possess its cardiovascular protective effects mainly through vasodilation which is endothelial-dependent by cGMP pathway and endothelial-derived hyperpolarizing factor (EDHF) [87]. Findings arising from animal and clinical studies have shown pomegranate juice can reduce BP in both short-term and long-term course. These effects are accompanied by antioxidant and anti-atherosclerotic actions that collectively improve cardiovascular health. The anti-hypertensive effects have been reported for both pomegranate juice and seed oil. Both systolic and diastolic pressures are affected [88]. Thus, the main constituents (Quercetin, naringin along with naritutins) present in seeds, peel, and juice have antihypertensive activity mainly through vasodilation and endothelial-derived hyperpolarizing factor (EDHF).

Preclinical Studies

Chronic intake of pomegranate juice (100 mg /kg and 300 mg/ kg intraperitoneally) for the period of 4 weeks in Angiotensin II-induced diabetic model produced beneficial effects. It reduced mean arterial blood pressure and reversed changes induced by diabetes. Antioxidant e.g. superoxide dismutase (SOD), catalase (CAT), and glutathione reductase (GSH) showed drastic elevation. Thiobarbituric acid reactive substances (TBARS) in kidneys as well as pancreas were drastically reduced. Angiotensin II and ACE activity were also reduced. So pomegranate juice showed protection against angiotensin II-induced hypertension by reducing mean arterial blood pressure and catecholamine-induced vascular reactivity changes and the biochemical changes induced by Angiotensin II and diabetes was reversed mainly *via* antioxidating properties [89]. Pomegranate fruit extract is rich in polyphenolic compounds having intense antioxidant properties reduce the oxidative sensitive gene expression. A comparative study between pomegranate fruit extract (PFE) and pomegranate juice (PJ) (6.25 ml of concentrated juice in 1 L of water) and seed oil (PSE) (1 ml/diet in 1 L of water) was done in Zucker rats induced metabolic disorder to check its protective effects. Ach induced vasorelaxation were more in PJ and PFE compared to PSE. PFE and PJ drastically reduced TSP-1 and TGβ1 expression. PSE produced more pronounced effects on TSP-1. PFE and PJE significantly increase NO and NO synthase (eNOS) expression and seed oil showed no any effects on it. Other parameters LDL-c, TC, MAP, heart rate (HR) were not significantly decreased by PFE. But TC and LDL-c were found to be increased by PSE. Plasma insulin and glucose did not significantly affect by either extract [90].

Preclinical comparative studies from juice fruit and seed extract of pomegranate revealed PJ and fruit extract was able to increase eNOS and NO production compared to Seed which did not affect it. The seed was helpful in other biomarkers (Table 7)

Clinical Studies

In clinical studies, hypertensive patients were given 150 mL of pomegranate juice for the period of 2 weeks. These results showed a drastic reduction in SBP and DBP but no effects on flow-mediated dilation (FMD), lipid profile and apolipoproteins A and B were

Table 6. Clinical Studies Showing Protective Effects of Pomegranate against Hyperlipidemias Dyslipidemias and Atherosclerosis.

Test substance	Study type/ subject/no of participants	Dose	Duration	Outcomes	References
PJ	Clinical trial/ carotid artery stenosis/ (N=10)	50mL/day, 1979 mg/L of ellagitannins	1 year and 3 years	↓↓↓IMT ↓↓↓ SBP ↑↑ PON1 ↓↓↓LDL oxidative state ↓↓↓Antibody oxLDL	[21]
PJ	ex vivo study/healthy nonsmokers male/(N=13)	50 mL PJ/day (1.5 mmol total polyphenols) and 80 mL/day	2 weeks	↑↑ PON1 ↓↓↓oxLDL	[26]
PPE	A double blind, randomized, placebo controlled pilot study /obese women with dyslipidemias/(N=38)	500mg/day	8 weeks	↓↓↓ SBP, hsCRP, TGs,TCs ↑HDL-c	[3]
CPJ	/Diabetic patients with hyperlipidemia/(N=22)	40 g/ day	8 weeks	↓↓LDL-c/HDL-c ↓↓ TC, TGs	[8]
PSO	Clinical study/ dyslipidemic patients/ (N=25)	400 mg twice /day	4 week	↔ TNF-α	[2]
	Meta-analysis				

Table 7. Outcomes of clinical study regarding pomegranate Cardiometabolic protective effects.

Type of study ,dose, duration ,number of participants in study	Clinical outcomes	References
In a clinical trial (50 mL PJ/day, 1979 mg/L of ellagitannins) for 1 year by carotid artery stenosis(N= 10)	Significant reduction in intima media thickness, SBP and Serum lipid peroxidation.	[27]
In a clinical trial 50 mL PJ/day (1.5 mmol total polyphenols for 2 weeks by healthy nonsmoker male (N=13 age 20–35 y)	Decreased LDL ability to coagulate, increase serum paraoxonase activity	[28]
In a clinical trial (150 mL PJ/day) for 2 weeks by hypertensive patients (N=21)	Significant reduction in blood pressure (SBP and DBP)	[12]
In a clinical trial (330 mL PJ /day) for 4 weeks by healthy women (N=51)	blood pressure by significant reduction in blood pressure but without affecting serum ACE activity	[18]
In a clinical study (150 mL PJ/day) after 4-6 hours by hypertensive male(N=13)	drastically reduces the blood pressure but without affecting the serum concentration of proinflammatory mediators	[18]
In a clinical study (150 mL PJ /day) for 2 weeks by hypertensive male (N=21)	Significantly decreased (SBP and DBP).Other beneficial effects were produced by improving endothelial function via decreasing serum concentrations of VCAM-1.	[20]
In double blind, randomized, placebo controlled trial hydroalcoholic peel extract of pomegranate (500 mg/ day) for 8 weeks by obese women (N= 38)	drastic reduction in systolic as well as diastolic blood pressure	[21]
In a clinical study (50 mL PJ 1.5mmol of total polyphenols / day) for 2 weeks by hypertensive patients (N=10)	36% reduction was seen in serum ACE activity 5% reduction in systolic blood pressure occurred.	[26]
In quantitative meta- analysis for weeks (>12 week and <12 weeks) Doses (>240 and <240cc)	It causes significant reduction in systolic as well as diastolic blood pressure.	[30]
In a clinical trial (500 mg PE/day) for 8 weeks by obese women with dyslipidemias (N=38)	Showed beneficial effects against dyslipidemias by reducing serum total cholesterol (TC) LDL-cholesterol (LDL-C), triglycerides (TG), Blood Pressure (systolic BP).	[3]
In a clinical trial (40 g PJC/ day) concentrated for8 week by 22 diabetic patients with hyperlipidemia (N= 22)	Showed beneficial effects in lowering total cholesterol (LDL-c), low density lipoprotein cholesterol /high density lipoprotein cholesterol (LDL-c/HDL-c), and total cholesterol / HDL-c.	[8]
A meta- analysis from 12 RTCs	No any significant relation seen with duration of supplements and impact of pomegranate consumption on total cholesterol; high density lipoprotein cholesterol [HDL-C].	[7]
In a clinical study (400 mg PSO /2 times/day) for 4weeks by dyslipidemic patients (N=25)	showed insignificant reduction in serum TNF-α	[2]
A single-blind, randomized clinical trial (200 ml of PJ / day) for 6 weeks by type2 diabetic patient with oxidative stress (N= 60)	Decreased the amount of oxidized LDL and anti-oxidized LDL- antibody and other anti-oxidants were enhanced	[11]
Randomized placebo controlled clinical trial (250 mL PJ/ day for 12 weeks by diabetic patients (N=44)	Significantly affecting Plasma sE-selectin concentration, NF-κB and SIRT1 levels	[12]
In a randomized, placebo controlled cross over study (500 ml 1685 mg/l polyphenols PJ /day) for 4 weeks by obese and over weight (male N=12, Females N=16).	significant reduction in fasting plasma insulin as well as insulin resistance	[26]
A double-blind, randomized, and placebo-controlled trial PV(1.5 g acetic acid and 700 µg ellagic acid/200 mL/day) for 8 weeks by overweight subjects (N =80)	caused reduction in adipose and potentiates AMPK phosphorylation compared	[12]
In a randomize double- blinded placebo controlled clinical trial(120 mL/day PJ) for 1 month obese (N=20)	Did not significantly modify insulin secretion as well as sensitivity of insulin in obese subjects.	[10]
In a clinical evaluation study PJ(1000 mg/day(610 mg of Gallic acid equivalent) for 4 week in obese subjects (N=22)	Pomegranate protective effects were seen with significant reduction in plasma thiobarbituric acid reactive substances	[11]

seen. Pomegranate could be used as a hypotensive agent in pharmacological therapy [33]. In a clinical study done on healthy adults pomegranate juice (330 ml/day) was given for the period of 4 weeks produced favorable effects on blood pressure by the significant reduction in systolic and diastolic blood pressure but no effects were seen on pulse wave velocity (PWV) and ferric reducing power (FRAP) which is an antioxidating biomarker. The reduction in blood pressure was not due to its serum ACE activity as serum ACE was not changed [91]. In another clinical study pomegranate juice (150 ml/day) was consumed by hypertensive male following a 12 hour fast. The results were seen at baseline and after 4-6 hrs. The results showed a significant reduction in the Systolic and diastolic blood pressure. Systolic blood pressure slightly more reduced compared to diastolic. Flow-mediated dilation (FMD) was slightly increased. But other parameters e.g. serum concentration of proinflammatory mediator like IL-6, C-reactive protein, intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin was found to be slightly reduced or no significant changes were observed [42]. Consumption of pomegranate juice (150 ml/day) by hypertensive patients caused a significant reduction in systolic and diastolic blood pressure. Other beneficial effects were produced by improving endothelial function by decreasing serum concentrations of VCAM-1. According to this study, pomegranate is proven as beneficial substance in hypertensive patients [55]. A clinical study was done on the hydroalcoholic peel extract of pomegranate (500 mg/ day) administered in obese women with dyslipidemias. The results showed a drastic reduction in Systolic blood pressure SBP and highly sensitive C reactive protein hsCRP and serum total cholesterol (TC) and triglycerides (TGs). HDL-c was also increased. But Diastolic blood pressure DBP and body mass index BMI were not changed significantly [61]. In a study done in which Pomegranate juice was consumed (50 ml, 1.5 mmol of total polyphenols/day) by hypertensive patients. This showed a drastic reduction in SBP but the negligible reduction in DBP. A dose-dependent reduction in Angiotensin-converting enzyme (ACE) was also seen. But it was not directly related to a reduction in blood pressure (SBP). Hypotensive effects were probably due to its antioxidating effects.

Pomegranate juice and its effects on BP and relation with ACE are still in question S. Pomegranate juice is prudent to be called as heart-healthy fruit juice as quantitative meta-analysis showed significant results in favor of its cardiac protective effects. It causes a significant reduction in systolic as well as diastolic blood pressure. The reduction in systolic blood pressure was seen regardless of the duration of action (either >12 weeks and or <12 weeks). But greater reduction effects were seen with higher doses (>240) as the compared low dose (<240 cc). It is concluded from the clinical studies PJ is very effective in reducing SBP at lower as well as higher doses (50 ml to 330 ml) but DBP reduction was seen only at higher doses (>330 ml). PPE (500 mg/day) was more effective is reducing hsCRP and improving Lipid profile compared to PJE. BP and ACE reduction and its relation with pomegranate juice are still in question.

Pomegranate protective effects against Myocardial Infarction (MI)/ Myocardial Ischemia and Reperfusion MI/R

Punicalagin from the pomegranate is the most abundant Ellagitannins in pomegranate juice having greater antioxidant and anti-inflammatory properties. *In-vitro* studies show that Punicalagin can activate AMPK pathway by reducing ATP/ADP in cardiomyocyte and can be helpful in Cardiometabolic disorders. Acute myocardial infarction is currently most pervasive ischemic heart disease that is the prime cause of elevated morbidity and mortality worldwide. The pathophysiology related to cellular damage due ischemia is composite. Restoration of blood circulation is compulsory for ischemic myocardial rescue. Myocardial ischemia/ reperfusion injury occurs due to reperfusion which results in cardiomyocyte apoptosis. Reactive oxygen species (ROS) play a pivotal role in the pathophysiology of MI/R. ROS causes intense myocardial injury and cardiac dysfunction by calcium overload and activates successive Inflammation infiltration Punicalagin (30 mg/kg/ day for one week) is most effective in MI/R as the increase in antioxidant status and AMPK and ACC phosphorylation.

Preclinical

A study performed in an animal model showed cardio-protective action against ischemia and reperfusion (I/R) by the consumption of pomegranate juice. Different biomarkers like lactate dehydrogenase troponin 1 and creatinine were significantly reduced. Antioxidants activity of superoxide dismutase, glutathione peroxidase, catalase, and malondialdehyde showed significant improvement. The cardioprotective action of pomegranate was due to an increase in antioxidant properties and production of NO. Another mechanism may be responsible. Pomegranate (Punicalagin 30 mg/kg/ day for one week) in the rat model confirms the protective role against MI/R injury. Pomegranate potential target in I/R induced myocardial is oxidative stress. It exerts its effects by reducing reactive oxygen species (superoxide content), malondialdehyde formation and increases antioxidants. Pomegranate exerts its protective role against myocardial injury by increasing adenosine monophosphate-activated protein kinase (AMPK) and acetyl CoA carboxylase (ACC) phosphorylation. Pomegranate juice from seed (100 and 300 mg/kg) and (100 mg/kg) Butanol PJ (100 mg/kg) presented a protective effect against isoproterenol (ISO) induced myocardial infarction in Wistar rats. It was proven effective as significant reduction was seen in lactate dehydrogenase LDH and creatinine kinase CK. The significant escalation in antioxidant enzyme superoxide dismutase SOD and catalases CAT was seen. Heart rate, pressure rate index, and ECG showed improvements. A significant reduction was also seen in vascular reactivity to various substance. Pomegranate juice and seed have proven exceptional beneficial effects in MI/R and Isoproterenol induce myocardial infarction in the rat model by combating various biomarkers (Table 8).

Clinical Studies

Randomized, placebo-controlled, double-blind study was done in 45 patients who had Coronary Heart Disease (CHD) and myocardial ischemia. Patients were divided into two groups as control and other treated with Pomegranate juice. Pomegranate juice reduced myocardial ischemia and produced improvement in myocardial perfusion compared to control group. other their beneficial effects could be related to lipids, blood glucose, hemoglobin A1c, body weight, or blood pressure, which showed no mark of negative effects among all above-mentioned parameters [92]. Another study performed in 100 patients diagnosed with unstable angina or MI. pomegranate juice was given. Different parameters like occurrence, intensity, and duration of angina

Table 8: Clinical studies showing Protective Effects of Pomegranate against Hypertension.

Test substance	Study type/ subjects/ no of subjects	Dose	Duration	Outcomes	References
PJ	Clinical study/ hypertensive patients (N=21)	150 mL	2 weeks	↓↓↓ SBP, DBP ↔ FMD, apolipoprotein A and B	[12]
PJ	Clinical study/healthy women/(N=51)	330 mL/ day	4 weeks	↓↓↓ SBP, DBP ↔ ACE , PWV, FRAP	[18]
PJ	Clinical study /Hypertensive male/ (N=13)	150 mL / day	4 -6 hrs	↓↓ SBP ↓DBP ↑FMD ↔E-selectin IL-6,CRP, ICAM-1,VCAMP-1	[19]
PJ	Clinical study/ hypertensive male (N=21)	150 mL / day	2 weeks	↓↓↓ SBP, DBP ↓↓VCAMP-1	[20]
PJ	Clinical study/hypertensive patients (N=10)	150 mL(1.5 mmol of total polyphenols/day)	8 weeks	↓ACE ↓SBP ↕DBP	[26]
PPE	Double blind, randomized ,placebo controlled trial/obese women (N= 38)	500 mg/day	8 weeks	↓↓↓ SBP, hsCRP, TGs,TCs ↑HDL-c ↔DBP ,BMI	[21]
PJ	Quantitative meta-analysis	> 240and < 240cc	>12< and < 12 weeks	↓↓↓ SBP, ↓↓↓DBP	[30]

e-ISSN:2321-6182
p-ISSN:2347-2332

Table 9. Clinical Study Showing Protective Effects of Pomegranate against Myocardial Infraction (MI)/ Myocardial Ischemia and Reperfusion MI/R.

Test substance	Study type/subjects/ no of participants	Dose	Duration	Outcomes	References
PJ	Clinical study/ unstable angina or myocardial infarction/ (N=100)	220ml/ daily	5 days	↓↓↓troponin, malondialdehyde ↔IL-6,TNF-α, hsCR	[1]
PJ	Randomized, placebo controlled, double-blind study/ CHD and myocardial ischemia/(N=45)	240 ml/ day	3 months	↓myocardial ischemia, myocardial perfusion	[5]
↓↓↓ (significant reduction) ↓↓ (decrease) ↓ (little decrease) ↔ (not affected) ↕ (insignificant effect) ↑↑↑ (significant escalation) ↑↑ (decrease) ↑ (little increase) ↔ (not affected) ↕ (insignificant effect)					

pectoris with unstable angina were significantly reduced. Significant reduction in serum troponin and malondialdehyde also occurs. Other parameters like interleukin-6, tumor necrosis factor alpha and high-sensitive C-reactive protein were not changed significantly. Thus pomegranate has a protective role against myocardial ischemia and reperfusion injury. PJ (220 ml to 240 ml / day between 5 days to 3 months) is effective against myocardial infarction CHD and myocardial ischemia specifically decreasing troponin, malondialdehyde irrespective of other biomarkers (IL-6, TNF-α, hsCRP) (Table 9) which needed further investigation at higher doses.

CONCLUSION

Constituents from leaf, juice, peel, seed exert protection against obesity, diabetes, hyperlipidemias, dyslipidemias, atherosclerosis, hypertension myocardial infarction (MI) myocardial ischemia and reperfusion MI/R. Studies from marine and human subjects disclosed that Pomegranate leaf and vinegar has many promising effects against obesity these areas needed further clinical interrogations to reveal other hidden perspectives of it. According to preclinical in-vitro and in-vivo all parts possessed anti-diabetic properties but peel and leaf exerted significant antidiabetic properties. Juice produced restoration properties in the pancreas of Langerhans in preclinical and clinical studies. But clinical data is not sufficient to conclude it. Pomegranate juice and peel have many promising effects against atherosclerosis, hyperlipidemia, dyslipidemia, and hypertension. Juice at higher doses is significant against DBP and SBP but lipid profile wasn't affected much at a higher dose and longer duration of action compared to peel which covers lipid profile in a better way at higher doses and longer duration of action. PJ gives protective shreds of evidence in myocardial infarction (MI) myocardial ischemia and reperfusion MI/R but some biomarkers could cover better results by the peel. Sufficient to conclude it Pomegranate juice and peel have many promising effects against atherosclerosis, hyperlipidemia, dyslipidemia, and hypertension. Juice at higher doses is significant against DBP and SBP but lipid profile wasn't affected much at a higher dose and longer duration of action compared to peel which covers lipid profile in a better way at higher doses and longer duration of action. PJ gives protective shreds of evidence in myocardial infarction (MI) myocardial ischemia and reperfusion MI/R but some biomarkers could cover better results by the peel.

Future Perspective

Pomegranate covers the wider range of satiety in cardiometabolic syndromes. If pomegranate juice and peel are combined together it could be proved as an unprecedented exemplary juice for combating cardiometabolic syndromes.

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