

A Review on Antidiabetic and Antioxidant Activity of *Punica Granatum L.*

Pallavi Raju Daf

Submitted: 20-01-2024

Accepted: 30-01-2024

I. INTRODUCTION:

Diabetes mellitus is a major chronic illness that occurs in most parts of the world. It is defined as a high blood glucose level either due to an insufficient amount of insulin or insulin resistance in which cells cannot react effectively to the adequate amount of insulin. According to statistics, the number of adults diagnosed with diabetes in 2019 was 463 million, and it is estimated that this number could increase up to 578 million in 2030.[1]

People who have diabetes mellitus usually need to take certain medications to lower their blood glucose levels and reduce the development of complications. Although the use of medication can control high blood glucose levels, the long-term effect of certain antidiabetic agents can cause water retention, gastrointestinal problems, weight gain, increase the risk of acidosis and the risk of bladder cancer. This could lead to the preference of a natural product as compared to the synthetic drug in a patient with diabetes mellitus.

Recent studies have shown that many people start to practice the use of natural products as an alternative form of medicine as they believe that natural products are generally safer as compared with the synthetic drug in treating and preventing the development of diabetes mellitus. Besides, oxidative stress which occurs due to the imbalance of free radicals and the number of antioxidants have been proven to be linked to the development of diabetes complications.[2]

Punica granatum L. commonly known as pomegranate and belonging to the family of *Punicaceae* is a unique plant. It is considered to be an ancient, mystical plant and to possess diverse medicinal and dietary uses. Pomegranate plants prefer a semi-arid, mild-temperate to subtropical climate and are naturally adapted to regions with cool winters and hot summers. The term pomegranate is derived from the Latin word "punom" meaning apple and "granatum" which means seeded. Pomegranate is a highly revered plant in the Bible, the Jewish Torah, and the Quran, and as a sacred fruit. Pomegranate was also used

extensively in various ceremonies in the ancient Egypt, Greece, and Babylonia. The fruits are the most important plant part and are known as "the fruit of the dead".[3]



Fig 1: Plant of *Punica granatum L.*

Punica granatum L. originated in the Middle East, and their cultivation was extended to different regions in the world through the propagation of its seeds, which resulted in a broad genetic diversity. The largest *P. granatum* germplasm collection is presently found at the Garrygala Research Station in Turkmenistan with 1117 accessions, followed by India with 810, Russia with 800, Iran with 770, Ukraine and Turkey with 370, China with 289, the USA with about 200, and Israel with 150 accessions. In the European Union, the largest germplasm collection is located in Spain, with more than 140 accessions. New accessions have been characterized in the last few years, demonstrating the wide diversity and the growing interest in this fruit around the world.

The total area of pomegranate production worldwide is estimated to be well above 300,000 ha, with more than 76% found in 5 countries (India, Iran, China, Turkey, and the USA)

Iran, India, and China are responsible for 80% of the global production, estimated to be about 3 million tons. The primary use of pomegranate is fresh consumption; however, in the last decades, there has been an increase in demand for industrially-processed products such as juices, alcoholic drinks, jams, dehydrated seeds, nutritional fiber, dry rind for making infusions, and extracts from its different parts. This growing interest in the use of pomegranate and its parts is motivated both the increasing demand by the nutrition, pharmaceutical, and cosmetic industries in addition with the incipient interest of consumers for its fresh consumption.

During 2018, the consumption of fresh fruit in Spain accounted for 9.3% of the average budget of a household devoted to food. This increasing importance may be due to the latest scientific research studies, which have indicated that pomegranates contain substances with antimicrobial, anti-cancer, cardio-protective, and anti-inflammatory activity. Also, the plant could be used for the treatment of diabetes mellitus and obesity, and can also improve sperm quality, among other uses. The pomegranate fruit is considered to be part of the so-called Super Fruits group, which is a term used to highlight the excellent nutritional qualities and health promoting phytochemicals of certain fruits. This is perhaps the

reason why pomegranates have been used for pharmaceutical purposes, since ancient times, and it continues today, as pharmaceutical companies are extracting the bioactive compounds of the fruit to create capsules for dietary supplementation. Pomegranates contain many bioactive compounds such as alkaloids, ellagic acid, punicalagin among other ellagitannins, anthocyanins, flavonoids, tannins, and other phytochemicals that may play an essential role in human health and the prevention and treatment of many illnesses.

Different varieties normally have different physico-chemical characteristics and may, therefore, differ in the amount and types of bioactive compounds. Thus, the bioactive profile is influenced by the cultivar, growing region, climate, maturity, cultivation practice, and storage conditions. The aim of this review is to analyze and summarize the recent research studies conducted with pomegranates to identify the main bioactive compounds present in the different plant parts (fruits, flowers and leaves) which shows antidiabetic and antioxidant activities. This will allow us to elucidate the consumption trends and/or preferences in relation with both the pomegranate variety and pomegranate part consumed (that is related with the type of consumption) to obtain health benefits.[4]

II. PHARMACOGNOSTIC STUDY:

2.1 Scientific Classifications:

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Subdivision	Rosidae
Order	Myrtales
Family	punicaceae
Genus	Punica
Species	P.granatum
Binomial Name	Punicagranatum L.
Synonyms	Punicamalus

Table 1: scientific classification of punicagranatum l. [5]

2.2 Morphological Discription:

Pomegranate (*Punicagranatum L.*) or anar is a deciduous shrub or small tree, growth of 1.8-4.6 m tall, belonging to family punicaceae.

2.2.1 Leaves: Leaves are around 7.6cm long and shiny.

2.2.2 Flower: It has orange-red, trumpet-shaped flowers with disarranged petals and about 5cm long.

2.2.3 Fruit: The fruits are globose, bright berry types, and 5-7.6 cm in diameter, but when get matured, the colour is reddish or yellowish-green. The seeds are crunchy having acidic pump enclosed in a membranous skin.[5]

2.3 Geographical Source:

P.granatum is originally native to the Iranian plateau and the Himalayas in north Pakistan and India. However, with time through traders and

warriors, the plants have got distributed to other parts of the world. Today p.granatatum is cultivated over the whole Mediterranean region, throughout India and the drier parts of Southeast Asia, Malaya, parts of America (California and Arizona) and tropical Africa.

2.3 Varieties Of Pomegranate:

Depending on either the organoleptic properties or from the place of cultivation different varieties of pomegranate are found. Some of the important cultivated varieties are the bedana, kandhari, alandi (vadki), dholka, Kabul, muscat red, poona, Spanish ruby, ellodu, muscat white, belegal, cloud, crab, early wonderful fleshman, francis, Granada, green globe, king, Phoenicia, Utah sweet and wonderful.[3]

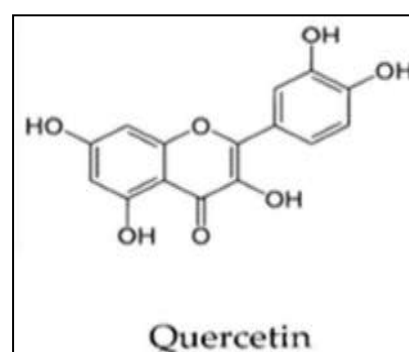
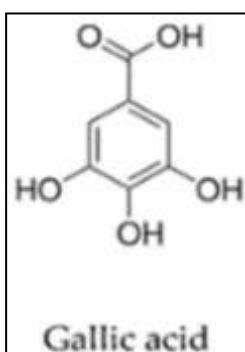
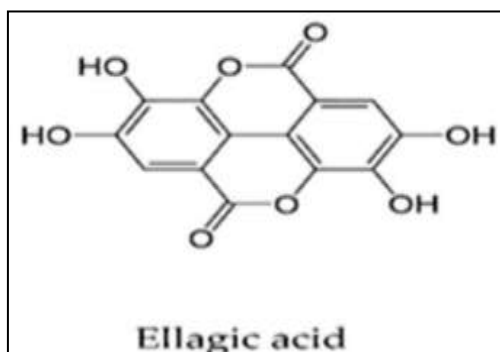
2.4 Biochemical Constituent:

Over the past decade, significant progress has been made in establishing the pharmacological mechanisms of pomegranate and the individual constituents responsible for them. Extracts of all parts of the fruit appear to have therapeutic properties, and some studies report the bark, roots, and leaves of the tree have medicinal benefit as well. Current research seems to indicate the most therapeutically beneficial pomegranate constituents are ellagic acid ellagitannins (including punicalagins), punicic acid, flavonoids, anthocyanidins, anthocyanins, and estrogenic flavonols and flavones.

Table 2 lists the principal constituents of the Punicagranatum tree

PLANT PARTS	CHEMICAL CONSTITUENTS
Pomegranate Fruit juice	anthocyanins; glucose, ascorbic acid; ellagic acid, gallic acid, caffeic acid; catechin, EGCG; quercetin, rutin; numerous minerals, particularly iron; amino acids
Pomegranate seed oil	95% punicic acid; ellagic acid; other fatty acids; sterols
Pomegranate pericarp (peel, rind)	phenolic punicalagins, gallic acid and other fatty acids; catechin, EGCG; quercetin, rutin, and other flavonols, flavones, flavonones, anthocyanidins
Pomegranate leaves	tannins (punicalin and punicafolin), and flavone glycosides, including luteolin and apigenin
Pomegranate flower	gallic acid, ursolic acid; triterpenoids, including maslinic and asiatic acid;
Pomegranate roots and bark	Ellagitannin, including punicaline and punicalagin, and numerous piperidinealcolloids

Table No 2: Punica Granatum L. Parts and Chemical Constituents



Ellagitannins

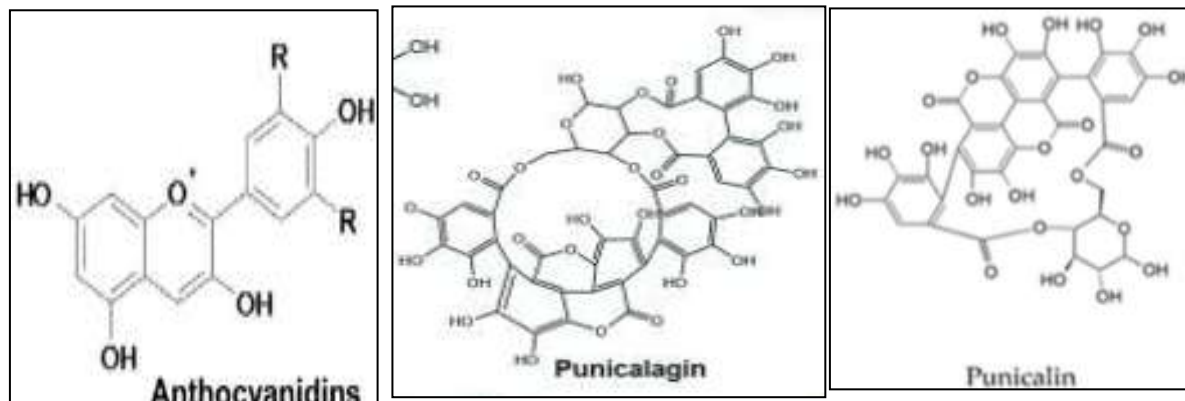


Fig 2: Active chemical constituents of punicagranatum

2.5 Nutritive Composition:

The fruit of pomegranate per 200 gm serving 10-12% daily value of vitamin C and folate and 16% of vitamin K and 20% dietary fibres. The total carbohydrates present is about 9-14% and contains 8% of vitamin B6, and other nutritional values. [5]

2.6 Traditional Uses Of Punica Granatum L:

In the recent, punicagranatum (anar) have been studied for various therapeutic and essential uses including, in Antidiabetic, antioxidant, bacterial infection, anti-arthritic, anti-inflammatory atherosclerosis or arteriosclerosis, immunomodulation, fungal infection, periodontal disease, parasitic infection, skin disorder and food poisoning, and gastro-intestinal infection. Their have even been much preliminary toxicity studies and approved data in mice/rats (rodents) to report punicagranatum as non-toxic at all concentrations/doses, especially at a high dose.[3]

III. ANTIDIABETIC AND ANTIOXIDANT ACTIVITY OF PUNICAGRANATUM L.

Ant diabetic property:

Diabetes mellitus is a metabolic disorder caused by inherited and/or acquired deficiency or inadequate secretion of hormone insulin (type I or insulin-dependent diabetes mellitus) or due to an inadequate response of target cells to insulin (type II or non-insulin-dependent diabetes mellitus – NIDDM), or by a combination of these factors that ultimately culminates in hyperglycemia. Hyperglycemia leading glycation end products, activation of sorbitol pathway, free radical

generation and depletion of antioxidants, stimulation of inflammatory reactions, is the mechanisms implicated in the etiopathogenesis of diabetic complications like retinopathy, neuropathy, nephropathy and cardiovascular disorder.

Recent reports indicate that the prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and 4 4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030, Estimations of International Diabetes Federation shown that worldwide, nearly 285 million people are suffering from diabetes and that annually around 3.2 million deaths are attributed to it. It is expected that the number will increase to more than 438 million by the year 2030. While exogenous insulin and other medications can control hyperglycemia, they are ineffective in preventing the secondary complications. In milieu of these observations it is imperative that novel agents possessing both anti-hyperglycemic and effective in preventing the secondary complications are required. Innumerable studies carried out in the past one decade have shown that pomegranate flowers, peel juice and seed possess beneficial effects.

In the Following sections the scientific observations pertaining to the antidiabetic effects of pomegranate and some of its phytochemicals are addressed. Since antiquity, pomegranate has been used in the various traditional and the folk systems of medicine to treat diabetes. Scientific studies carried out in the past one decade have also shown that the extract of pomegranate flower, seed, seed oil and seed hull and the phytochemicals like ellagic acid, gallic acid, quercetin and punicalagins

possess ant diabetic effects in various preclinical animal models of study. Additionally the seed juice is shown to ameliorate the diabetes-induced hyperlipidemia and to prevent the various secondary complications of diabetes. In the following sections the various antidiabetic effects and the mechanisms responsible for the beneficial used will be addressed. [3]

Antioxidant property:

In a human body, variable chemicals are created as free radicals through an oxidation process, and these free radicals can destroy cell membranes and other structures as their amount increases in the human body. Antioxidants work on these free radicals to remove and neutralize it from the body to make a correct balance.

The phenolic compounds and tocopherols present in Punicagranatum have been studied for antioxidant activity by using various methods as differential pH methods, HPLC analysis. The hydrolysis of ellagitannins and gallotannins produced two hydroxybenzoic acids, i.e., ellagic acid and gallic acid, respectively, that are responsible for antioxidant activity. It was investigated that the seed oil contains a high volume of tocopherols having great activity as antioxidant using ORAC and FRAP assays .The aqueous and ethyl acetate extracts of P. granatum evaluated for antioxidant activity using reagents and methods like DDPH test, chemiluminescence assay, and 5-lipoxygenase assay and this study investigated that the peel, juice, and extracts of pomegranate possess a significant antioxidant activity.

The ethanolic, methanolic and aqueous extracts of peel and seed of pomegranate exhibited a various degree of antioxidant activity that is determined with the bleaching of β -carotene and DDPH methods. The methanolic extracts of pomegranate peel possess the highest potential as antioxidants .The antioxidant action of Egyptian Punicagranatum peel extracts was studied using HPCL modified analysis and standardization, ellagic acid, and gallic acid was considered as markers or positive control. The peel extraction with 70% ethanol showed the highest capacity to scavenge DDPH free radicals to exhibit a pronounced antioxidant activity.[5]

3.1 Antidiabetic And Antioxidant Activity Of The P.Granatum Flower



Fig.3 : Flower of Punica Granatum L.

In the Indian traditional Unani system of medicine, the male abortive flowers of pomegranate are used to treat diabetes. Scientific studies by Jafri et al. 2000 showed for the first time that the oral administration of the hydro alcoholic extract (500 v/v) of the Bowers was effective in decreasing the blood glucose level in both normal and type I diabetic (alloxan-induced) rats. Of all the doses studied, the optimal effects were observed at 400 mg kg b. wt.[3] Studies have also shown that the aqueous extract of the flowers was effective in streptozotocin-induced type I diabetes in rats .The flowers are also reduced the serum lipids and blood glucose levels in the E (0) mice. Recently, it has been reported that the aqueous ethanolic (50% v/v) extract from PGF showed hypoglycemic activity in a diabetic animal model. The action mechanism for the anti-diabetic effects of PGF, however, is still unknown.

The peroxisome proliferator-activated receptors (PPARs) form a subfamily of the nuclear receptor superfamily and three isoforms encoded by separate genes have been identified so far: PPAR-a (NR1C1), PPAR-h/y (also referred to as NUC1; NR1C2), and PPAR-g (NR1C3). PPARs are ligand-dependent transcription factors that regulate target gene expression by binding to specific peroxisome proliferator response elements (PPREs) in enhancer sites of regulated genes .PPARs are activators of key metabolic pathways that control fatty acid oxidation, adipocyte differentiation, and insulin sensitivity .For non-insulin-dependent diabetes mellitus (NIDDM) patients, insulin resistance develops as a result of pancreatic h-cell dysfunction and diminished ability to respond to circulating insulin .Activation of PPAR-g by agonists such as thiazolidinedione's

(TZDs) helps improve endogenous insulin sensitivity. In the current study, we investigate the effects and action mechanism of the methanol extract from PGF on hyperglycemia in Zucker diabetic fatty (ZDF) rats, a genetic model for obesity and NIDDM and on receptor function in a cell line system.[7]

Flowers of pomegranate contain anthocyanin's which shows antioxidant activity. Anthocyanin's were extracted and separated by reverse-phase high performance chromatography and sephadexLH-20 chromatography. Anthocyanin's shows antioxidant activity. Antioxidant activities of purified anthocyanin's were screened for their antioxidative potential using 2,2-diphenyl-1-picryl hydrazyl (DDPH) and 3-ethyl-benzo-thiazoline-6-sulphonate (ABTS) systems. The purified anthocyanin's showed strong radical scavenging activities. [7]

3.2 Antidiabetic And Antioxidant Activity Of P. Granatum Fruit



Fig.4 : Fruit of Punica Granatum L.

Clinical studies have also shown that the consumption of 40 g day of concentrate pomegranate juice for 8 consecutive weeks was effective in improving the lipid profiles in diabetic patients with hyperlipidemia. Pomegranate juice cause significant reduction in the levels of total cholesterol, LDL-C, ratio of LDL -C/HDL-C and ratio of TC/ HDL-C were observed. However, no significant changes in the serum triacylglycerol and HDL-C concentrations were observed. The study also showed that the anthropometric indices, physical activity level, types and doses of oral hypoglycemic agent and intake of nutrients and flavonoid-rich food did not change during consumption of pomegranate juice.

Supporting these observations studies have also shown that daily consumption of 50 ml day of the pomegranate juice for 3 consecutive month did not reduce the blood glucose, cholesterol and triglyceride level in both health and in NIDDM patients. However in the patients verses control significant reduction in the level of serum lipid peroxides and, TBARS, and increase in the level of SH groups and paraoxonase 1 activity was seen. Consumption of the pomegranate juice reduced the cellular peroxides and increased GSH level in the patients monocytes-derived macrophages Consumption, of pomegranate juice also reduced the uptake of OX-LDL by the macrophages in diabetic Patients.[3]

Pomegranate fruit juice extract possesses antioxidant effect, and has therapeutic potential in the prevention and treatment of vascular complications in diabetic patients. An in vitro study observed that preincubation of observed that cultured human umbilical vein endothelial cells with pomegranate juice extract (250 microgram per ml) prevented increase in lipid peroxidation and decrease in antioxidant cause by glycated protein-iron chelate. very recently ,have observed that daily consumption of 250 ml of pomegranate juice for 4 consecutive weeks was effective in increasing the levels of plasma antioxidant capacity and decreased plasma carbonyl content, and that the effect was better than that of orange juice. Studies have also shown that consumption of wonderful variety pomegranate juice (50 ml per day for 4 weeks) as well as pomegranate polyphenol extract (5ml per day for 6 weeks) contribute to paraoxonase 1 stabilization, increased association with HDL, and enhanced catalytic activity.[3]

3.3 Antidiabetic And Antioxidant Activity Of P.Granatum Pericarp (Peel And Rind)



Fig. 5 :Peels of Punica Granatum L.

Preliminary studies showed that *P. granatum* rind extract possessed significant blood sugar lowering activity. Also the scientific studies by Enas A. M. Khalil shows the antidiabetic activity of pomegranate peel powder aqueous extract in its human therapeutic dose on beta cell numbers, blood glucose and plasma insulin levels in alloxan diabetic rats for 4 –weeks of treatment and shows the mechanism of hypoglycaemic effect of the extract. Punicagranatum aqueous peel extract significantly lowered blood sugar and increased insulin level and the number of β cells increased. Alloxan has shown to induce free radical production and cause tissue damage. The pancreas is especially susceptible to the action of alloxan – induced free radical damage and protect β cells from damage. Punicagranatum aqueous peel extract possesses strong antioxidant property. And can act as free radical scavenger in blood sugar and elevation in insulin level. The number of β cells increased.[9]

Pomegranate (*punicagranatum*) is rich in bioactive molecules, it has shown myriad medicinal properties due to its high phenolic content. Pomegranate, specifically its rind, contains high amounts of hydrolysed ellagitannins, classified especially as ‘pomegranate ellagitannins’ which involve punicalins, punicalagins and pedunculagins [8]. Ellagitannins are esters that comprise of hexahydroxydiphenic acid and a polyol, which can be quinic acid or a glucose. ellagitannins, pomegranate rind also encompasses hydroxybenzoic acids (such as gallic acid, ellagic acid, and ellagic acid glycosides), anthocyanidins (such as cyanidin, pelargonidin, and delphinidin) and flavonoids (such as kaempferol, luteolin, and quercetin).

Also scientific studies shows that the pomegranate rind and aril are rich in phenolic compounds. Phenolic compounds are known for their antioxidant potential, which can have radical scavenging power and/or transition metal chelating power. Antioxidants quench free radicals by undergoing oxidation and acting as a reducing agent towards the radicals. Free radicals are highly reactive and unstable, with the capability of reacting with the human’s DNA, proteins, carbohydrates and lipids causing cell damage. Antioxidants can terminate the spontaneous radical reactions avoiding its harmful effect on the human cells, tissues and organs. Lipid peroxidation, carcinogenesis, cardiovascular diseases and nucleic acid oxidation are caused by the reaction of free reactive radicals with macromolecules. Pomegranate, as a fruit rich in antioxidants, can

intensively and positively contribute in humans’ health.[8]

3.4 Antidiabetic And Antioxidant Property Of *P. Granatum* Leaves



Fig 6: leaves of Punica Granatum L.

Various parts of the pomegranate plant contain different types of phytochemicals that possess various pharmacological activities. The leaves of pomegranate are abundant with tannins (punicalin and punicafolin), flavones (luteolin and apigenin), and glycosides. The extracts obtained from different parts of the *Punicagranatum* have been studied in the treatment of various ailments. An earlier study has suggested that the methanolic extract of *Punicagranatum* leaves (MEPGL) might have an antidiabetic effect. Nevertheless, the mechanisms by which MEPGL exerted this effect were not well-recognized. Different studies carried out a comprehensive investigation on the possible mechanisms of the antidiabetic activity of MEPGL in the nicotinamide / streptozotocin-induced type 2 diabetes model.

Additionally, in the current study, various biochemical and antioxidant (in liver and kidneys) and parameters, as well as histopathological changes in the pancreas were evaluated. The literature suggests that the treatment of rats with streptozotocin alone damages pancreatic β -cells resulting in inadequate production of insulin and thereby these animals manifest with type 1 DM. However, nicotinamide partly protects β -cells of the pancreas via nitric oxide-mediated mechanisms and thereby partly preserves the pancreatic β -cells. Therefore, rats that are treated with nicotinamide / streptozotocin produce type 2 DM. also the antioxidant property of MEPGL might have a role in increasing insulin levels by protecting the β -cells

of the pancreas against oxidative stress-induced cellular injury.[10]

Numerous studies have demonstrated the *in vitro* antioxidant activity and polyphenol content of pomegranate. According to Amjad et al., the antioxidant activity of pomegranate leaves is directly related to the presence of phenolic compounds and antioxidant components which act as hydrogen donors, contributing to the concentration of total phenols.[12]The authors demonstrated that pomegranate n-butanol, ethyl acetate, hydroethanol, and aqueous leaf extracts contained ellagic acid, an efficient free radical scavenger[11] Vinodhini et al. reported that the aqueous extract of pomegranate leaves had the greatest antioxidant activity and contained significant levels of total phenols and flavonoids.The leaf extracts showed antioxidant activity *in vivo* by protecting yeast cells against oxidative stressing agent H₂O₂. The authors found pomegranate a good source of natural compounds with health benefits, which makes it possible to use it in diets to reduce oxidative stress. [13]

IV. OTHER PHARMACOLOGICAL ACTIVITIES

Preliminary research findings suggest that, in addition to its potential benefits for heart, diabetes, skin, teeth, cancer, and so on, the pomegranate may confer a multitude of other health promoting effects in the body. However, more conclusive studies are needed to confirm these effects, because, there are very few references present in the scientific literature to substantiate these results.

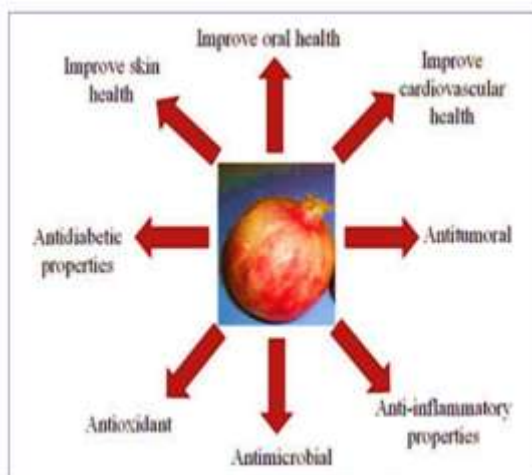


Fig.7 :pharmacological activities of Punica Granatum L.

1. Improved cardiovascular health
2. Antitumoral activity
3. Anti-inflammatory property
4. Antimicrobial property
5. Improved skin health
6. Improved oral health
7. Antihypertensive property
8. Antiviral property
9. Antidiarrheal property
10. Spermquality
11. Obesity
12. Ensure Liver Health

4.1 Improved cardiovascular health:

One of the major risk factors for the development of coronary heart disease is dyslipidemia, which is mainly characterized by elevated levels of low-density lipoprotein cholesterol (LDLC) and/or reduced high-density lipoprotein cholesterol (HDL-C). Oxidation of low-density lipoprotein (LDL) is thought to contribute to atherosclerosis and cardiovascular disease. Oxidation of LDL lipids is thought to render the lipoprotein atherogenic, because oxidized LDL is more readily taken up by macrophages via scavenger receptors. Epidemiological studies have shown that high concentrations of serum total cholesterol and LDL-C are independent risk factors for cardiovascular disease and could produce atherosclerosis. Atherosclerosis, a major degenerative disease of arteries involves a series of inflammatory and oxidative modifications within the arterial wall. Oxidative excess in the vasculature reduces levels of the vasodilator nitric oxide, causes tissue injury, promotes protein oxidation and DNA damage, and induces proinflammatory responses .Oxidative stress induces inflammation by acting on the pathways that generate inflammatory mediators like adhesion molecules and pro-inflammatory cytokines. *In vitro*, animal, and human trials have examined the effects of various pomegranate constituents on the prevention and attenuation of atherosclerosis and LD Loxidation .The several studies has shown that the effect of pomegranate juice consumption by healthy males on lipoprotein oxidation and found that it decreased LDL susceptibility to aggregation and retention and increased the activity of serum paraoxonase (an HDLassociated esterase that can protect against lipid peroxidation) by 20%. [15]

4.2 Antitumoral activity:

The studies shows that pomegranate extract of 3 pomegranate compartments (peels, juice, andseeds) has been shown to in habiting

prostate cancer cell proliferation, invasion and phospholipase A-2 expression. The studies shows that the pomegranate juice and pomegranate extracts were more potent in inhibitors of cell growth than isolated individual polyphenols in cell lines, suggesting synergistic and/or additive effects of several phytochemicals present including proanthocyanidins, anthocyanins, and flavonoid glycosides.[15]

4.3 Anti-inflammatory properties:

Cold pressed pomegranate seed oil has been shown to inhibit both cyclooxygenase and lipoxygenase enzymes in vitro. Cyclooxygenase, a key enzyme in the conversion of arachidonic acid to prostaglandins (important inflammatory mediators), was inhibited by 37 percent by a cold pressed seed oil extract. Lipoxygenase, which catalyzes the conversion of arachidonic acid to leukotrienes, also key mediators of inflammation, was inhibited by 75 percent by a cold pressed pomegranate seed oil. Cold pressed pomegranate seed oil has been shown to inhibit both cyclooxygenase and lipoxygenase enzymes in vitro. Cyclooxygenase, a key enzyme in the conversion of arachidonic acid to prostaglandins (important inflammatory mediators), was inhibited by 37 percent by a CPSO extract. Lipoxygenase, which catalyzes the conversion of arachidonic acid to leukotrienes, also key mediators of inflammation, was inhibited by 75 percent by a CPSO extract. By comparison, a fresh pomegranate juice extract resulted in a 23.8-percent inhibition of lipoxygenase in vitro.

Another in vitro study that may have far-reaching implications for those suffering from osteoarthritis (OA) demonstrated PFE has a significant and broad inhibitory effect on matrix metalloproteinases (MMPs), a subgroup of collagenase enzymes expressed in high levels in arthritic joints and involved in the turnover, degradation, and catabolism of extracellular joint matrix. In pretreated human femoral OA chondrocytes, PFE inhibited IL-1 β -induced destruction of proteoglycan, expression of MMPs at the cellular level, and phosphorylation and activation of mitogen-activated protein kinases (signal transduction molecules involved in MMP expression). The suppression of MMP expression in OA chondrocyte cultures by PFE suggests pomegranate constituents prevent collagen degradation and may inhibit joint destruction in OA patients extract.

By comparison, an FPJ extract resulted in a 23.8-percent inhibition of lipoxygenase in vitro.¹⁴ Another in vitro study that may have far-

reaching implications for those suffering from osteoarthritis (OA) demonstrated PFE has a significant and broad inhibitory effect on matrix metalloproteinases (MMPs), a subgroup of collagenase enzymes expressed in high levels in arthritic joints and involved in the turnover, degradation, and catabolism of extracellular joint matrix. In pretreated human femoral OA chondrocytes, PFE inhibited IL-1 β -induced destruction of proteoglycan, expression of MMPs at the cellular level, and phosphorylation and activation of mitogen-activated protein kinases (signal transduction molecules involved in MMP expression). The suppression of MMP expression in OA chondrocyte cultures by PFE suggests pomegranate constituents prevent collagen degradation and may inhibit joint destruction in OA patients[6]

4.4 Antimicrobial activity:

The only human trials examining the antibacterial properties of pomegranate extracts have focused on oral bacteria.^{49,50,70,71} However, several in vitro assays demonstrate its bacteriocidal activity against several highly pathogenic and sometimes antibiotic-resistant organisms. Brazilian researchers evaluated the synergistic effect of a *P. granatum* methanolic extract with five antibiotics on 30 clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *S. aureus*.⁷⁵ Antibiotics tested were chloramphenicol, gentamicin, ampicillin, tetracycline, and oxacillin.

Although synergistic activity between the pomegranate extract and all five antibiotics was noted in the *S. aureus* isolates, synergy with ampicillin was the most pronounced. A combination of the two increased the lag time to bacterial growth by three hours (over that of ampicillin alone) and was also bacteriocidal as evidenced by a 72.5-percent reduction in methicillin-sensitive organisms and a 99.9-percent reduction in MRSA. Based on earlier research⁷⁶ and the results of this study, the ellagitannin, punicalagin, is thought to be the primary constituent responsible for the observed antibacterial effects. [14]

Another organism that can cause significant disease in humans is enter hemorrhagic *Escherichia coli* (*E. coli* O157:H7), which can present with diarrhea, hemorrhagic colitis, thrombocytopenic purpura, and hemolytic uremic syndrome. *P. granatum* and seven other Thai medicinal plant extracts were tested for in vitro activity against *E. coli* O157:H7. An ethanolic

Pomegranate peel extract, one of the two most effective extracts against *E. coli* O157:H7, was shown to be both bacteriostatic and bacteriocidal, indicating PPE may be an effective adjunct treatment for *E. coli* O157:H7 infection.[6]

4.5 Improve skin health:

Damage to the skin occurs as a consequence of the natural aging process and damage is exacerbated in chronically sun exposed skin. Prolonged exposure to ultraviolet (UV) radiation has been identified as a cause of serious adverse effects to human skin, including oxidative stress, premature skin aging, sunburn, immunosuppression, and skin cancer. studies shows that pomegranate seed oil, but not aqueous extracts of fermented juice, peel, or seed cake was shown to stimulate keratinocyte proliferation in monolayer culture. In contrast, pomegranate peel extract (and to a lesser extent, both the fermented juice and seed cake extracts) stimulated type I procollagen synthesis and inhibited matrix metalloproteinase-1 (MMP-1; interstitial collagenase) production by dermal fibroblasts, but had no growth-supporting effect on keratinocytes. These results suggest pomegranate aqueous extracts (especially of pomegranate peel) promoting regeneration of dermis, and pomegranate seed oil promoting regeneration of epidermis.[15]

4.6 Improved oral health:

Pomegranate contains agents, especially polyphenolic flavonoids, which exert actions that could be considered conducive to good oral health, particularly in relation to gingivitis development. A gel containing pomegranate extract applied 3 times per day for 15 d was effective for patients afflicted by candidiasis associated with denture stomatitis. Mouth-rinsing with pomegranate extracts lowered saliva activities of aspartate aminotransferase, an indicator of cell injury, shows high values with periodontal disease. Studies shows that the effect of the hydroalcoholic extract from pomegranate fruits on dental plaque microorganisms. Additionally, rinsing the mouth for 1 min with a mouthwash containing pomegranate extract effectively reduced the amount of microorganisms cultured from dental plaque.[15]

4.7 Antihypertensive property:

A small clinical trial demonstrated PJ inhibits serum ACE and reduces systolic blood pressure in hypertensive patients. Ten hypertensive

subjects (ages 62-77; seven men and three women) were given 50 mL/ day PJ containing 1.5 mmol total polyphenols for two weeks. Two of seven patients were also diabetic and two were hyperlipidemic. Seven of 10 subjects (70%) experienced a 36-percent average decrease in serum ACE activity and a small, but significant, five-percent decrease in systolic blood pressure.[6]

4.8 Antiviral properties:

The scientific studies evaluated the 4 major polyphenols in pomegranate extracts, EA, caffeic acid, luteolin, and punicalagin and identified punicalagin as the anti-influenza component, because this compound blocked replication of the virus RNA, inhibited agglutination of chicken RBC's by the virus, and had viricidal effects. Indeed, it inhibited the replication of human influenza A/Hong Kong (H3N2) in vitro. Anti-influenza viricidal activity has also been associated with other flavonoid compounds. The pomegranate has been used in phage amplification assays as a viricidal agent. In addition, pomegranate extract has been reported to have microbiocidal effects on HIV-1.[15]

4.9 Ant diarrheal properties:

Studies investigated the antidiarrheal activity of aqueous and alcohol extracts of the pomegranate fruit rind in 3 experimental models using albino rats. The extracts exhibited significant activity in rats when compared to loperamide hydrochloride, a standard antidiarrheal drug. The studies evaluated the antidiarrheal effects of the aqueous extract of pomegranate peels in rats. The results revealed that the extract exhibited a concentration-dependent inhibition of the spontaneous movement of the ileum and attenuated acetylcholine-induced contractions. Studies evaluated the antidiarrheal effect of pomegranate peel extract in rats given an oral dose of 400 mg/kg. The results showed that pomegranate peel extract decreased the number of defecations and the weight of feces in comparison with the control.[15]

4.10 Sperm quality:

Pomegranate juice consumption led to an increase in epididymal sperm concentration, sperm motility, spermatogenic cell density, and the diameter of seminiferous tubules and germinal cell layer thickness; it also decreased the abnormal sperm rate when compared to the control group. In a similar study, suggested that EA has a protective effect against testicular and spermatozoal toxicity induced by cyclosporine A. This protective effect

of EA seems to be closely involved with the suppression of oxidative stress. Therefore, EA may be used combined with cyclosporine A after transplantation and in autoimmune diseases to improve cyclosporine A-induced injuries in sperm quality and oxidative stress parameters.[15]

4.11 Obesity:

According to the World Health Org., there are currently more than 1 billion overweight adults, 300 million of whom are obese. The studies investigated the effects of pomegranate extract (6% punicalagin) in female rats following exposure to a diet containing 20% of the extract for 37 d. The exposure to pomegranate extract resulted in an intake of 4800 mg punicalag in/kg/d. A significant decrease in feed consumption and body weight of the animals during the early part of the study was noted. Lei and others (2007) investigated the antiobesity effects of pomegranate leaf extract in a mouse model of high-fat diet-induced obesity, finding that the extract inhibited the development of obesity and hyperlipidemia. The effects appear to be partly mediated by inhibiting pancreatic lipase activity and suppressing energy intake.[15]

4.12 Ensuring liver health:

Kaur and others evaluated antioxidant and hepato protective activity of pomegranate flowers. The efficacy of extract was tested in vivo and it was found to exhibit a potent protective activity in acute oxidative tissue injury animal model: ferric nitrilotriacetate (Fe-NTA) induced hepatotoxicity in mice. These results indicate pomegranate flowers to possess potent antioxidant and hepatoprotective property, the former being probably responsible for the latter.[15]

V. CONCLUSION AND SUMMARY

This review has highlighted the previous studies related to the antidiabetic and antioxidant activities of pomegranate plant (*punicagranatum* L.). This review shows that the extract of pomegranate (*punicagranatum*) parts like flowers, fruit, peels, rinds, and juice possesses highly antidiabetic and antioxidant activities that are contributed by several phytoconstituents present in extract.

The main compounds that present antidiabetic properties are polyphenols, which may affect glycemia through different mechanisms, including the inhibition of glucose absorption in the gut or of its uptake by peripheral tissues. Also several active chemical constituents like

anthocyanins, oleanolic, ursolic, and gallic acid present in pomegranate shows highly antidiabetic activity and to ameliorate hyperglycemia, hyperlipidemia, oxidative stress, B-cell destruction, formation of advanced glycation end products and sorbitol in diabetic animals.

Similarly, The phenolic compounds and tocopherols present in *Punicagranatum* have been studied for antioxidant activity by using various methods as differential pH methods, HPLC analysis. The hydrolysis of ellagitannins and gallotannins produced two hydroxybenzoic acids, i.e., ellagic acid and gallic acid, respectively, that are responsible for antioxidant activity.

The consumption of pomegranate has grown tremendously due to its reported health benefits. Pomegranate and derivatives, such as juice, peel, and seeds, are rich sources of several high value compounds with potential beneficial physiological activities. The rich bioactive profile of pomegranate makes it a highly nutritious and desirable fruit crop. Accumulating research offers ample evidence that routine supplementation with pomegranate juice or extract may protect against and even improve several diseases, including diabetes and cardiovascular disease, it may even help to prevent and arrest the development of certain cancers, in addition to protecting the health of the mouth and skin. Side effects are very rare. Using concentrated, low-cost pomegranate juice or standardized pomegranate extract capsules offers consumers a way of reaping the broad spectrum of health benefits of this fruit.

REFERENCES

- [1]. Saeedi P, Petersohn P, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract.* 157(2019);10784. Available from: <http://www.sciencedirect.com/science/article/pii/S0168822719312306>.
- [2]. Grossman LD, Roscoe R, Shack AR. Complementary and alternative medicines for diabetes. *Can J Diabetes.* 2018;42(1):154-61. Available from: [https://www.canadianjournalofdiabetes.com/article/S14992671\(17\)30833-X/fulltext](https://www.canadianjournalofdiabetes.com/article/S14992671(17)30833-X/fulltext).
- [3]. Baliga M.S, Shivashankara A.R, Shetty C.B, Thilakchand K.R, Periera N.

- Antidiabetic effect of punicagranatum (pomegranate): A Review Bioactive Food As Dietary Interventions For Diabetes. 2013.
- [4]. Pablo Melgarejo- Sánchez, DámarisNúñez- Gómez, Juan J. Martínez- Nicolás, Francisca Hernández, PilarLegua and Pablo Melgarejo.Pomegranatevariety and pomegranate plant part, relevance from bioactive point of view: a reviewBioresources and Bioprocessing (2021)8:2 <https://doi.org/10.1186/s40643-020-00351-5>.
- [5]. Ashish,Dixit Praveen, SahooJagannath. Pharmacognostical And Pharmacological Activity of PunicaGranatum (Pomegranate): An Overview international journal of research in pharmaceutical sciences DOI:<https://doi.org/10.26452/ijrps.v11i3.2758>.
- [6]. Julie Jurenka, MT (ASCP) .Therapeutic Applications of Pomegranate (Punicagranatum L.): A Review Alternative Medicine Review 2008, number 2(13) :<https://www.researchgate.net/publication/5261934>.
- [7]. Tom H.W. Huang,1, Gang Peng,1, Bhavani P. Kotaa, George Q. Lia, JohjiYamaharab, Basil D. Roufogalisa, YuhaoLia, Anti-diabetic action of Punicagranatum flower extract: Activation of PPAR-g and identification of an active component, Toxicology and Applied Pharmacology 207 (2005) 160–169.
- [8]. Awatef M Hasan^{1*}, Ali AliRedha and QaherMandeel, Phytochemical Investigations of Pomegranate (Punicagranatum) Rind and Aril Extracts and their Antioxidant, Antidiabetic and Antibacterial Activity, Natural Products Chemistry & Research, 2018, 6:4 DOI: 10.4172/2329-6836.1000332.
- [9]. Enas A. M. Khalil,(2004) Antidiabetic effect of an aqueous extract of Pomegranate (Punicagranatum L.) peels in normal and alloxan diabetic rats, The Egyptian Journal of Hospital Medicine Vol., 16 : 92 – 99.
- [10]. Pottathil S, Nain P, Mohamed A. Morsy , kaur J, Bandar E. Al-Dhubiab , Jaiswal S and Nair A. Mechanisms of Antidiabetic Activity of Methanolic Extract of Punicagranatum Leaves in Nicotinamide/Streptozotocin-Induced Type 2 Diabetes in Rats, Plants(2020) 9, 1609; doi:10.3390/plants9111609.
- [11]. Cheurfa M, Achouche M, Azouzi A, Abdalbasit MA. Antioxidant and anti-diabetic activity of pomegranate (Punicagranatum L.) leaves extracts. Foods and Raw Materials. 2020;8(2):329–336. DOI: <http://doi.org/10.21603/23084057-2020-2-329-336>.
- [12]. Sreedevi P, Vijayalakshmi K, Venkateswari R. Phytochemical evaluation of punicaGranatum L. leaf extract. International Journal of Current Pharmaceutical Research. 2017;9(4):14–18. DOI: <https://doi.org/10.22159/ijcpr.2017v9i4.1159>
- [13]. Vinodhini S, ShriPreethi M, NusrathFathima N, Kushwaha SS, Devi Rajeswari V. Antioxidant and free radical scavenging capacity extensively used medicinal plant of Punicagranatum. Asian Journal of Pharmaceutical and Clinical Research. 2016;9(6):140–146. DOI: <https://doi.org/10.22159/ajpcr.2016.v9i6.13941>.
- [14]. Maria G. Miguel*, Maria A. Neves and Maria D. AntunesPomegranate (Punicagranatum L.): A medicinal plant with myriad biological properties - A short reviewJournal of Medicinal Plants Research Vol. 4(25), pp. 2836-2847, 29 December Special Review, 2010 Available online at <http://www.academicjournals.org/JMPR> ISSN 1996-0875 ©2010 Academic Journals
- [15]. M.Viuda-Martos, J.Fernández-López, andJ.A.Pérez-Álvarez (2010) Pomegranate and its Many Functional Components as Related to Human Health: A Review Comprehensive Reviews in Food Science and Food Safetyvol 9 doi:10.1111/j.1541-4337.2010.00131.