SLJoAS Sri Lankan Journal of Applied Sciences

Review Article

# Pomegranate (*Punica granatum*) as a Promising Hypoglycaemic Agent: A Review

A.L.A.P. Randika[a], M.D.T.L. Gunathilaka[b*]

[a] Department of Biomedical Science, Faculty of Science, NSBM Green University

[b] Department of Basic Science and Social Science for Nursing, Faculty of Nursing, University of Colombo

*** Corresponding author email address**: thilina@dss.cmb.ac.lk

(Received 5th June 2023; accepted 21st August 2023)

**Abstract:**

Diabetes mellites (DM) is a chronic metabolic disorder that is caused due to elevated glucose levels which leads to cause most severe effects on the heart, blood vessels, kidneys, eyes, and nerves as complications. Type 1 diabetes mellites is an autoimmune condition caused due to the autoimmune destruction of pancreatic cells. Whereas type 2 DM is mainly caused by insulin resistance. Patients with type 2 DM rely on hypoglycaemic drugs to reduce blood glucose level, which leads to several complications such as hypoglycaemia, weight loss, sleepiness, pain in urination etc. Therefore, research focused on the bioactive compounds present in plant extracts to treat diabetes as long-term use of synthetic drugs may cause side effects. *Punica garantum* (pomegranate) is a plant rich with many medicinal values in indigenous medicine and western medicine. Bioactive compounds present in the juice of the pomegranate fruit such as flavonoids, polyphenols, and other antioxidants help to treat hyperglycaemia and its complications. Therefore, the present review mainly aims how *Punica granatum* aids blood glucose reduction in diabetes and its complications. The present review aims to discuss the potency of *P.granatum* fruit to reduce hyperglycaemia and its complications in diabetes.

Keywords: Diabetes mellitus, Punica *granatum*, Alpha-amylase, Alpha-glucosidase, Hyperglycaemia

## 1. Introduction

The definition of diabetes varies with one's perspective. From the medical perspective it can be defined as a series of metabolic conditions associated with an increase in the blood glucose level due to partial or total insufficiency of insulin. Therefore, diabetes is a condition that requires daily attention to diet, lifestyle, and self-monitoring of the blood glucose level throughout the lifetime [1]. Diabetes is the 6th cause of mortality worldwide. Diabetes accounted for four million global deaths in 2017. The global diabetes prevalence in 2019 is estimated to be 9.3% rising to 10.2% by 2030 and 10.9% by 2045 [2]. Prevalence is higher in urban areas than the rural. The highest number of diabetes is reported to be in China and the lowest is estimated in Lithuania, Estonia, Ireland, Sweden, Luxembourg [2] . Compared to other regions South Asians are more likely to grow diabetes than others due to genetic factors, behavioural and cultural factors [3]. As Sri Lanka is a low and middle-income country most people experiencing rapid transformations including aging, obesity due to material comfort and urbanization. A rapid increase in diabetes patients can be seen (8% - 15%) in the 2000 – 2010s. The latest studies showed that the prevalence of adult diabetes patients in Sri Lanka in 2019 was 23% [4].

Diabetes mellites is of 4 types. They are type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types. Type 1 diabetes is an autoimmune inflammatory disease that is caused due to the destruction of the beta cells of the pancreas, which leads to the release of serum autoimmune markers including glucose, glycated molecules, C- peptide and auto antibodies. These autoimmune markers trigger inflammatory reactions within the body. Type 2 diabetes is a serious condition that may be due to an alteration in insulin production of the pancreas or may be due to the insulin resistance of the patient [5]. Insulin is a peptide hormone that is produced by pancreatic beta cells, and it plays an important role in regulating carbohydrate and fat metabolism in the body [6]. Insulin converts the excess glucose into glycogen by glycolysis and glycogenesis and stores in the liver. Any alteration that alters the insulin action may lead to an imbalance in the blood glucose level.

Alpha-amylase and alpha-glucosidase are enzymes that participate in carbohydrate digestion hence the inhibitors of those enzymes can substantially decrease the postprandial blood glucose level after a mixed carbohydrate diet. Therefore, regulating the action of those enzymes is an important strategy in controlling diabetes. Natural plant extracts have been long used in traditional treatments of diabetes due to fewer side effects compared

to the synthetic hypoglycaemic drugs [7]. Therefore, natural extracts that inhibit carbohydrate hydrolysing enzymes can be used as natural treatment remedies to reduce hyperglycaemia in diabetes [8].

*Punica granatum* is a fruit rich in antioxidants and flavonoids, both of which are known to prevent free radicals from damaging the cells. Fresh juice of pomegranate contains phenolic compounds including gallic acid, caffeic acid, chlorogenic acid and coumaric acid and non-phenolic acids including citric acid, malic acid, oxalic acid, and ascorbic acid which can lead to reduce hyperglycaemia and its complications in diabetes [9]. The present review aims to discuss how the extracts of P.*granatum* fruit led to reduce hyperglycaemia and its complications in diabetes.

## 2. Therapeutic targets of Diabetes Mellitus

This section further explains the therapeutic targets that are used to treat the type 2 diabetes mellites in various aspects.

### 2.1 Alpha-amylase and alpha-glucosidase inhibition

Amylases are of different types, out of them alpha, beta and gamma amylases play an important biological role in carbohydrate metabolism. Pancreatic α-amylase acts on the α-1,4 glycosidic linkages of the insoluble starch molecules within the diet and hydrolyzes the bond. Pancreatic alpha-amylase acts within the lumen of the small intestine and digest large carbohydrates into small sugar molecules such as dextrin and glucose units which leading to cause hyperglycaemia [10].Therefore, the inhibitors of alpha amylases create an environment within the body to delay the carbohydrate breakdown and reduce the postprandial blood glucose level. Flavonoids play a major role in medicinal chemistry. Some tests revealed that flavanol glycosidases can inhibit the α- amylase activity. Flavanol glycosidases are compounds that are derived from the glycation of flavonoids such as hesperidin, quercitrin, rutin [11].

Alpha-glucosidase enzyme is a digesting enzyme that catalyzes the conversion of disaccharide into glucose which is the last step of carbohydrate digestion. Therefore the natural extracts that can inhibit the action of alpha-glucosidase enzyme block the breakdown of starchy foods and slow down the absorption of dietary sugars [12].

### 2.2 Inhibition of Advanced Glycation End Products

Advanced glycation end products (AGE) are a heterogenous group of chemical compounds that are formed due to non-enzymatic glycation with proteins, lipids and nucleic acids. AGEs are also identified as key players in diabetic progression and diabetes-induced vascular complications [13]. Adjacent AGE molecules can crosslink with each other and with certain proteins, altering their structure and interfering with their functional capabilities. Due to the creation of covalent crosslinks, biologically active proteins and enzymes are inactive and become resistant to proteolytic degradation and affect intracellular signalling and contributes to a variety of metabolic and physiological disturbances [14]. Furthermore, the interaction of AGEs with a diverse set of cell surface receptors induces a slew of cell-mediated pathophysiological reactions that may provide mechanistic linkages between the beginning of diabetes mellitus and AGE accumulation. AGEs activate various signals that can directly impact on cellular function and metabolism through the upregulation of oxidative stress and inflammation.

### 2.3 Inhibition of aldose reductase enzyme

The aldose reductase enzyme is the first enzyme in the polyol pathway in which glucose is converted into fructose in the presence of NADPH. In this pathway glucose is first converted into sorbitol and the reaction is catalyzed by sorbitol dehydrogenase using NAD+ as a cofactor [15]. In hyperglycaemia, increased glucose concentration within the blood enhances the aldose reductase activity. Increasing of glucose flux in the pathway and formation of reactive oxygen species activates the aldose reductase enzyme. Enhanced activity of reductase enzyme lowers the NADPH / NADP+ ratio. This may cause an impact on the other NADPH-dependent enzymes such as nitric oxide synthase. Decreased levels of nitric oxide result in nerve conduction and end up with microvascular degeneration. Inhibiting this enzyme reduces the complications of diabetes mellites [16].

### 2.4 Inhibition of Sodium-glucose co-Transporter -2 (SGLT-2)

Another newest hyperglycaemic therapeutic target is the inhibition of the sodium-glucose cotransporter 2 (SGLT 2). SGLT 2 is a human protein that is encoded by the SLC5A2 (Solute carrier family 5) gene. It plays a major role of the kidney in maintaining homeostasis. Normally urine is free from glucose, but it is different in diabetes mellites. In diabetes conditions the filtered glucose level exceeds the transport capacity of the kidney tubular system and thus glucose appears in urine (glycosuria). This therapeutic approach is named ‘pharmacological inhibition of kidney SGLT – 2’ which inhibits renal reabsorption of glucose and increases the urinary excretion of glucose which leads to reduction in plasma glucose levels. Therefore SGLT – 2 inhibitory agents improves the glycaemic control of the body [17].

## 3. Bioactive compounds in *Punica granatum*

P.*granatum* is a long-lived small tree that belongs to the Punicaceae family which maximum grows up to 3 to 5 meters. The edible and delicious fruit of this tree is a round shaped berry, and it is covered with a thick reddish covering (figure 1. a). The cover is dry and consists of two layers as outer hard layer (pericarp) and the soft inner layer (mesocarp) (figure 1. b).

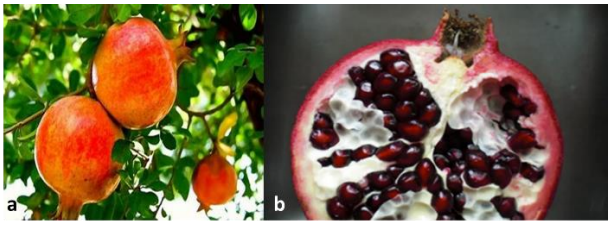


Figure 1: Outer (a) and inner (b) appearance of *Punica granatum*

All the compartments of the pomegranate plant such as peel, juice, seed, flower, bark, leaf, and roots stimulate different pharmacological activities which effect all over the body. All the compartments contain various phytochemicals which exhibit numerous medicinal properties. [18]. Bioactive compounds in natural plants are known as phytochemicals that have an impact on main metabolic processes exhibiting several health benefits. Due to its nutritious qualities and bioactive components, pomegranates are now recognized as a superfruit. The main sugars present in *Punica granatum* are composed of glucose, fructose, sucrose, and maltose with a combination of vitamin C, $B_1$, $B_2$ and beta carotene [15]. Other significant organic acids in *Punica granatum*.L include malic acid, fumaric acid, oxalic acid, succinic acid, citric acid, and tartaric acid . The pomegranate fruit is the main edible part, and it is a high source of hydrolyzable tannins, anthocyanins, and phenolic acids, despite the fact that other sections of the pomegranate tree contain diverse classes of phytochemicals such as flavonoids, hydrolyzable tannins, and condensed tannins [19].

Phenolic compounds are major secondary metabolites that present in *Punica granatum*. Other than phenols flavonoid group is a major group of phenolic compounds which present in *Punica granatum*. Luteolin and its glucosides, quercetin, kaempferol, delphinidin, catechin, epicatechin, gallocatechin, epigallocatechin and proanthocyanins (condensed tannins) are flavonoids which are present in pomegranate juice extract. The extraction of the whole fruit of pomegranate contains high flavonoid content (30%) more than that in the peel extraction [20]. Higher amount of flavonoids are present in the pomegranate peel in its glycoside form [21]. Anthocyanin is responsible for the colour and mainly six anthocyanins, which include cyanidins (red and deep red), pelargonidin (orange and red colours), and delphinidins (blur and purple colours). Flavonoids are reported to exhibit anti-diabetic, anti-inflammatory, preventing mutation, anti-cancer and controlling important cellular enzyme activities [22]. Phenolic compounds are absorbed in the small intestine, duodenum, and jejunum through digestive enzyme activity, including cytosolic β-glucosidase (CBG) in liver, kidneys, and intestine. Phenolic compounds can be absorbed through passive diffusion or transporters like P-glycoprotein and sodium-glucose cotransporters (SGLT) in enterocyte membranes. Polyphenols' transport and permeability are influenced by molecular weight, lipophilicity, stereochemistry, and hydrogen bonding groups [23]. High molecular weight proanthocyanins are degraded, while gallic acid and isoflavones are easily absorbed. [24] [25]

Tannins are found in high quantities in the pericarp and mostly in the wild species compared to the commercial varieties. Tannins are of two types as hydrolyzable and condensed. Hydrolyzable tannins are found in the whole plant in juice, in fruit or seeds, leaves or bark and in peel [26].

Fatty acids are present in the pericarp, in the leaf, in the fruit, peel, seeds, whole fruit and juice in different concentrations.

Other than these there are more compounds. Vitamin $B_6$ is crucial for immune system function in older people and for the smooth operation of metabolic processes including fat and protein metabolism [27]. Vitamin C aids in iron absorption, tissue regeneration and repair, scurvy prevention, reduction of triglycerides and cholesterol, and protection against heart disease [28]. Positive effects of vitamin E on immunological function, oxidative damage defence, and cancer prevention are all possible [29]. $B_1$ vitamins aid in calming and maintaining a healthy neurological system [30]. They also assist with adrenal function. Other than vitamin $B_1$, pomegranate contains vitamin $B_2$, $B_3$, $B_5$, $B_9$.

*P.granatum* is rich in calcium, iron, phosphorus, sodium, zinc, copper, manganese, selenium, and fluoride. Pomegranate is a rich source of iron which can quickly replenish iron deficiency anaemia [31]. Pomegranate fruit powder is also used as a spice for food because it eases digestion, and its extract is helpful for treating diseases such as ordinary diarrhoea, dysentery, and stomach disorders. Pomegranate is particularly good for patients who are suffering from ulcerations anywhere in the gut because of its cooling effects on the body [32].

**Table 1**:- Bioactive compounds contain in *Punica granatum*.

| COMPARTMENT | BIOACTIVE COMPOUNDS |
|---|---|
| JUICE | Anthocyanin, glucose, ascorbic acid, ellagic acid, ellagitannins, caffeic acid, catechin, quercetin, delphinidin, Punicalin, punicalagin, rutin, minerals, amino acids, vitamins [23] [18][19] |
| ROOTS AND BARK | Punicalin and punicalagin, piperidine, alkaloids, ellagitannins [18] |
| FLOWERS | Gallic acid, ursolic acid, triterpenoids, maslinic acid, Asiatic acid, Punicalin, ellagic acid [18] |
| LEAF | Tannins, flavone glycosides, luteolin, apigenin, Ellagic acid, fatty acids [18] |
| PERICARP **(PEEL AND RIND)** | Phenolic punicalagins; gallic acid and other fatty acids, catechin, EDCG, quercetin, rutin, and other flavanols, anthocyanidins, cinnamic acid, chlorogenic acid, vitamin [25]. |
| SEED OIL | Ninety-five percent punicic acid, ellagic acid, other fatty acids, sterols, conjugated linolenic acid, linoleic acid, oleic acid, stearic acid, eleostearic acid, catalpic acid [18] |

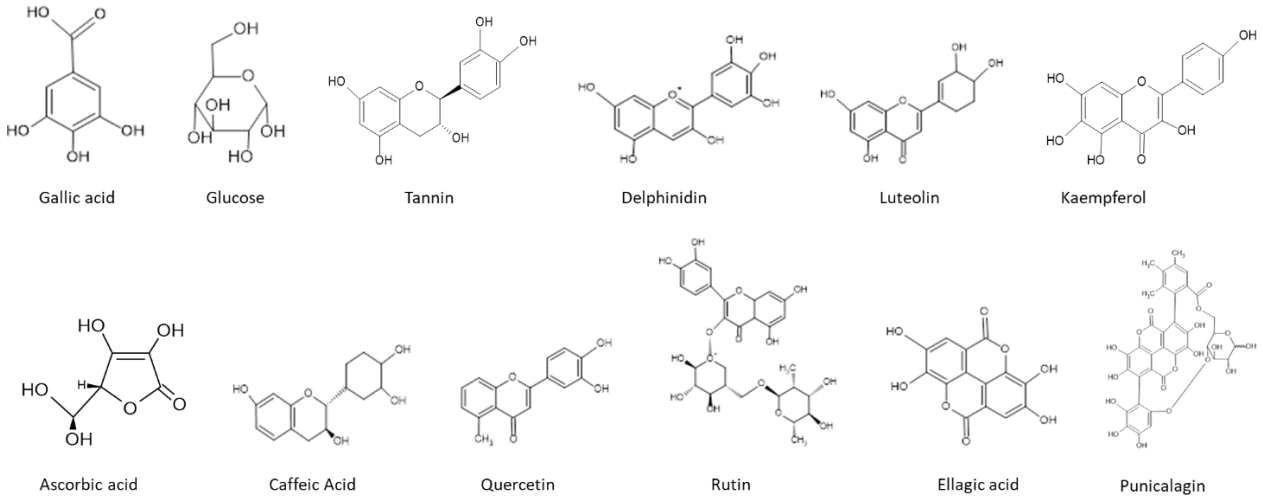


**Figure 2**:- Molecular structures of the compounds include in *Punica granatum* fruit extract.

## 4. In vitro/in vivo hypoglycaemic effect of *Punica granatum*

In this section, tests that have been done by aiming at the above-mentioned therapeutic targets were further discussed.

A study has proved that rutin which extracted from *Punica granatum* could induce glucose absorption from the small intestine by the inhibition of alpha-glucosidases and alpha-amylases which involves in the digestion of carbohydrates. Rutin was known for its effect on increase in the secretion of insulin. In the beta cells of rats, induced the insulin secretion which is induced by glucose and preserves the glucose-sensing ability at a high glucose condition. The inhibition of glucose absorption within the intestine leads to preventing the sharp rise in the post-prandial blood glucose level. The reduction in the blood glucose level also can be resulted by stimulating the secretion of insulin from the beta cells and increasing the blood glucose uptake of the tissues. Diabetes nephropathy is a major microvascular complication and end-stage renal disease. The pathogenetic mechanisms of diabetic nephropathy involve hyperglycaemia-induced metabolic and hemodynamic alterations. Chronic hyperglycaemia increases AGE formation, induces oxidative stress, stimulates PKC, and enhances the polyol pathway. Rutin supplementation has been shown to improve kidney function in diabetic subjects. Oral administration of rutin for 10 weeks reduced proteinuria, decreased blood urea nitrogen (BUN), and serum creatinine levels in diabetic rats. Rutin also decreases oxidative stress, AGE formation, and content of hydroxyproline and collagen in renal tissue.

It also increases the activity of matrix metalloproteinases (MMPs) in the kidney, which play a crucial role in maintaining the balance between synthesis and degradation of ECM. Rutin can suppress the signalling pathway of TGF-β1/Smad, which is involved in ECM accumulation, preventing renal fibrosis and mesangial expansion [25].

A study was conducted to investigate the effect of quercetin, glycosylated conjugated rutin and the combination understand the possible mechanisms that they used in hydrolyzing the alpha-amylases and alpha-glucosidases which are associated with type 2 diabetes mellites. Rutin and quercetin, which are the main components in pomegranate juice extract, could inhibit some pro-oxidants which induce lipid peroxidation in the rat pancreas. In addition, rutin has a stronger inhibition on alpha-glucosidase ($IC_{50}$ =0.037µM) activities. Similarly, quercetin has an inhibitory effect on alpha-amylase ($IC_{50}$= 0.061µM) on alpha-glucosidase ($IC_{50}$ = 0.038µM) [33].

A rat study was conducted by extracting ellagic acid and punicalagin that are contained in the pomegranate juice extract to assess the inhibitory activity of alpha-glucosidase enzyme. Two isomers of ellagic acid, punicalagin and Punicalin together effectively inhibit the rat intestinal glucosidases with an $IC_{50}$ value of 140.2 and 380.9µmol/L [34].

Another in vitro study was conducted on the inhibition of alpha-glucosidase enzyme using the polyphenols contained in the pomegranate juice extract. Pomegranate juice exhibits a similar inhibitory effect as acarbose, which is a reference inhibitor of the alpha-glucosidase enzyme. Main polyphenols such as punicalagin and ellagic acid that are contained in pomegranate juice results the inhibition. Punicalagin acts as the best inhibitor with an $IC_{50}$ value of 0.055mg/mL. Other than the glucosidase inhibition punicalagin and ellagic acid act on the inhibition of dipeptidyl peptidases -4 (DPP-4) with $IC_{50}$ values as 0.059mg/mL, 0.025mg/mL respectively [35].

Oxidative stress arises due to the disproportion between the antioxidants and the oxidants which contributes to arise in both physiological and pathological conditions. Upregulation of aldose reductase enzyme is carried out by reactive oxygen species. A rat study was conducted using the pomegranate juice extract to analyse the inhibition of aldose reductase enzyme and elimination of consequences of oxidative stress that arises with the accumulation of reactive oxygen species. which can provide long-term diabetes complications such as macrovascular and microvascular disorders. The study shows the induction of enzymatically active aldose reductase in rat smooth muscle cell lines by various oxidative stresses. The physiological reason remains unclear, but recent observations suggest two possible explanations. The best natural substrates are glucose with lower K1 values ( 9 and 34 tm, respectively). [36].

In diabetic conditions, the accumulation of polyol in lens fibres is most common, which may cause an influx of water and generation of osmotic stress which leads to cataracts. This study was conducted to evaluate the inhibitory activity of the aldose reductase enzyme and the anticataract activity of the methanolic extract of *Punica granatum.* Goat lenses were used to evaluate inhibitory activity. Methanolic extract of pomegranate exhibited in vitro aldose reductase inhibition activity with $IC_{50}$ of 300.43(4.36) µg/ml. Therefore this study proves that goat lenses treated with methanolic pomegranate helps to prevent the formation of cataracts by glucose [37].

An in vitro test has been done to analyse the advanced glycation end products crosslink cleaving activity of pomegranate extracts and pomegranate-derived compounds. As for the comparison of crosslink cleaving actions, 6 hydroxy benzenes compounds were used. Ellagitannins contained in the pomegranate juice was involved with its mechanism and some of the compounds had collagen crosslinks cleaving activity which corelates with advanced glycation end products crosslinking activity. Pomegranate extracts and compounds exhibited AGE and collagen crosslink cleaving activity, with a significant positive correlation among samples ($r = 0.635$, $p = 0.034$) [38] .

Another in vitro test has been done on inhibiting the formation of advanced glycation end (AGE) products scavenging reactive carbonyl species. Punicalagin had the strongest inhibitory effects on all the 3 stages of glycation. Moreover, pomegranate extract and the purified phenolics all exhibited methylglyoxal scavenging activity by scavenging reactive carbonyl species, which might be one of the mechanisms for the inhibitory effect of AGEs formation. Pomegranate extract has a strong inhibitory effect on middle-stage glycation, even at low doses, with 6.29% inhibition. Its inhibitory effect increases to 87.91% when concentration is increased to 100 µg ml $^{1}$. Compounds punicalagin, gallic acid, ellagic acid, Urolithin A, and Urolithin B all show anti-glycation activities and inhibit the formation of middle-stage fluorescent AGEs. Punicalagin has the strongest inhibitory effect, with an IC50 value of 47.32 µM. gallic acid and ellagic acid are more potent glycation inhibitors than aminoguanidine. Urolithin A and Urolithin B have similar anti-AGE activities with aminoguanidine [39].

Another study has been conducted to determine the potential ability of *Punica granatum* to scavenge free radicals generated in alloxan female rats. This study proved that *Punica granatum* has an in vivo prevention effect against the damage of DNA fragmentation of the alloxan rats due to the free radical scavenging ability. Therefore, this confirms the antioxidant potential of pomegranate extract which leads to decreases oxidative stress-related diseases. The study found that pomegranate administration significantly increased glucose levels in diabetic rats, while the administration of peel or juice significantly decreased glucose levels. The administration of pomegranate significantly increased insulin levels in rats with diabetes who was treated with pomegranate peel compared to the diabetic rats who were fed with pomegranate juice extract. However, the activity of alpha amylase decreased in above groups, and an inhibition in alpha amylase activity was observed in pomegranate juice treated rats more than in pomegranate peel treated rats [40].

Ellagic acid has a protective effect against free radical-induced damage such as gastric lavage, hepatic injury, and hyperlipidaemia. A rat test have been conducted by extracting ellagic acid from *Punica granatum* fruit juice to assess the anti-inflammatory effects of ellagic acid, stated that ellagic acid is known to exhibit its pro-oxidative action of some metals such as nickel and iron and decrease the DNA damage that cause due to oxidative stress [41]. Various pro-inflammatory cytokines, such as macrophage MIF, are released and play important roles in mediating inflammatory responses. MIF has been demonstrated to enhance inflammation by inducing nuclear translocation of NF-B and chemotaxis of peripheral blood mononuclear cells. According to [23] ellagic acid (50 M) suppresses MIF tautomerize activity and MIF-mediated pro-inflammatory reactions in peripheral blood mononuclear cells (IC50 4.77 0.52 M). Although the specific mechanism is unknown, the scientists speculate that ellagic acid's potential to suppress tautomerase activity or the cytokine's tautomerase-active site may have contributed to the inhibition.

Another test exhibits the antioxidant properties of pomegranate juice by using a rat model of diabetes. Diabetes-induced rats were administered daily with the pomegranate juice and the results of the treatment specify that in the reduction of the levels of 8 hydroxy-2'deoxyguanosine and malondialdehyde which is a marker of oxidative DNA damage. Glutathione level and glutathione peroxidase activities were higher in pomegranate juice- administered rats compared with other diabetes rats' group ( p= 0.010, p= 0.042 respectively) [42].

## 5. Conclusion

*Punica granatum* is a fruit rich in various antioxidants, polyphenols, flavonoids, fatty acids, vitamins, and minerals. Rutin which is a major phytochemical that contain in pomegranate juice induce the glucose absorption by inhibiting the alpha amylase enzyme which leads inducing the glucose absorption in the small intestine. Rutin also have the ability of inhibiting the alpha glucosidase enzyme which involve in converting oligosaccharides in to glucose. Punicalagin which is a major component in pomegranate juice which is known for the ability to inhibit aldose reductase enzyme and reducing the formation advanced glycation end products. Ellagitanins also have the ability to reduce the formation of advanced glycation end products. Phlorizin is a SGLT 2 inhibitor which effect on regulating the glucose excretion through the proximal convoluted tubule in the nephron. With the inhibition of SGLT 2, it increases the glucose excretion through urine and regulate the glycaemic control in the body. As there are no evidence of the hypoglycaemic potential of Sri Lankan varieties of Punica granatum, it is warranted to determine the potency of Sri Lankan varieties of *Punica granatum* extract to reduce hyperglycaemia and its complications in diabetes. As there are no evidence of the hypoglycaemic potential of Sri Lankan varieties of *Punica granatum*, it is warranted to determine the potency of Sri Lankan varieties of *Punica granatum* extract to reduce hyperglycaemia and its complications in diabetes.

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