REVIEW ARTICLE

Promising Antidiabetic Effects of Pomegranate Fruit Parts

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ABSTRACT

Diabetes is a physiological illness that develops as because of decreased insulin secretion and/or its and /or how it functions within the body. Food metabolism becomes altered as a result of low or inactive insulin. As the illness worsens, the body begins to experience pathological alterations such as nephropathy, retinopathy, and cardiovascular problems. Diabetes mellitus is treated through oral hypoglycemic agents, which are synthetic drugs. As there are many side effects are associated with a longer duration of treatment of synthetic drugs, there is need to develop herbal medicine. There is much evidence that almost all parts of the pomegranate fruit help avoid and control numerous illnesses and conditions, such as diabetes. This review highlights the pathophysiological conditions of diabetes and also summarizes many laboratory and clinical studies of pomegranates that have examined the pomegranates its elements with regard to physiological and biochemical events of diabetes and related considerations.

Keywords: Diabetes mellitus and its types, Peel extract, Arils extract, Flowers extract, Punicalgin.

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INTRODUCTION

Hyperglycemia brought on by abnormalities in insulin secretion, action, or both is the hallmark of a class of metabolic illnesses known as diabetes mellitus (DM). Organs in various systems, like eyes, excretory systems, nervous systems, and cardiovascular systems, stop working as a result of chronic hyperglycemia and varied degrees of impairment in the metabolism of proteins, lipids, and carbohydrates.[1] Nowadays, it is widely acknowledged that diabetes is a pandemic that is only now starting to spread over the world and that it impacts almost every country, demographic, and economic system. Industrialization and lifestyle changes have significantly impacted society, politics, the environment, and interpersonal relationships over the past 50 years.[1] The International Diabetes Federation (IDA) reported that 415 million people had diabetes in 2015, and it is expected to rise to 640 million by the year 2040. About 50% of diabetes patients are unaware of their illness, which increases the likelihood that they may develop diabetic complications. Sadly, the cost of controlling diabetes can occasionally become prohibitive in terms of the resources required and the number of civilian deaths.[2] In 2015, diabetes and its associated issues accounted for over 12% of worldwide healthcare spending despite being linked to over 5.0 million deaths.[3]

Polyuria, fluid retention, loss of weight, sometimes link with polyphagia, and hazy eyesight are signs of severe hyperglycemia. Along with prolonged hyperglycemia, physical retardation and sensitivity to specific illnesses are possible complications. Many complications related to DM include dental disease, dysfunction of peripheral nerves, kidney failure, retinopathy, cardiac complications, stroke and diabetic foot syndrome.[3,4] On the basis of etiology and pathophysiology, DM is classified as follows (1) Type 1 diabetes mellitus (T1DM), (2) Type 2 diabetes mellitus (T2DM), (3) Gestational diabetes mellitus (GDM) and other specific types of diabetes.

Type 1 diabetes mellitus or, juvenile diabetes or insulin-dependent diabetes, is a long-term illness. It is a genetic disease caused as a result of the devastation of the function of beta cells of islets of Langerhans that are present in the pancreas.[5] Type 2 diabetes mellitus is a genetic condition resulting in insulin resistance or deficiency. It is also known as adult-onset diabetes. Several genes are involved, most of which are still unknown. These genetic components control a number of biochemical processes related to cell function, such as the production of β-cells, insulin secretion, and insulin's activity at the cellular level. The generation of an enzyme is regulated by a distinct gene for every phase of this procedure. Any one of these genes can have a defect that restricts the synthesis of enzymes and prevents insulin from doing its job. Such a barrier

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can inhibit the absorption of fatty acids and sugars by fat cells, enhance glucose absorption by the liver, increase triglyceride degradation, and result in numerous metabolic abnormalities. As a result, it might be challenging to comprehend the physiology of these complex disease.[6]

Gestational diabetes mellitus (GDM) is a class of diabetes observed in women who experience diabetes during her pregnancy. B-cell deficits and elevated tolerance to insulin characterize GDM. In many circumstances, particularly in areas where diabetes and obesity are highly prevalent. These problems probably exist before pregnancy. The physiological alterations that transpire during gestation increase the stress on β-cells. Because of these pre-existing anomalies, women with a history of gestational diabetes are more likely to acquire type 2 diabetes (T2DM) in subsequent years after delivery.[7]

One of the major healthcare issues of the 21st century is diabetes, particularly type 2 diabetes. Diabetes has grown to be a greater problem during the last 20 years, both in industrialized and developing nations. Diabetes is becoming more common among younger generations, which means that its effects will probably get worse. Diabetes can negatively affect productivity through premature morbidity and mortality. Since many phytoconstituents show significant antidiabetic activity, the development of phyto-formulations increased. Using pure bioactive molecule as compared to using whole fruit or other crude preparations for therapeutic or experimental reasons have several advantages. Novel drug delivery dosage forms provide higher bioavailability and ultimately higher therapeutic value against specific diseases. Pharmaceutical nanotechnology includes nanotools like liposomes, carbon nanotubes, niosomes, bilosomes, and phytosomes that improve the solubility and bioavailability of herbal extracts.[8, 9]

Various antidiabetic medicines are being developed using nanotechnology, showing significant potential. Silver nanoparticles showed notable diabetic wound healing activity on alloxan-induced diabetic rats. Administration of a single dose of silver nanoparticles lowered blood glucose. The generated Ag-NPs have the potential to be better antibacterial agents for the treatment of *P. aeruginosa*-contaminated wounds caused by diabetes, according to the current study.[10] Nanotechnology can be used as a promising tool that improves the bioavailability of pomegranate herbal extract and produces desired antidiabetic effect.

Pathophysiology of Diabetes Mellitus

Usual physiology consists of food that we eat is broken down in the digestive system and absorbed into the blood flow. While some of the food is used right away, the majority of food is kept for later use. Particularly, this applies to fats and carbohydrates. Fat cells are where the fat is kept in order to be used as fuel. Carbohydrates are preserved as glycogen in the cells of the liver and muscles for later use as fuel, particularly for the central nervous system, which runs entirely on glucose. Insulin is required to transport glucose into the cells for use as fuel or storage. Additionally, it aids in the import of amino acids by all tissues and the preservation of fatty acids by fat cells. The effects of insulin deprivation thereafter cause a reverse of such mechanisms, thereby resulting in a condition similar to starving.[11]

Increased blood glucose levels, and physiological and behavioral actions are closely related. When blood glucose level is elevated, when the brain notices it, it signals the digestive system and other organs to decrease its effects *via* sensory neurons.[12] The pancreas produces insulin from the beta cells of Langerhans as nerve signal is received. Released insulin is then stored in the cellular compartments. It subsequently enters the blood and travels to the body's cells via the circulatory system. A series of intracellular processes activated after the interaction of insulin with insulin receptors. Each of these is performed by a distinct enzyme, which leads to the synthesis of a new protein known as a glucose transporter. Higher molecular weight nutrients like protein and glucose are readily taken in by cells when the glucose transporter moves to the cellular membrane or goes through it. Glucose transporter protein is produced by peroxisome proliferator-activated receptor-γ enzyme by producing messenger ribonucleic acid.[13] This enzyme also prevents the destruction of tissues occurs in hyperglycemia. Different types of cells need insulin for a variety of reasons. It promotes the preservation of important nutrients in the cells and their absorption into the cells. Insulin stimulates the production of glycogen and fat-producing enzymatic agents and it controls the decomposition of glycogen and fat-producing enzymes. In very little quantity glucose can also be synthesized from liver from gluconeogenesis. Among the most significant mechanisms causing the increased blood glucose level, either from insulin insufficiency or from insulin resistance, is glucose synthesis by the hepatic cells.[12,14]

In T1DM, degeneration of beta cells occurs from genetic or environmental factors that cause deficiency of insulin secretion. Along with beta cells, pancreatic alpha cell secretion function also disturbed and causes increased glucagon formulation. Usually, high blood glucose level causes a reduction in glucagon release; whereas, in people with T1DM, hyperglycemia has no effect on glucagon release (Figure 1).[15]

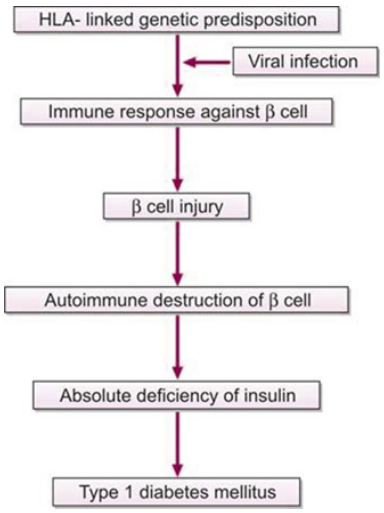

Figure 1: Pathogenesis of type 1 DM

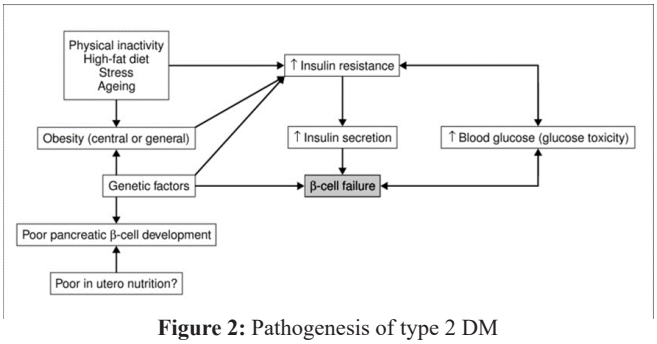

Figure 2: Pathogenesis of type 2 DM

In T2DM, insulin resistance-related reduced insulin action and pancreatic beta-cell dysfunction-related decreased insulin production are the two primary pathophysiological abnormalities associated with diabetes where the pancreas makes less insulin than used to, and your body becomes resistant to insulin. Most cells change as a reaction to increased insulin resistance, which can offset the high demand for insulin and boost its supply. Generally speaking, the level of insulin resistance determines how little serum insulin is needed to sustain appropriate equilibrium of glucose, even if the amount is usually higher in relative terms (Figure 2).[16]

Treatment of diabetes includes regulation of blood glucose level and many physical activities with proper diet plan. Nowadays, T1DM treated with insulin therapy and T2DM treated using hypoglycemic agents.[17] Many previous incidences cause limited use of glitazones and other hypoglycemic agents that are used to cure T2DM. Many synthetic drugs show side effects on complications of diabetes. Proactive steps are necessary to combat the rising rates of diabetes and obesity. Peroxisome proliferator-activated receptor (PPAR) regulation is a choice for developing side effects-free formulation. Bioactive molecules from the plants that control PPAR-linked processes can be used to form standardized formulations. According to the authors, PPAR activators (α, β/γ, δ ligands) are an effective therapeutic option to treat metabolic diseases. These ligands lower serum triglyceride (TG) and glucose levels, enhance insulin sensitivity, increase high-density lipoprotein (HDL) levels, and lower the danger of developing adult-onset diabetes. Pomegranate is a potential plant in this situation.[18,19]

Pomegranate is also known as *Punica granatum* Linn, a family of Punicaceae. In traditional Indian medicine, several portions of this plant are being used to treat various illnesses, most notably diabetes. In laboratory and clinical trials pomegranate juice was found to be efficient in reducing cardiac risk factors, and oxidation of low-density lipoproteins. Seeds and juice of pomegranate are well known for its use in various purposes like skin toning nose bleeding. Also, it is used as a nutritional medication for heart, skin, throat, lungs, eyes.[20] Phytochemical constituents of pomegranate show many pharmacological and toxicological properties that contain antioxidant, anti-inflammatory, anti-cancer and so on.[21,22]

Chemical composition of a pomegranate can be given according to phytoconstituents present in each part of the pomegranate. Peels contain hydrolyzable tannins, phenolics, flavonoids, ellagitannins, proanthocyanidine chemicals, minerals, and complex polysaccharides. The arils comprise water, sugars, pectin, organic acids, phenolics, and flavonoids (mostly anthocyanins). Seeds composed with many nutritional metabolites.[23] Oil derived from seeds is high in polyunsaturated fatty acids such as linolenic and linoleic acids. Seeds also contain lipids such as punicic acid, oleic acid, stearic acid, and palmitic acid.[24,25]

Indications that Pomegranate Reduces the Risk of Diabetes

Pomegranate seeds and flowers are being used for centuries for management of diabetes, heart disease. Recent advances in research facilitate an understanding of the pharmacological studies of this fruit. Various laboratory and clinical studies have demonstrated that pomegranate has potential antidiabetic activity.

Effect of pomegranate peels

In obese mice produced by a high-fat diet, pomegranate peel extracts have been demonstrated to lower inflammation and low-density lipoprotein (LDL) cholesterol.[26] Aqueous pomegranate peel extract reduced lipid peroxidation in the heart, liver, and kidneys and blood glucose levels at 200 mg per kg. Pomegranate peel extract, which is high in polyphenols and lowers fasting serum glucose and raises insulin levels while also having an anti-lipid peroxidation effect, was administered to rats with diabetes induced by alloxan. In multiple animal intervention experiments, the extract improves glycemic control, increases the number of relative beta cells in rats with diabetes produced by alloxan, and decreases hepatocellular oxidative damage to lipids and circulating glucose levels in normal rats.[27]

An additional 3,5-dinitro salicylic acid assay experiment was conducted to explore the antidiabetic properties of pomegranate peel. Peel extract impeded the activity of α-amylase, an enzyme necessary for the breakdown of starch, and limited the conversion of oligosaccharides into glucose. Therefore, serum glucose levels were lowered by α-amylase blocking. Acarbose, the positive control, demonstrated a 64.07 ± 1.43% restriction of α-amylase activity.[28]

Methanolic extract of antioxidant-rich pomegranate fraction was tested on three parameters i.e., human low-density lipoprotein oxidation, lipid peroxidation, and hydroxyl radical scavenging activity. The extract considerably suppressed the thiobarbituric acid technique, hydroxyl radical scavenging activity, and LDL oxidation at 100 ppm, with the results being 56, 58, and 93.7%, respectively.[29]

Author assessed the impact of activity-based pomegranate peel separation on extracts made by sequential extraction followed by its fractionation's antidiabetic potential. According to the findings, several fractions' antioxidant and antidiabetic activities dramatically increased after crude extracts were fractionated. The peel active fraction's antidiabetic effects could be attributed to increased glucose absorption and a-glucosidase inhibition. By preventing LDL oxidation and

ACE, It was discovered that the active portion helped to lessen heart problems related to diabetes.[30,31]

The effects of peel extract on circulating glucose and levels of insulin in beta cell counts were investigated in healthy and diabetic rats for 28 days of treatment. The results showed that aqueous extract dramatically reduced serum glucose levels while insulin amount went higher in normal and insulin resistance treated rats. Beta cells were improved in pancreas. It was determined that by stimulating the renewal of beta cells, pomegranate peel water extract can lower blood glucose levels.[32]

Effect of pomegranate arils

Study showed that aqueous extract of aril showed highest restriction of α-amylase when observed with petroleum ether, and dichloromethane extracts.[28]

When diabetic mice were given pomegranate juice, their peritoneal macrophages' total peroxide level significantly decreased. Pomegranate Juice sugar fraction exhibited potential antioxidative effects on the J774 macrophage cell-line and on mouse peritoneal macrophages under diabetic conditions examined by higher oxidative stress. Glucose-containing juice sugar fraction decreased macrophage oxidative stress.[33]

Methanolic extract of seeds of pomegranate was examined for hypoglycemic activity. The 150, 300 and 600 mg/kg seed extract was given orally to streptozotocin-induced diabetic rats. Deplition in blood glucose level was observed by 40, 47, 52%, respectively, at the end of 12 hours. About 10% higher reduction in blood glucose level was observed as compared to positive control, chlorpropamide, known oral hypoglycemic agent.[34, 35]

Effect of pomegranate flowers

In a folk medicines flowers are used for the treatment of pomegranate. Hydroalcoholic (50% v/v) extract of flower has been found to have hypoglycemic activity when extract given to the normal and alloxan induced diabetic rat. Extended oral therapy of flower extract of pomegranate (500 mg/kg) to Zucker fatty diabetic rats reduced heart triglycerides, plasma triglycerides, total cholesterol, and fatty acids.[36]

The peroxisome proliferator-activated receptor-a is activated by pomegranate flower extract (PFE). PPAR-a is a cardiac transcription factor that has a role in fatty acid absorption and oxidation in myocardial energy production, because of activation of PPAR-a, the absorption of lipids reduced. Due to this there could be decrease in triglyceride content in tissue. These findings show that pomegranate flower can be used as a nutraceutical to treat and prevent chronic illnesses with hyperlipidemia and impaired glucose metabolism.[37]

The primary substances with antidiabetic characteristics are polyphenols, which can influence blood sugar levels through a variety of mechanisms, such as by preventing gastrointestinal absorption of glucose or peripheral tissues from absorbing it. Diacetylated anthocyanins were found to have hypoglycemic effects in a 10 mg/kg dosage.[38]

An atherosclerosis mouse model was supplemented with pomegranate flower extract (POMf) for three months, and the results showed a substantial decrease in the atherosclerotic lesion area as compared to the water-treated group. When set aside to the control group, mice treated using POMf, which contained greatest quantity of total dietary fiber (30.2%), experienced the largest reduction in lesion size (70%) and concurrent reductions in serum glucose and cholesterol levels.[39]

In industrialized nations, chronic diseases will become increasingly prevalent as people age. Pomegranate, an enriched origin of potent ingredients, has been used for traditional medicine for centuries.[40] Heart disease, cancers, diabetes, rheumatoid arthritis, Alzheimer's, and oral health issues are some of these chronic diseases. Significant antioxidant properties in pomegranates have potential health benefits. It was majorly used as a medicine. Pomegranate appears to provide a variety of medicinal effects. The phenols and antioxidants ellagitannin and anthocyanin are abundant in pomegranate juice. Many laboratory and human studies are pomegranate shows potent antioxidant activity. Recent studies have shown the effectiveness of peel extract inatherosclerosis.[41,42]

CONCLUSION

Extracts of pomegranate and their active components show higher efficiency in treating diabetes mellitus. They can provide safe and effective treatment for diabetes, minimizing side effects related to synthetic drugs. They have an impact on type 2 diabetes, mostly through combating reactive oxygen species' negative effects by boosting the activity of specific antioxidant enzymes. Additionally, these fruit fractions show inhibition or activation of several transcriptional regulators of dextrose homeostasis, including nuclear factor-kB and PPAR-γ, and decrease resistin production.

From the many studies it can be concluded that reduced blood glucose level is due to punicic acid, aqueous and methanolic extract of peel, and alcoholic extract of seed. Juice has significant effect on diabetes mellitus variables because of its constituents like antioxidants, polyphenols, and tannins.

FUTURE SCOPE

There are many important properties of pomegranate related to human health, still there is need to obtain more efficient data suggesting its use for extended studies on human. Numerous research detailing the antibacterial, antimicrobial, and antioxidant properties of pomegranates used *in-vitro* cell-based assays need to be supplemented with *in-vivo* assays for greater accuracy.

Even though diabetes mellitus costs a lot of money and creates serious health problems every year, not much progress has been made in terms of medicine availability or managing the illness. Furthermore, the limitations of the current patient preparations necessitate the use of straightforward, non-invasive methods with prolonged hypoglycemic effects and patient compliance. The progressive development in awareness of new approaches, formulations, and technologies in relation to the treatment of diabetes is demonstrated by nanoparticulate systems, where notable outcomes were

discovered. Pomegranate use in nanotechnology is still a very young topic of study, and only a small portion with this path was already traveled. Many additional studies on the safety and viability issues are required to find more uses.

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010 Jan; 33(1):S62-69.
2. Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of Diabetes 2017. J Diabetes Res. 2018. (Vol.2018):1-4.
3. Forouhi NG, Wareham NJ. Epidemiology of diabetes. Medicine (Abingdon). 2014 Dec;42(12):698-702.
4. Kumar PJ, Clark M. Textbook of Clinical Medicine. Saunders, (London, UK ed.). 2002. (8), 1099-1121.
5. Baynest, HW. Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. *Journal of diabetes & metabolism*. 2015*; 6:1*-9.
6. Verma SM, Gupta P, Harvinder, Aggarwal G. Diabetes mellitus treatment using herbal drugs. International Journal of Phytomedicine. 2018;10(1):1-10.
7. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nat Rev Dis Primers. 2019;5(1):47.
8. Abhinav M, Neha J, Anne G, Bharti V. Role of novel drug delivery systems in bioavailability enhancement: At a glance. International Journal of Drug Delivery Technology. 2016;6 (1):7-26.
9. Suttee A, Singh G, Yadav N, Pratap Barnwal R, Singla N, Prabhu KS, Mishra V. A review on status of nanotechnology in pharmaceutical sciences. Int. J. Drug Deliv. Technol. 2019;9:98-103.
10. Jasim TM, Latif AA, Redah M. The effect of Silver Nanoparticle Induced Diabetic on Wound Healing Full Thickness Pseudomonas aeruginosa Contaminated Mouse Skin Wound Models. International Journal of Pharmaceutical Quality Assurance. 2019; 10(4): 720-724.
11. Guthrie RA, Guthrie DW. Pathophysiology of diabetes mellitus. Critical care nursing quarterly. 2004; 27(2):113–125.
12. Sherwin R, Felig P. Pathophysiology of Diabetes Mellitus. Medical Clinics of North America. 1978; 62(4): 695-711.
13. Masur K, Thévenod F, Zanker KS. Pathophysiology of Diabetes Mellitus Type 2: Roles of Obesity, Insulin Resistance and β-cell Dysfunction. Diabetes and Cancer. Epidemiological Evidence and Molecular Links. Front Diabetes. 2008; (19): 1–18.
14. Ahmed A. History of Diabetes Mellitus. Saudi medical journal. 2019;23: 375-378.
15. Holt RI. Diagnosis, epidemiology and pathogenesis of diabetes mellitus: an update for psychiatrists. The British journal of psychiatry. Suppl. 2004;47: 55–63.
16. So WY, Ng MC, Lee SC, Sanke T, Lee HK, Chan JC. Genetics of type 2 diabetes mellitus. Hong Kong Med J. 2000;6(1):69-76.
17. Reddy VJ, Sahay R, Bhadada SK, Agrawal JK, Agrawal N. Newer Oral Antidiabetic Agents. 2003
18. Shishehbor F, Mohammad Shahi M, Zarei M, Saki A, Zakerkish M, Shirani F, Zare M.. Effects of Concentrated Pomegranate Juice on Subclinical Inflammation and Cardiometabolic Risk Factors for Type 2 Diabetes: A Quasi-Experimental Study. International journal of endocrinology and metabolism. 2016;14(1): 1-7.
19. Tenenbaum A, Motro M, Fisman EZ. Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: the bezafibrate lessons. Cardiovasc Diabetol 2005;4(14): 1-5.
20. Bhowmik D, Gopinath H, Kumar BP, Duraivel S, Aravind G, Sampath Kumar KP. Medicinal Uses of Punica granatum and Its Health Benefits. Journal of Pharmacognosy and Phytochemistry. 2013;1(5): 28-35.
21. Fateh MV, Ahmed S, Mohammed A, Bandyopadhyay S. A Review on the Medicinal Importance of Pomegranate. Rajiv Gandhi University of Health Sciences Journal of Pharmaceutical Sciences.2013;3: 23-25.
22. Rahimi HR, Arastoo M, Ostad SN. A Comprehensive Review of Punica granatum (Pomegranate) Properties in Toxicological, Pharmacological, Cellular and Molecular Biology Researches. Iranian journal of pharmaceutical research. 2012; 11(2): 385–400.
23. Tezcan F, Gultekin-Ozguven M, Diken T, Ozcelik B, Erim FB. Antioxidant Activity and Total Phenolic, Organic Acid and Sugar Content in Commercial Pomegranate Juices. Food Chemistry 2009; 115(3):873-877.
24. Verardo V, Patricia G.S, Baldi E, Carretero AG, Fernandez AG, Caboni MF. Pomegranate seeds as a source of nutraceutical oil naturally rich in bioactive lipids. Food Research International. 2014; 65: 445-452.
25. Khan NH, Ying ALT, Tian CGZ. Screening of Punica Granatum seeds for antibacterial and antioxidant activity with various extracts. J Gastroenterol Dig Dis. 2017;1(1):1-7.
26. Parmar HS, Kar A. Antidiabetic potential of Citrus sinensis and Punica granatum peel extracts in alloxan treated male mice. Biofactors. 2007;31:17-24.
27. Parmar HS, Kar A. Medicinal values of fruit peel from Citrus sinensis, Punica granatum, and Musa paradisiaca with respect to alterations in tissue lipid peroxidation and serum concentration of glucose, insulin, and thyroid hormones. J. Med. Food. 2006; 11:376-381.
28. Redha A, Hasan A. and Mandeel Q. Phytochemical Determinations of Pomegranate (Punica granatum) Rind and Aril Extracts and their Antioxidant, Antidiabetic and Antibacterial Activity. Natural Products Chemistry & Research. 2018; 06(4): 1-9.
29. Singh RP, Chidambara Murthy KN, Jayaprakasha GK. Studies on the antioxidant activity of pomegranate (Punica granatum) peel and seed extracts using in vitro models. J Agric Food Chem. 2002; 50(1):81-6.
30. Li Y, Guo C, Yang J, Wei J, Xu J, Cheng S. Evaluation of antioxidant properties of pomegranate pulp extract. Food Chemistry. 2006; 96: 254-260.
31. Arun K, Jayamurthy P, Anusha CV, Mahesh SK, Nisha P. Studies on Activity Guided Fractionation of Pomegranate Peel Extracts and Its Effect on Antidiabetic and Cardiovascular Protection Properties. Journal of Food Processing and Preservation. 2017; 41(1):1-12.
32. Khalil E. Antidiabetic effect of an aqueous extract of Pomegranate (Punica granatum L.) peels in normal and alloxan diabetic rats. The Egyptian Journal of Hospital Medicine. 2004; 16(1): 92-99.
33. Rozenberg O, Howell A, Aviram M. Pomegranate juice sugar fraction reduces macrophage oxidative state, whereas white grape juice sugar fraction increases it. Atherosclerosis. 2006; 188(1): 68–76.
34. Banihani S, Swedan S, Alguraan Z. Pomegranate and type 2 diabetes. Nutrition Research. 2013; 33(5):341-34.

35. Das AK, Mandal SC, Banerjee SK, Sinha S, Saha BP, Pal M. Studies on the hypoglycaemic activity of Punica granatum seed in streptozotocin induced diabetic rats. Phytother. Res. 2001; 15:628-629.
36. Jafri MA, Aslam M, Javed K, Singh S. Effect of Punica granatum Linn. (flowers) on blood glucose level in normal and alloxan-induced diabetic rats. Journal of ethnopharmacology. 2000; 70(3): 309–314.
37. Li Y, Qi Y, Huang TH, Yamahara J, Roufogalis BD Pomegranate flower: a unique traditional antidiabetic medicine with dual PPAR-α/-γ activator properties. Diabetes, obesity & metabolism. 2008; 10(1): 10–17.
38. Al-Muammar M N, Khan F. Obesity: the preventive role of the pomegranate (Punica granatum). Nutrition. 2012; 28(6): 595–604.
39. Al-Zoreky NS. Antimicrobial activity of pomegranate (Punica granatum L.) fruit peels. International journal of food microbiology. 2009; 134(3): 244–248.
40. Sreekumar S, Sithul H, Muraleedharan P, Azeez JM, Sreeharshan S. Pomegranate fruit as a rich source of biologically active compounds. BioMed research international. 2014; 1-12.
41. Medjakovic S, Jungbauer A. Pomegranate: a fruit that ameliorates metabolic syndrome. Food & function. 2013; 4(1): 19–39.
42. Katz SR, Newman RA, Lansky EP. Punica granatum: heuristic treatment for diabetes mellitus. Journal of medicinal food. 2007; 10(2): 213–217.