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Jamun *Syzygium cumini skeels* in the Treatment of Diabetes

Jagetia GC*

Department of Zoology, Mizoram University, India

***Corresponding author:** Ganesh Chandra Jagetia, 10, Maharana Pratap Colony, Sector 13, Hiran Magri, Udaipur-313 002, India, Email: gc.jagetia@gmail.com

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Introduction

Diabetes mellitus is characterized by hyperglycemia and glucose intolerance. Diabetes is caused by dysregulation of hormones and defects in cellular functions that lead to increased fasting blood glucose levels. Usually, the individuals showing fasting blood glucose levels greater than 110mg/ dL (6.1mmol) and post meal glucose levels of 200mg/dL (11.1mmol) are considered diabetic according to the world health organization [1]. The disruption of hormonal homeostasis is the major cause of increased blood sugar levels in diabetes. The insulin in concert with glucagon, corticosteroids, growth hormone, and epinephrine tightly regulates the blood glucose levels [2]. Diabetes occurs due to the absence of insulin production, defective action of insulin, or both due to the malfunctioning and/or damage to the pancreas. Depending on the etiology and clinical presentation diabetes is classified into four categories. Type I insulin-dependent *diabetes mellitus* (IDDM, Type I) and non-insulin-dependent *diabetes mellitus* (NIDDM, Type II). The other types of diabetes include gestational diabetes, and other specific types [3,4]. Type I diabetes (IDDM) is an autoimmune disease produced due to the destruction of β-cells of islets of Langerhans by the body's T-lymphocytes leading to local inflammation and suppression of insulin secretion and this needs insulin replacement therapy [2,5,6]. It is more common in children than in adults and has a genetic predisposition and its incidence is on the rise [7,8]. Type II is the most common type of diabetes and is characterized by the development of peripheral insulin resistance and impaired secretions of insulin by the pancreas. Type II diabetes is characterized by intermediate stages of impaired fasting glucose and impaired glucose tolerance, and therefore it is also known as pre-diabetes.

Obesity is one of the major causes of type-II diabetes and 85-95% of diabetic patients suffer from Type II diabetes [9,10]. The symptoms of diabetes include polyuria, polydipsia, polyphagia, fatigue, blurred visions, dry mouth, burning sensation, numbness of feet, acanthoses nigricans, erectile dysfunction, hunger, hyperglycemia, itching, excess thirst, and weight loss [4,10,11]. Several treatment modalities are available for the treatment of both type I and II diabetes in the modern medicine. The diabetes leads to various complications including, cerebrovascular disorders cardiomyopathies, neuropathy, nephrotoxicity, and wound healing disorders [12,13]. Type II diabetes is a lifestyle disease and changing lifestyle can reduce the incidence of this disorder [14,15].

Diabetes is the 9th killer disease in the world and leads to various complications. Diabetes afflicted 537 million individuals in the age group of 20 to 79 years in 2021. The number of individuals suffering from diabetes will increase up to 643 million by 2030 and is projected to rise to 783 million by the year 2045. Approximately 6.4 million individuals (1 individual 5 every second) succumbed to death in the year 2021. China has the highest number of diabetic patients in the world amounting to 140.9 million, whereas 74.2 million individuals suffered from diabetes in India in the year 2021. Pakistan has 33 million diabetic patients and ranks third in the world and USA ranks fourth where the number of diabetic patients is about 32.2 million in the year 2021. Diabetes is a major health problem in the world including the US. Diabetes has emerged as one of the major public health problems in the world and the global healthcare cost for diabetes in the year 2021 has been around 966 billion USD [10]. Several treatment modalities are available for the treatment of both type I and II diabetes in the modern medicine. Ayurveda an ancient system of medicine gives an account of the treatment of diabetes using Jamun and I will focus on the use of Jamun, *Syzygium cumini* to control diabetes.

Botanical Description

Jamun has been classified scientifically (Taxonomy) into Kingdom: Plantae; Division: Magnoliophyta; Class:

Magnoliopsida; Order: Myrtales; Family: Myrtaceae; Genus: Syzygium and Species: cumini. Jamun abundantly grows in the Indian subcontinent including India, Pakistan, Bangladesh, Myanmar, Ceylon, and Madagascar. It grows well in loamy, deep, and well-drained soils. Jamun has been introduced into different parts of the world including the United States of America for its fruits and timber [16,17]. It is also grown in Algeria, California, Israel, and West Indies [18]. Jamun is a fast-growing tree, which becomes fully grown in 40 years and reaches up to a height of 100 feet (30m). It may spread up to 36 feet (11m) with a trunk diameter of 2-3 feet (0.6-0.9m) (Figure 1). It forks into multiple branches at a short distance from the ground and its stem bark is rough, cracked, flaking, and discolored at the lower end and becomes smooth and light gray at higher levels (Figure 2). The leaves are opposite, 2 to 10 inch (5-25cm) long, 1 to 4 in (2.5-10cm) wide, oblong-oval or elliptical in shape, blunt or tapering to a point at the apex (Figure 3). The young leaves are pink colored become leathery, glossy, dark green above, lighter beneath, with yellowish midrib when fully matured having a turpentine smell. Jamun flowers during March-April, which are scented 1 to 4 inches long (2.5-10cm) in clusters of a few or 10 to 40 round to oblong shaped, 1/2 inch (12.7mm) wide with funnel-shaped 0.16 inch (4mm) long and toothed calyx. The petals are 4 to 5 united as a small disk (Figure 4). The flowers are greenish-white at first and become rose pink later [17-19]. The Jamun bears fruits in clusters during summer that ripens in June July. The cluster may contain a few fruits to as many 10 or even 40 in number. The fruits are round to oblong in shape and the size varies between 1/2 to 2 inches (1.2 to 5cm). The fruits are initially green colored and turn from light to dark purple or even black colored (Figure 5) once fully ripened [16-20]. The fruits of Jamun taste sweetish sour and eating Jamun fruits tends to color the tongue to purple. Jamun seeds are oblong, whitish purple that turns brown after drying (Figure 6). The Jamun tree is considered holy by Hindus and Buddhists and is commonly planted in the compounds of Hindu temples. Jamun is dear to Lord Krishna and the leaves and fruits of Jamun are offered to Lord Ganesha (Elephant God) during worship [17].

Figure 1: The whole tree of Jamun, *Syzygium cumini* in its natural habitat.

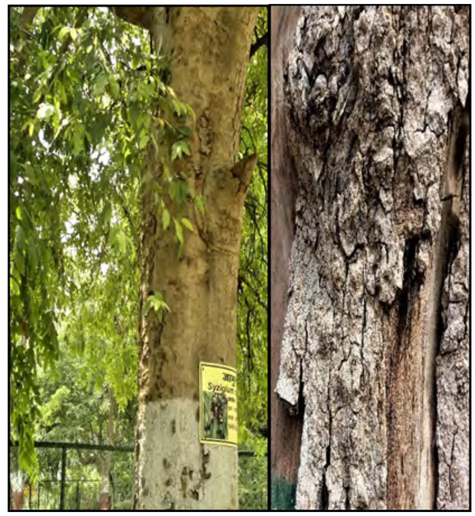

Figure 2: Jamun *Syzygium cumini* Stem. Left stem and right matured stem bark.

Figure 3: The leaves of Jamun, *Syzygium cumini*.

Figure 4: Jamun *Syzygium cumini* flowers.

Figure 5: Jamun *Syzygium cumini* fruits in natural form on the tree (top) and ripened fruits (bottom).

Figure 6: Jamun *Syzygium cumini* seeds. Fresh (top) and dried (bottom).

Phytochemical Analysis

Jamun synthesizes various phytochemicals and their presence has been detected in various parts including roots, stems, leaves, fruits, and seeds (Table 1). The leaves of Jamun extracted in water, ethanol, ethyl acetate, chloroform and petroleum ether, methanol, and hexane were found to possess high to low amounts of alkaloids, anthraquinones, flavonoids, glycosides, steroids, phenols, tannins, saponins phenols, proteins, triterpenoids, cardiac glycosides, phytosterols, amino acids, carbohydrates, fixed oils, volatile oil, terpenoids, mucilage, and fats. In addition to these Jamun leaves also contained nitrogen, phosphorus, potassium, magnesium, calcium, sulfur, copper, iron, manganese, and zinc as micronutrients [21-28]. The ethanol extract of Jamun leaves contained carbohydrates, flavonoids, terpenoids and tannins, whereas the methanol, ethyl acetate, and chloroform extracts showed the presence of carbohydrates only [29]. Jamun leaves extracted in acetone contained proteins, glycosides, phenols, resins and saponins whereas alkaloids, flavonoids were detected in the stem bark extract. The root extract contained all these phytochemicals except saponins. Chloroform leaf extract of Jamun contained alkaloids, proteins, and steroids whereas proteins were absent in the root extract. The alkaloids, phenols, tannins, carbohydrates, and proteins have been detected in seed extract. However, the chloroform stem bark extract showed the presence of alkaloids and tannins. The alkaloids, flavonoids, saponins, steroids, tannins carbohydrates, glycosides, phenols, and resins were detected in the methanol extract of the leaves and stem bark and root extract contained proteins additionally. N-hexane extract of stem bark contained proteins, alkaloids, and tannins, and the leaf extract also showed the presence of alkaloids. The root extract showed the presence of alkaloids and resins and carbohydrates and proteins were detected in the seed extract [30]. The ethanol stem bark extracts of Jamun showed the presence of terpenoids, anthraquinone glycosides, alkaloids, catechins, phenols, quinones, saponins, phytosterols, steroids and amino acids and tannins, whereas methanol extract contained flavonoids in addition to these phytochemicals. The aqueous stem bark extract only contained catechins, phenols, quinones, and flavonoids [31].

The methanol and water seed extracts of Jamun revealed the presence of saponins, tannins, phenolics, alkaloids, phytosterols, flavonoids, and amino acids [38]. The Jamun seed extracted in methanol, ethanol, and water contained tannins, alkaloids, flavonoids, terpenoids, glycosides, phenol, steroids, saponins, reducing monosaccharides, reducing sugars, and proanthocyanidins, whereas chloroform extract showed the presence of tannins, flavonoids, terpenoids, phenols, reducing monosaccharides, reducing sugars and proanthocyanidins. The diethyl ether extract contained tannins, flavonoids, phenols, reducing monosaccharides, reducing sugars, and proanthocyanidins. The flavonoids and steroids were detected in the n-hexane extract whereas the benzene extract contained flavonoids and terpenoids [32]. Ethyl acetate and methanol extracts of Jamun seeds were found to contain flavonoids, alkaloids, glycosides, triterpenoids, steroids, saponins, and tannins [34]. The phytochemical analysis of ethanol extract of Jamun seed and fruit pulp indicated the presence of alkaloids, flavonoids, proanthocyanins, tannins, saponins, phenols, cardiac glycosides, terpenoids, phytosterols, steroids anthocyanins, and amino acids [33,36,37]. The hydroalcoholic seed extract of Jamun contained alkaloids, flavonoids, tannins, and steroids [35]. The aqueous root extract of Jamun contained volatile oil, alkaloids, flavonoids, glycosides, saponins, steroids, tannins, terpenoids, carbohydrates, and mucilage [28].

S. No.	Parts used	Extract type	Phytochemicals	Reference
1.	Leaves	Methanol, ethanol, aqueous,chloroform petroleum ether, acetone, and hexane	Alkaloids, anthraquinones, flavonoids, glycosides, steroids, phenols, tannins, saponins phenols, triterpenoids, cardiac glycosides, phytosterols, resins	[21-27,29, 31]
2.	Stem bark	Aqueous, ethanol, methanol, hexane and chloroform	Catechins, phenols, quinones, flavonoids,terpenoids, anthraquinone glycosides, alkaloids, catechins, phenols, quinones, saponins, phytosterols, steroids tannins and amino acids	[30,31]
3.	Seed and fruit pulp	Ethyl acetate, methanol. ethanol, and hydroalcoholic	Alkaloids, flavonoids, proanthocyanins, tannins, saponins, phenols, cardiac glycosides, terpenoids, phytosterols, steroids, anthocyanins, tannins, proanthocyanidins, amino acids, monosaccharides, and reducing sugars	[32-38]
4.	Root	Aqueous, and hexane	Volatile oil, alkaloids, flavonoids, glycosides, saponins, steroids, tannins, terpenoids, carbohydrates and mucilage	[28,30]

Table 1: Phytochemical constituents of Jamun *Syzygium cumini*.

Antidiabetic Activity

Diabetes afflicts a large population in the world and Indians are more prone to this disease. Even though diabetes was not very common in ancient times, Ayurveda pharmacopeia mentions the antidiabetic effect of Jamun, where the seed powder is given to control high blood sugar levels. For more than 130 years, Jamun has been tried in Western countries to control blood sugar levels, but the clinical trials have been inconclusive because some patients responded well to the treatment, while others did not [39]. Since the nineteenth century, numerous experimental studies have been carried out in preclinical animal models to prove the efficacy of different parts of Jamun to treat diabetes (Table 2) but with mixed results. Some studies have reported that it reduced blood sugar levels, whereas others did not report any significant effect [17,20,39]. A report published in 1947 did not find any reduction in blood sugar levels in the alloxan-induced diabetic rats fed with Jamun seed extract [40]. Thereafter there has been a spurt of investigations in various animal models, which have shown that Jamun did reduce the blood sugar levels [20]. The aqueous seed extract of Jamun has been reported to reduce blood glucose levels in rabbits [41,42]. The blood glucose levels declined in the spontaneous diabetic rats treated with stem bark extract of Jamun [43]. The rats fed with ethanol extract of Jamun bark showed reduced blood glucose levels in the serum [44]. Several studies conducted in diabetic rats have shown that aqueous seed powder extract did reduce glucose [45-47].

Treatment of diabetic mice and rats with lyophilized powder of aqueous seed extract effectively lowered the serum blood glucose levels [48,55]. The water soluble seed extract containing gummy fibers effectively controlled diabetes in alloxan-induced diabetic rats, whereas the aqueous extract without gummy fiber was completely ineffective [53]. The streptozotocin-induced rats fed with different doses of Jamun seed powder in the aqueous medium reduced fasting blood glucose levels reducing diabetes [54]. The ethanol extract of Jamun seeds/kernel reduced the fasting blood glucose levels in alloxan-induced diabetic rats and rabbits [49]. The ethanol extract of seed kernel depleted blood glucose, urea, AST, ALT, and cholesterol levels, and increased glucose tolerance. The seed extract also restored the superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) enzyme activities, and reduced glutathione (GSH) contents in the liver and kidney of streptozotocin-induced diabetic rats [61-63]. The ethyl acetate and methanol extracts of Jamun seeds and the isolated compound mycaminose reduced blood glucose levels in the streptozotocin-induced diabetic rats [66].

S.No.	Parts used	Extract type	Species	Reference
1.	Seed	Aqueous	Rabbits and Rats	[41,42,45-53]
		Powder	Rats	[54]
		Aqueous	Mice	[55,56]
		Powder	Humans	[57-60]
		Ethanol	Rabbits and Rats	[49,61- 64,76]
		Ethyl acetate	Rats	[51,66-68]
		Methanol		
2.	Stem	Ethanol	Rats	[43,44,51]
3.	Fruit pulp	Lyophilized	Rat	[69]
		Aqueous	Rat	[70,71]
		Ethanol		[65,76,72]
4.	Leaf	Aqueous/ethanol Aqueous/methanol	Humans	[73,74]
			Rats	[51]
5.	Root	Aqueous	Rats	[28]

Table 2: Antidiabetic effect of different Jamun extracts in the various study systems.

The active principles separated from the ethanol fraction of seed extract of Jamun on Sephadex gel have been reported to reduce glucose level in the serum of alloxan-induced mild and severe diabetes in rats [64]. The aqueous seed extract of Jamun has been reported to bring the glucose level to near normal and also increase the expression of peroxisome proliferator activated receptor (PPARγ) and PPARα proteins in the streptozotocin-induced type-II diabetic rat liver [50]. The methanol extract of Jamun seeds also reduced serum glucose levels in alloxan-induced diabetic rats [67]. The aqueous and ethanol extracts of Jamun fruit pulp caused a decline in the blood glucose level in alloxan-induced diabetic rats where the aqueous extract was more potent than the ethanol extract [70]. The lyophilized Jamun fruit pulp extract was not effective in curing streptozotocin-induced diabetes in rats and could not reduce the raised blood sugar levels in a Brazilian study [69]. The aqueous extract of the Jamun fruit pulp has also been reported to reduce serum glucose level in streptozotocin-induced diabetes in female Wistar rats however, the combination of Jamun fruit extract with the stem bark extract of *Cinnamon zeylanicum* was more effective than either treatment alone [71].

The root, stem bark, leaf, and seeds of Jamun extracted in water or methanol did lower the serum glucose levels in alloxan-induced diabetic male Sprague Dawley rats [51]. The aqueous extract of Jamun seeds alleviated serum glucose levels in the alloxan-induced diabetic mice [56]. The methanol extract of Jamun fruit pulp, seed, and kernel showed inhibition of α-amylase activity, and the highest inhibition or antidiabetic effect was detected for the kernel extract in vitro [75]. The feeding of Sprague Dawley rats with hydroalcoholic (50% ethanol) extract of Jamun fruits and seeds in the diet for 60 days resulted in the decline in glucose and increase in insulin levels in diabetic rats [76]. The oral feeding of different doses of Jamun seed methanol extract for 14 days reduced serum glucose levels in alloxan-induced diabetic rats [68]. The oral administration of different doses of aqueous Jamun seed extract to streptozotocin-induced diabetic Wistar albino rats once daily for continuous 21 days reduced serum glucose, insulin, HOMA-IR and TNF-α levels followed by an increase in the PPARγ and PPARα expression in the liver. The aqueous Jamun seed extract increased the activities of catalase, SOD, and GPx and reduced the lipid peroxidation in the rat pancreas. It also reduced streptozotocin-induced damage to pancreatic β-cells [52]. Administration of triterpenoid-enriched Jamun fruit extract (60mg/mouse) once daily for ten days in streptozotocin-induced diabetic C57BL/6 mice reduced the fasting serum glucose and insulin levels and increased HOMA-β index. The Jamun fruit extract also elevated phosphorylation of serine/threonine kinase (AKT, a protein kinase) and p-AKT/AKT and reduction in the Forkhead box protein-1 (Foxo-1), peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC1α), glucose 6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) in the livers of streptozotocin-induced diabetic mice [72]. Oral administration of 200 and 400mg/kg of aqueous Jamun root extract or its isolated compound 4-(2-amino-2-(2-(2-hydroxy-3 methylbutyl)octahydropyrrolo[1,2-a] pyrazin-7-yl) ethyl)-2-ethylphenol daily for 15 days reduced glucose level in streptozotocin-induced diabetic rats [28].

Aqueous leaf extract of Jamun has been reported to reduce the adenosine deaminase (ADA) activity and glucose level in the serum of diabetic patients [73]. The 80% ethanol leaf extract of Jamun attenuated the activities of ADA and 5'-nucleotidase (5'NTase), and reduced glucose, triglycerides, and lipid peroxidation levels, and increased catalase activity in the diabetic patients [74]. The feeding of Jamun seed powder for 30 days to human diabetic patients reduced the fasting and postprandial blood glucose levels [57]. In another randomized double-blind placebo-controlled clinical trial 99 diabetic patients given 5g of seed powder before meals twice daily for 90 days reduced serum glucose level [58]. The supplementation of 2g of roasted Jamun seed powder for sixty days reduced serum glucose levels in type-II diabetes in patients [59]. A similar effect has been observed in another double-blind clinical study carried out between March 2018-March 2019 [60]. These studies indicate that Jamun can treat diabetes effectively.

Antihyperlipidemic Activity

Diabetes is usually accompanied by hyperlipidemia leading to cardiovascular morbidity and different parts of Jamun can lower serum cholesterol levels. The alloxan-induced diabetic rabbits treated with Jamun seed ethanol extract showed a reduction in the total serum cholesterol/high density lipoprotein cholesterol (HDL-c) ratio, serum low density lipoprotein cholesterol (LDL-c) levels, and depressed activity of HMG-CoA reductase [49]. The seed kernel ethanol extract of Jamun has been reported to reduce the LDL-c and very low density lipoprotein (VLDL) cholesterol and increase HDL cholesterol levels in streptozotocin-induced diabetic rats, [61]. The Jamun seed powder reduced serum cholesterol, LDL, VLDL cholesterol, and triglycerides in diabetic patients given two grams of Jamun seed powder for 60 days [59]. The active principles separated by Sephadex gel from the ethanol seed extract fraction of Jamun reduced triglycerides, total cholesterol and increased the HDL cholesterol in alloxan-induced diabetic rats [64]. The aqueous seed extract of Jamun reduced hyperlipidemia by restoring the levels of triglycerides, and total cholesterol to normal and increasing the amount of HDL cholesterol [56]. The ethanol extract of seeds and fruits of Jamun decreased the high levels of triglycerides, and LDL cholesterol and increased the HDL cholesterol in rats fed with high cholesterol diet [65]. The aqueous fruit pulp extract of Jamun also decreased triglycerides, total cholesterol and increased the HDL cholesterol in the streptozotocin-induced diabetic rats [71]. The streptozotocin-induced diabetic C57BL/6 mice treated with triterpenoid-enriched Jamun fruit extract (60 mg/mouse) once daily for ten days showed a reduction in the triglyceride and free fatty acid (FFA) contents in the serum and liver of diabetic mice followed by an attenuation of the mRNA levels of acetyl-CoA carboxylase 1 (ACC1), stearoyl-CoA desaturase-1 (Scd1), cluster of differentiation 36 (CD36), and fatty acid synthase (Fas) and ACC1 expression at the protein levels. It also increased the expression of p-ACC1 protein and normalized the expression of extracellular signal-regulated kinase (Erk1/2) and p-Erk1/2 in diabetic mice [72]. The oral administration of capsules of 4.5 g powder Jamun seed powder once daily for 84 days to the patients suffering from intermediate hyperglycemia significantly reduced the cholesterol and LDL cholesterol levels [77].

Anti-Obesity Activity

Obesity is one of the important problems in humans and is directly linked to diabetes. Different extracts of Jamun have been reported to reduce obesity in several preclinical studies. The oral feeding of Jamun seed powder for 56 days to high carbohydrate and fat diet to Wistar rats significantly decreased body weight gain, accumulation of white adipose tissue (WAT), blood glucose, serum insulin, total cholesterol, LDL-c, triglycerides, and lipid peroxidation in the plasma. The Jamun seed powder increased plasma HDL-c, GSH, SOD, and catalase levels when compared to obese rats. The seed powder also reduced advanced protein oxidation products, myeloperoxidase, lipid peroxidation, nitric oxide production, and subsequently increased GSH, catalase, and SOD levels in the liver of obese rats [78]. The combination of ethanol and acetone fruit extracts of Jamun orally administered into C57BL/6 obese mice restored the ratio of *Firmicutes to Bacteroidetes* in the gut, prevented body weight gain, accumulation of WAT in epidydimal, visceral, and subcutaneous tissues. The extracts also reduced serum glucose and insulin levels in obese mice followed by normalization of p-AKT and phosphoinositide 3-kinase-PI3k (p85) protein expression levels and attenuation in the phosphorylation levels of p-IRS (insulin receptor substrate)-1 at Ser318, mRNA levels of sterol regulatory element-binding protein (SREBP1c), ACC1, FAS, PPARγ, and CD36 in the obese mouse liver. The extract also decreased triglycerides, FFA, and cholesterol levels in the liver and plasma except for the cholesterol level in the latter which remained unaltered [79]. The oral administration of 0.5 or 1.0g/kg/day hydroalcoholic extract of Jamun leaves for 7 days resulted in a decline in the weight gain and WAT accumulation in the retroperitoneal and periepididymal regions of the monosodium L-glutamate-induced obesity in newborn Wistar rats. The extract decreased the serum glucose and FFA levels and also restored the total cholesterol and triglycerides to normal levels in the obese rats. The administration of hydroalcoholic Jamun leaf extract reverted nonalcoholic fatty liver disease in obese rats and alleviated AST activity. At the molecular level, the hydroalcoholic extract reduced endoplasmic reticulum stress by alleviating the translation of the KDEL (endoplasmic reticulum protein retention receptor) chaperone, G protein-coupled receptor (GPR98) expression, and a marginal reduction in GPR78 expression in the livers of obese rats. The expression of spliced XBP-1s (X-box binding protein) and unspliced XBP-1u, microsomal triglyceride transfer protein (MTP), and protein disulfide isomerase (PDI) was reduced in the hepatocytes by hydroalcoholic Jamun leaf extract in the obese rats [80].

Mechanism of Action

The exact mechanism by which Jamun reduced blood sugar and hyperlipidemia is not well known. However, several putative mechanisms seem to be operational in exerting the beneficial effect of Jamun in diabetic conditions. Since diabetes is caused by the production of excess free radicals/reactive oxygen species (ROS) [81,82], scavenging of free radicals by Jamun is one of the important mechanisms of action in preventing diabetes [83-85].

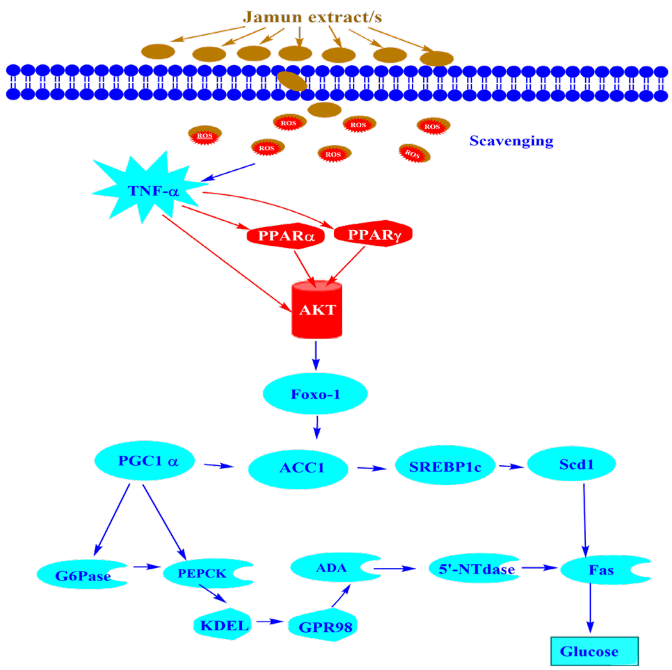

Figure 7: Jamun scavenges free radicals (reactive oxygen species ROS) that downmodulate TNF-α and upregulate protein kinase (AKT), peroxisome proliferator activated receptor (PPARγ) and PPARα that downregulates Forkhead box protein-1 (Foxo-1), peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC1α), sterol regulatory element-binding protein (SREBP1c), Acetyl-CoA carboxylase (ACC1), stearoyl-CoA desaturase-1 (Scd1), endoplasmic reticulum protein retention receptor (KEDL), G protein-coupled receptor (GPR98) fatty acid synthase (Fas), sterol regulatory element-binding protein glucose 6-phosphatase (G6Pase), and phosphoenolpyruvate carboxykinase (PEPCK), adenosine deaminase (ADA) and 5'-nucleotidase (5'NTase).

The activation of AKT, PPARα and PPARγ and subsequent downregulation in the expression of Foxo-1, PGC1α, ACC1, SREPB1c, Scid 1, endoplasmic reticulum protein retention receptor (KEDL), and GPR98 by Jamun seem to reduce ADA, 5'NTase, Fas, G6Pase, and PEPCK activities and decrease glucose level (Figure 7) [52,57,72,73]. The dysfunction of the (Nuclear factor E2-related factor 2) Nrf2/Keap1/ARE (Antioxidant Response Element) signaling pathway is reported in diabetes [82,86] and Jamun seems to restore this pathway by sequestration of Nrf2/Keap1 that causes translocation of Nrf2 into the nucleus. Once Nrf2 is in the nucleus, it activates ARE leading to the stimulation of heme oxygenase-1 (HO1) and NAD[P]H: quinone oxidoreductase-1 (NQO1) that cause the rise in the antioxidants like GSH, GPx, glutathione reductase (GR), catalase, SOD, glutathione-s-transferase (GST) by Jamun in diabetic condition and subsequently reduce lipid peroxidation (Figure 8) [87-89]. In addition to this Jamun may also activate mechanisms that are still unknown to exert its antidiabetic action.

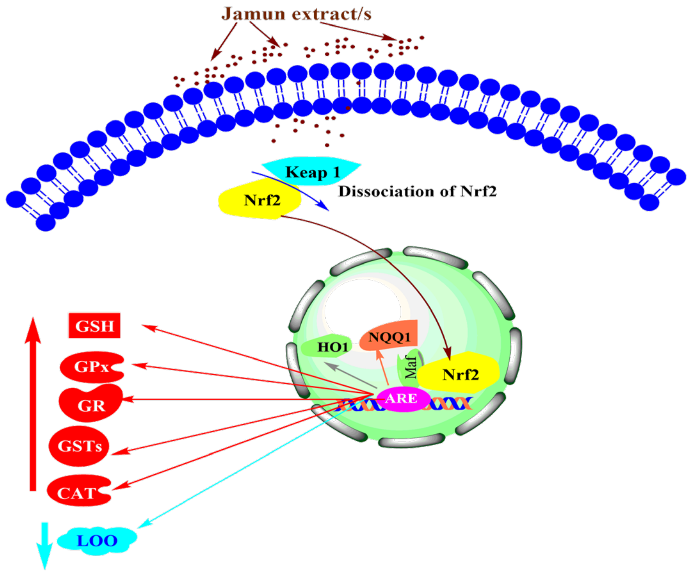

Figure 8: The antidiabetic action of Jamun is due to its ability to dissociate (nuclear factor E2-related factor 2) Nrf2/Keap1 that translocates Nrf2 into the nucleus. Once Nrf2 is in the nucleus it activates antioxidant response element (ARE), heme oxygenase-1 (HO1) and NAD[P]H: quinone oxidoreductase-1 (NQO1) and increases glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-s-transferase (GST) and catalase (CAT) and reduces lipid peroxidation (LOO).

Conclusion

Jamun has been used traditionally to treat several diseases including diabetes. Jamun contains several phytochemicals which may exert their diabetic and hypolipidemic action in concert with each other. The Jamun reduce the activities of ADA, 5'NTase, Fas, G6Pase, and PEPCK and decrease glucose concentration by upregulating AKT, PPARα and PPARγ gene expression and subsequently downregulating Foxo-1, PGC1α, ACC1, SREPB1c, Scid 1, KEDL, GPR98 expression. Jamun activates Nrf2 signaling pathway that increases the level of GSH, GPx, GST, SOD and catalase followed by the alleviation in LOO in diabetic conditions. Future studies need to be directed to understand the molecular mechanisms of Jamun in diabetic conditions in vitro and in vivo.

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