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A Review on Antidiabetogenic Activity of Jamun, Syzygium Cumini Family- Myrtaceae

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Abstract

Jamun or Syzygium cumini family Myrtaceae belongs to the angiosperms group of plants. Jamun has been used in India to treat diabetes since the Vedic era. Diabetes is not a fetal disease as such, but it results in several complications of different organs including the heart, kidney, etc. Diabetes has been increasing throughout the world due to lifestyle changes including alterations in food habits. Here an attempt has been made to delineate information on the use of Jamun in diabetes. The relevant information on the antidiabetic effect of Jamun has been collected by searching Google PubMed, Google Scholar, SciFinder, Science Direct, and various websites on the internet. The review provides an articulate overview of the botanical profile, phytochemistry, and antidiabetic properties of Jamun. In Ayurvedic medicine, Jamun is acrid, astringent, carminative, digestive, refrigerant, diuretic, and sweet-sour. Ethnomedicinally, Jamun has been used in the treatment of fever, piles, leucorrhea, wounds, stomachache, dental, gastric, and skin disorders. Different parts of Jamun have been used by Ayurvedic practitioners to cure arthritis, asthma, bowel spasms, diabetes, dysentery, flatulence, obesity, stomach pain, and urinary diseases. Modern scientific evaluation has shown the utility of Jamun to treat different diseases. The different phytochemicals including anthraquinones, alkaloids, cardiac glycosides, catechins, flavonoids, glycosides, steroids, phenols, saponins, and tannins are synthesized by Jamun. Jamun activates AKT, PPARα and PPARγ and increases fatty acid and glucose metabolism. Jamun inhibits the expression of Foxo-1, PGC1α, ACC1, SREPB1c, Scid 1, endoplasmic reticulum protein retention receptor (KEDL), and GPR98. The scientific evaluation of Jamun could help substantiate its ethnomedicinal use in the treatment of numerous disorders and may be a step forward in translational research for its medicinal use in modern medicine.

Keywords: Jamun; Traditional Medicine; Antidiabetic; Cytotoxicity; Cytokine; Phytochemicals

Abbreviations

HDL-c: High-Density Lipoprotein Cholesterol; LDL-c: Low Density Lipoprotein Cholesterol; HMG-CoA: 3-Hydroxy-3 Methyl Glutaryl CoA; VLDL: Very Low Density Lipoprotein; FFA: Free Fatty Acid; ACC1: Acetyl-Coa Carboxylase 1; CD36: Cluster of Differentiation 36; Scd1: Stearoyl-CoA Desaturase-1; FAS: Fatty Acid Synthase; Erk1/2: Extracellular Signal-Regulated Kinase; WAT: White Adipose Tissue; PDI: Protein Disulfide Isomerase; ROS: Reactive Oxygen Species; HO1: Heme Oxygenase-1; GR: Glutathione Reductase; GST: Glutathione-S-Transferase; PPARγ: Peroxisome Proliferator Activated Receptor.

Introduction

Angiosperms constitute 80% of all living green plants on earth and consist of approximately more than 300,000-400,000 species. The numerous secondary metabolites synthesized by Angiosperms serve as drugs and are of great healthcare importance to humans [1,2]. The application of herbal medicines and natural products in human healthcare dates back 5000 years and the Vedic text Atharva Veda mentions 50 plants used to treat different human diseases [3,4]. Approximately 400-500 varieties of Jamun are found on the earth and only a few varieties of fruits are edible. The Jamun foliage serves as fodder for cattle and its wood is used in making agricultural implements, construction of buildings, and railway sleepers [5-8]. This article on the antidiabetic activity of Jamun has been written consulting various websites like Google PubMed, Google Scholar, SciFinder, and ScienceDirect on the internet.

Profile of Jamun

Jamun or Syzygium cumini (L.) Skeels, is also known as Calyptranthes Jambolana Willd., Calyptranthes oneillii Lundell, Eugenia cumini Druce, Eugenia djouat Perr. Eugenia caryophyllifolia Lam., Eugenia jambolana Lam., Syzygium jambolana (Lam.) DC., Syzygium jambolanum DC, Syzygium caryophyllifolium (Lam.) DC., and Myrtus cumini L. The common names of Jamun are Indian blackberry, black plum, Damson plum, Java plum, jambul, jambolan, jamblang, Malabar plum, purple plum, Duhat plum, Jambolan plum, rose-apple or Portuguese plum in English (Table 1) [8-11].

Jamun is indigenous to Indian subcontinent and is known as jamun, duhat, jaman, or jam in Hindi; Jambuphalam, jambu, mahaskandha, meghamodini, phalendra, or raja-jambuh in Sanskrit; Jambu in Pali; Jammulo and jambulo in Prakrit; Lenhmui or Hmuipui in Mizo; Chomshathei in Tangkhul; Gulamchat or jam in Manipuri; Kala jamu or jamu in Assamese; Kala jam in Bengali; Jaambu, and jambu in Gujrati; Jambunerale, nerale hannu, jambuva, jumnerale, nainerale, naayinaerale and neeram in Kannada; Gnaval, naga, naivil, njaval, perinnaralnjara, perin-njara, palamper, and naval-pazham in Malayalam; Jam, jambul, jaman, rajale, rajjambula and thorajambula in Marathi; Jamkoli in Oriya; Jaman in Punjabi; Areconitamaram, arukatam, arugadam, cattuvalam, caccanam, kavarkalimaram, neretu, nampu, turavam, and turkolum in Tamil; Goyya-pandu, jamba, jam-pandu, jambu, naredu and raacahnaeredu in Telegu; Jaman, jamun and poast jamun in Urdu.

Jamun is called Jaamun, kaalo jaamun, phanir, jaambu and jamunaa in Nepal; Jambul, jambu, madan and naval in Sri Lanka; Thabyay-hypyoo in Myanmar; Hakhiphae, ma-ha, lukwa, and wa in Thailand; Duhat or lomboi in Philippines; Duwet, djoowet, jambhool, and jamblang in Indonesia; Jambulan, jambul, jambulana, jiwat, jumbul, and juwet in Bali; Pring bai in Cambodia; Pring das krebey and pring bai, in Khmer; Jambolan, obah jambulana, and jiwat in Malaysia; Va in Laos, Trâm môc, and voi rung in Vietnam; Jambolanapflaume, rosenapfel and wachsjambuse in Germany; Aceituna dulce and pomo della Malesia in Italy; Sitsigiui dzhamboza in Russia; Guayabo pesgua and yambolana in Spain (Spanish); Ciruelo de Java, Jambolan in Costa Rica, Jamboleiro and jambolao in Portugal (Portuguese); Jamelongue, faux-pistachier, jambolanier, jamelongier, and jamelon-guier in France; Jambolanäpplein in Sweden; Azeitona, jambulao, jambol, jamelao jalao, and murta in Brazil; Koeli, jamoen and druif in Surinam; Guayabo pesjua and pesjua extranjera in Venezuela; Jamelonguier in New Caledonia; Paramu in Cook Islands (Aitutaki)); Damson plum in Jamaica; Pistati and kaika in Cook Islands; Mesekerrak and mesigerak in Palau; Duhat in Guam; Jammun and Kavika ni India in Fiji; Indian blackberry in Jamaica; Jambol in West Indies; Janboran, Murasaki futo momo, and Madan in Japan; Rotra in Madagascar; Dza mbu, dzam-bu, and ka ka dz mbu in Tibet; Msambarau and mzambarau in Kenya, Uganda and Tanzania (Table 1) [8-11].

S. No.	Language/Country	Names
1.	Scientific names	Syzygium cumini (L.) Skeels, Syzygium jambolana (Lam.) DC., Calyptranthes oneillii Lundell, Eugenia cumini Druce, Syzygium jambolanum DC, Syzygium caryophyllifolium (Lam.) DC., Eugenia djouat Perr. Calyptranthes jambolana Willd. Eugenia caryophyllifolia Lam., Eugenia jambolana Lam., and Myrtus cumini L.
2.	English	Indian blackberry, black plum, jambolan, Java plum, purple plum, Malabar plum, jambul, jamblang, Damson plum, Duhat plum, Jambolan plum, rose-apple and Portuguese plum
3.	Hindi	Jamun, jaman, duhat and jam
4.	Sanskrit	Jambu, jambuphalam, phalendra, mahaskandha, raja-jambuh, or meghamodini
5.	Prakrit	Jambu in Pali; jambulo, and jammulo
6.	Assamese	Jamu and kala jamu
7.	Bengali	Kala jam
8.	Gujrati	Jambu, and jaambu
9.	Kannada	Nerale hannu, jambunerale, jumnerale, nainerale, jambuva, naayinaerale and neeram

10.	Manipuri	Gulamchat and jam
11.	Malayalam	Gnaval, naga, naivil, palamper, perinnaralnjara, njaval, perin-njara, and naval-pazham
12.	Mizo	Hmuipui and Lenhmui
13.	Oriya	Jam, jaman, jambul, rajale, rajjambula and thorajambula in Marathi; Jamkoli
14.	Punjabi	Jaman
15.	Tamil	Areconitamaram, arugadam, arukatam, caccanam, cattuvalam, nampu, neretu, kavarkalimaram, turavam, and turkolum
16.	Tangkhul	Chomshathei
17.	Telugu	Goyya-pandu, jam-pandu, jamba, jambu, naredu and raacahnaeredu
18.	Urdu	Jaman, jamun and poast jamun
19.	Brazil	Azeitona, jambol, jambulao, jamelao, Murta and jalao
20.	Cambodia	Pring bai
21.	Khmer	Pring bai, Pring das krebey
22.	Cook Islands	Paramu (Aitutaki)); Damson plum in Jamaica; Pistati and kaika
23.	France	Jamelongue, jambolanier, jamelongier, faux-pistachier and jamelon-guier
24.	Germany	Jambolanapflaume, rosenapfel and wachsjambuse
25.	Fiji	Duhat in Guam; Kavika ni India and jammun
26.	Indonesia	Jambhool, Duwet, Djoowet, and jamblang
27.	Bali	Jambul, Jambulan, Jambulana,Jumbul, Jiwat, Juwet
28.	Italy	Pomo della Malesia and Aceituna dulce
29.	Laos	Va
30.	Japan	Janboran, Murasaki futo momo, Madan
31.	Madagascar	Rotra
32.	Malaysia	Jambolan, obah jambulana, and jiwat
33.	Nepal	Jaamun, kaalo jaamun, phanir, jaambu and jamunaa
34.	New Caledonia	Jamelonguier
35.	Palau	Mesekerrak and mesigerak
36.	Philippines;	Lomboi and Duhat
37.	Portugal	Jamboleiro and jambolão
38.	Russia	Sitsigiui dzhamboza
39.	Spain	Guayabo pesgua and yambolana
40.	Costa Rica	Ciruelo de Java, and Jambolan
41.	Sri Lanka	Jambu, jambul, madan and naval
42.	Surinam	Koeli, jamoen and druif
43.	Sweden	Jambolanapplein
44.	Thailand	Thabyay-hypyoo in Myanmar; Hakhiphae, lukwa, ma-ha, and wa
45.	Tibet	Dza mbu, dzam-bu, and ka ka dz mbu in
46.	Kenya, Uganda and Tanzania	Msambarau and mzambarau
47.	Venezuela	Guayabo pesjua and pesjua extranjera
48.	Vietnam	Va in Laos, Tram moc, and voi rung
49.	West Indies	Indian blackberry in Jamaica; Jambol

Table 1: Colloquial and scientific names of Jamun (Syzygium cumini) [8-11].

Botanical Description

The scientifically Jamun is placed in Kingdom: Plantae; Subkingdom: Viridiplantae Infrakingdom: Streptophyta; Division: Tracheophyta; Subdivision: Spermatophytina; Infradivision: Angiospermae; Class: Magnoliopsida; Superorder: Rosanae; Order: Myrtales; Family: Myrtaceae; Genus: Syzygium and Species: cumini. Jamun is native to the Indian subcontinent and abundantly grows in India, Bangladesh, Pakistan, Ceylon, Myanmar, and Madagascar and it grows profusely in well-drained, deep, and loamy soils. Jamun is cultivated for its fruits and timber in Israel, the United States of America, and the West Indies [8,11-13]. Jamun tree gets fully grown and matured in 40 years. Jamun is usually 100 feet (30 m) tall, has a 2-3 feet (0.6-0.9 m) trunk diameter and its canopy spreads up to 36 feet (11 m) (Figure 1).

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

Jamun branches off from the ground at a short distance with a discoloured stem bark initially and becomes smooth and light grey upwards. Jamun stem bark is rough, cracked, and loose (Figure 2). Jamun leaves are elliptical, oval, oblong, opposite, blunt, or tapering at the apex and are normally 8 to 10 inches long, and 4 inches wide (Figure 3). The young leaves of Jamun are pink and fully mature leaves are leathery, glossy, dark green above, and light underneath with yellowish midrib and emanate a characteristic turpentine smell. The Jamun flowers are in clusters of a few or 10 to 50 or more and are scented and bloom during March-April. A flower cluster is normally 1 to 4 inches long (2.5-10 cm). The shape of Jamun flowers is round to oblong, funnel-like. Each flower is 1/2 inch (12.7 mm) wide and 0.16 inch (4 mm) long. The young flowers are greenish-white and become rose-pink finally. The flowers possess 4 to 5 petals (united as a small disk) and a toothed calyx (Figure 4) [6,8,11,14]. Jamun flowers turn into fruits and ripened fruits are available in June-July. The raw Jamun fruits are green and turn light to dark purple or even black coloured when fully ripened. The fruits are round to oblong, measuring between 1/2 to 2 inches (1.2 to 5 cm) long and 1 to 2.8 cm wide (Figure 5) [6,8,11,12,14,15]. Jamun fruits taste sweetish sour and the tongue becomes purple after eating Jamun fruit. Jamun seeds are oblong whitish purple coloured when fresh and become brown after drying (Figure 6). Jamun is venerated as a holy tree by the Hindus and Buddhists and it is commonly planted in the Hindu temples. Lord Ganesha (Elephant God) is offered with Jamun fruits and leaves while worshiping and it is loved by Lord Krishna (Jamboo phala saara bhakshitam) [8,11].

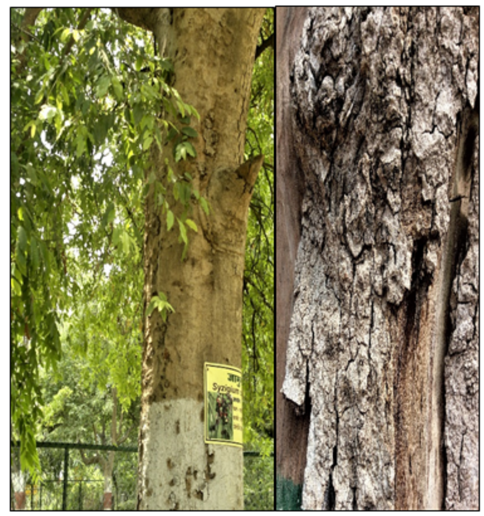

Figure 2: Jamun Syzygium cumini Stem. Left stem and right matured stem bark.

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).

Ethnomedicinal Uses

The ethnomedicinal practices have used Jamun in diverse forms to treat different human diseases [8,11,16]. The Verse 140 of Charak Sutrasthana, 27 characterizes Jamun as medicinally kashaya (slightly astringent), madhura (sweet), amla (sour), ruksha (dry), in taste, guru (heavy), vishtambhi (producing wind in the abdomen, causing bloating), sheetala (cooling), grahi (absorbent, bowel binding), vatakara-aggravates vata, (subtle energy associated with movement) and balances pitta (related to body's metabolism) and kapha (related to body structure), pramehagna (cures urinary diseases including diabetes), and medoroga (obesity) [17]. Jamun is a blood purifier and is a marvelous general health tonic for humans. The stem bark of jamun is antibacterial, astringent, anthelmintic, carminative, constipating, diuretic, digestive, febrifuge, sweet, and stomachic refrigerant. Jamun is used in Ayurveda to treat anorexia, cold, cough, diarrhea, diabetes, emaciation, dental, dysentery, digestive, erectile disorders, liver, skin, worm infestation, and wheezing difficulty. Ayurveda treats diabetic patients by orally feeding 1-3 g of dried Jamun seed powder.

Ethnomedicinally different parts of Jamun are used to cure diabetes, colic, dysentery, diarrhea, digestive complaints, mouth blisters, stomachache, pimples, piles, and cancer [18]. Diabetes in humans is treated by administering 2.5-10 mL (half to two teaspoons) of Jamun ripe fruit juice three times a day [8,11,19,20]. Jamun fruits and seeds are given to cure asthma, bronchitis, diabetes, and splenopathy [8,11,15,21-23]. The acne and blemishes of skin blackheads are erased by Jamun seed powder. Using a mixture of honey and fresh Jamun fruit pulp keeps the body healthy. Taking fruit Jamun juice cures enlarged spleen and urinary complaints [8,11,24]. The dysentery and diarrhea can be treated by eating Jamun seed powder mixed with jaggery [8,11]. The topical application of Jamun leaf juice poultice cures skin disorders and dysentery [8,25,26]. Likewise, topical application of Jamun leaf ash treats bleeding gums and also keeps teeth healthy [8,11,20]. The bed-wetting complaints of children can be prevented by feeding one teaspoon of Jamun seed powder with water. The administration of 3 g of Jamun seed powder cures metrorrhagia in women. The consumption of tablets made from Jamun seed powder and honey (1:1 ratio) with milk helps to treat cataract and the decoction of Jamun leaves relieves conjunctivitis [20].

The Unani medicine considers Jamun as a liver tonic and the topical application of leaf paste heals wounds. Jamun is known to enrich blood, strengthen teeth and gums, and disinfect ringworm and head lice [8,11,27]. Eating Jamun normally for 2-4 months cures hemorrhoids and Jamun fruit pulp also treats gingivitis [8,11]. The dyspepsia, diarrhea, and dysentery can be treated by drinking a decoction of Jamun stem bark, root bark, or dried seeds which also acts as an enema [8,11,26]. The dried stem bark powder mixed in yogurt treats menorrhagia [8,11,19]. The cough and cold can be treated with a mixture of Jamun stem bark powder and fruit juice. Also taking a mixture of half a teaspoon of stem bark powder and one glass of Jamun fruit juice daily acts against infections of the urinary tract and urinary diseases. Jamun seed powder helps to treat strychnine poisoning in India [8,11,25]. Jamun stem bark decoction helps to cure asthma and bronchitis [28]. Jamun stem bark decoction acts as a mouthwash and cures spongy gums, mouth ulcerations, and stomatitis [8,11,24,26]. The topical application of Jamun stem bark ash mixed in oil treats burns and a mixture of Jamun stem bark ash and water is a good anti-inflammatory agent [11,24]. The strain and fatigue can be palliated by the Jamun seed [8,11]. The present article reviews the effect of Jamun on diabetes.

Phytochemical Analysis

Numerous phytochemicals are produced by leaves, roots, stems, fruits, and seeds of Jamun (Table 2). Jamun leaves extracted in ethanol, water, chloroform, hexane, ethyl acetate, petroleum ether, and methanol showed the presence of alkaloids, anthraquinones, cardiac glycosides, glycosides, flavonoids, phenols, phytosterols, saponins, steroids, tannins, proteins, triterpenoids, mucilage, carbohydrates, amino acids, fats, fixed oils, volatile oil, and terpenoids. The micronutrients including copper, calcium, iron, manganese, magnesium, nitrogen, potassium, sulfur phosphorus, and zinc were reported from Jamun leaves [29-36]. Analysis of the ethanol leaf extract of Jamun indicated the presence of flavonoids, tannins, terpenoids, and carbohydrates, whereas the chloroform, ethyl acetate, and methanol Jamun leaf extracts contained carbohydrates only [37]. The glycosides, resins, phenols, saponins, and proteins were detected in the Jamun leaf acetone extract whereas acetone stem bark extract showed alkaloids and flavonoids. The analysis of acetone Jamun root extract showed the presence of alkaloids, flavonoids, glycosides, phenols, resins, saponins, and proteins. Jamun leaf and root extracted in chloroform contained alkaloids, steroids, and proteins. Likewise, chloroform Jamun seed extract did show the presence of alkaloids, phenols, tannins, proteins, and carbohydrates whereas the stem bark extract showed the presence of alkaloids and tannins. The alkaloids, glycosides, flavonoids, phenols, resins, saponins, steroids, tannins, and carbohydrates were detected in the methanol Jamun leaf and stem bark extract and additionally, the proteins were also detected in the root extract. Analysis of the n-hexane extract of stem bark did show the presence of alkaloids, tannins, and proteins, whereas the leaf extract only contained alkaloids. Likewise, the n-hexane root extract contained alkaloids, resins, and carbohydrates and the seed extract contained proteins [38]. The ethanolic and water extracts of Jamun leaves showed the presence of alkaloids, flavonoids, glycosides, resins, saponin tannin, and protein [39]. Similarly, flavonoids, glycosides, phenols, saponins, steroids, tannins, terpenoids, volatile oils, lipids, and sugars were detected in the aqueous and alcoholic extracts of Jamun leaves [40].

S. No.	Parts used	Extract type	Phytochemicals
1.	Leaves	Methanol, ethanol, aqueous, chloroform petroleum ether, acetone and hexane	Alkaloids, anthraquinones, flavonoids, glycosides, steroids, phenols, tannins, saponins, phenols, steroids triterpenoids, cardiac glycosides, phytosterols, resin [29-40].
2.	Stem bark	Aqueous, ethanol, methanol, hexane and chloroform	Terpenoids, flavonoids anthraquinone glycosides, alkaloids, catechins, phenols, quinones, saponins, phytosterols, quinones steroids tannins and amino acids and flavonoids [41].

3.	Seed and fruit pulp	Ethyl acetate, methanol, ethanol, hydroalcoholic	Alkaloids, anthocyanins, tannins, cardiac glycosides, flavonoids, phenols, terpenoids, glycosides, steroids, saponins, reducing mono-saccharides, reducing sugars and proanthocyanidins, proantho-cyanins, saponins, steroids, tannins and phenolic, amino acid, and phytosterols [42-49].
4.	Root	Hexane Aqueous	Alkaloids and resins and carbohydrates Volatile oil, alkaloids, flavo-noids, glycosides, saponins, steroids, tannins, terpenoids, carbohy-drates and mucilage [36,38].

Table 2: Phytochemical constituents of Jamun (Syzygium cumini).

The stem bark extracted in ethanol of Jamun showed alkaloids, anthraquinone, catechins, glycosides, phenols, phytosterols, quinones, saponins, steroids, tannins, terpenoids, amino acids, whereas methanol stem bark extract contained flavonoids additionally. The aqueous Jamun stem bark extract showed flavonoids, catechins, phenols, and quinones [41]. The flavonoids, alkaloids, phytosterols, phenols, tannins, saponins, and amino acids were extracted from the aqueous and methanol Jamun seed extracts [42]. The alkaloids, flavonoids, glycosides, phenol, proanthocyanidins, saponins, terpenoids, steroids, tannins, reducing sugars, and reducing monosaccharides were detected in the aqueous, ethanol, and methanol extracts of Jamun seeds. The chloroform seed extract showed alkaloids, glycosides, saponins, and steroids. The diethyl ether Jamun seed extract showed the presence of flavonoids, phenols, proanthocyanidins, tannins, reducing sugars, and monosaccharides. The steroids and flavonoids have been detected in the n-hexane extract of Jamun seeds and additionally, terpenoids were reported in the benzene extract apart from the flavonoids [43].

The ethyl acetate and methanol extracts of Jamun seeds contained alkaloids, glycosides, flavonoids, steroids, saponins, tannins, and triterpenoids [44]. The alkaloids, anthocyanins, cardiac glycosides, flavonoids, phenols, phytosterols, proanthocyanins, saponins, steroids, tannins, terpenoids, and amino acids have been reported from the ethanol extract of Jamun fruit pulp and seeds [45-47]. The hydroalcoholic Jamun seed extract showed the presence of alkaloids, flavonoids, steroids, and tannins [48]. The alkaloids, glycosides, flavonoids, saponins, steroids, tannins, terpenoids, volatile oils, carbohydrates, and mucilage were reported from the aqueous root extract of Jamun [36]. Methanol and aqueous extracts of Jamun seed contained alkaloids, flavonoids, phenols, saponins tannins, and terpenoids except terpenoids in the aqueous extract. All these phytochemicals were detected in the Jamun leaf extracted in methanol and water except alkaloids in the aqueous leaf extract [49].

Antidiabetic Activity

Diabetes is a lifestyle disease and the number of individuals living with diabetes in 2021 was 537 million globally, which will increase to 643 million by the year 2030 and is projected to rise to 1.31 billion globally in the year 2050. One in every ten individuals suffered from diabetes in 2021 and diabetes is regarded as the ninth-leading killer disease in the world. One diabetic patient died in every five seconds of diabetes in the year 2021 totaling 6.7 million deaths due to diabetes. Health expenditure costs for diabetes in the year 2021 have been 966 billion USD [50-52]. An estimate shows that China has the highest number (141 million) of diabetic individuals followed by India, where individuals living with were 77 million in the year 2021. The prevalence of diabetes in Pakistan is 30.8% and stands number one in the top ten countries with a high rate of diabetes [50,53,54]. Diabetes results in numerous health complications including diabetic kidney disease, retinopathy, coronary heart disease, heart failure, peripheral neuropathy, peripheral vascular disease, stroke, and even cancer [55].

WHO describes diabetes as a chronic metabolic disorder associated with high fasting blood glucose usually greater than 110 mg/ dL (6.1 mmol) and 200 mg/dL (11.1 mmol) postprandial glucose levels [56]. Hyperglycemia in diabetes is the result of defective hormone regulation and the inability of pancreatic β-cells to synthesize and release insulin in the blood due to various factors [57-59]. The homeostasis glucose in human blood is tightly controlled by insulin in liaison with glucagon, corticosteroids, epinephrine, and growth hormone [60]. The damaged pancreas causes dysregulated secretion or cessation of insulin from a nonfunctional or injured pancreas. Diabetes is grouped into three types depending on clinical presentation and etiology. 1. Insulin-dependent diabetes mellitus or Type 1 (IDDM, Type 1). 2. Type 2 diabetes- a non-insulin-dependent diabetes mellitus (NIDDM, Type 2). 3. Gestational diabetes. In addition, the other specific types of diabetes are also described [50,61,62]. IDDM or Type 1 is caused due to the severe damage of of islets of Langerhans of the pancreas by the lymphocytes of own body. This results in the local inflammation and suppression of secretion of insulin synthesis and release by pancreatic β-cells and is regarded as an autoimmune disorder. IDDM or Type 1 diabetes is treated by insulin replacement therapy [63-65]. IDDM or Type 1 diabetes is caused due to genetic predisposition and is more common in children than in adults. The incidence of Type 1 diabetes is constantly increasing [66,67]. Approximately, 8.4 million individuals were living with Type 1 disease globally in the year 2021. Approximately, 0.5 million (median age of onset 29 years), new cases were diagnosed in that year and 35000 non-diagnosed IDDM individuals died within 12 months of symptomatic onset [68]. Type 2 or NIDDM is the most prevalent type 95% of the individuals are living with Type 2 diabetes globally. Type 2 or NIDDM is caused due to insufficient secretion of insulin by the pancreatic β cells and/or the insensitivity of insulin-sensitive tissues to respond to insulin secretion [69]. Ayurvedic texts provide a detailed account of reducing high blood sugar levels in diabetic (Mudhumeha) individuals using Jamun seed powder, although diabetes was not of common occurrence in ancient India.

Preclinical studies

Some of the earlier studies did not find Jamun to treat diabetes in experimental animals, particularly a study conducted on alloxan-induced diabetic rats orally given Jamun seed extract failed to show a decline in blood sugar level [70]. Likewise, streptozotocin-induced diabetes rats treated with lyophilized Jamun fruit pulp extract also could not alleviate raised blood sugar levels [71]. Despite these negative studies, the reports that have shown a reduction in blood sugar level by Jamun are plenty both in preclinical and clinical models [8,15,23,72]. Alleviation in blood glucose level has been reported in rabbits given aqueous Jamun seed extract [73,74]. Similarly, spontaneous diabetic rats fed with ethanol stem bark extract of Jamun have shown a significant reduction in the blood glucose level earlier in the diabetic rats [75,76]. The feeding of rabbits with 1, 2, 4, and 6 g/kg body weight aqueous suspension of Jamun seed powder depleted blood glucose level significantly after 3 h of feeding and 4 g/kg of Jamun seed powder suspension reduced the blood glucose level by 42.64% [77]. The feeding of 2.5 and 5 g/kg body weight Jamun seed aqueous extract once daily for 6 weeks to alloxan-induced diabetic rats reduced blood glucose significantly [78]. A similar effect was reported in diabetic rats fed with Jamun fruit pulp, where an attrion in blood glucose levels was detected within 30 min and a significant hypoglycemic effect of Jamun seed extract was reported by 24 h post-feeding [79].

The high fructose diet fed rats administered with ethanol and aqueous extracts of Jamun seeds decreased blood glucose followed by a rise in insulin levels [80]. The administration of aqueous Jamun seed extract resulted in a significant depletion in serum blood glucose in streptozotocin-induced diabetic mice [81]. The alloxan-induced diabetic rats fed with 15% unextracted, 15% defatted Jamun seed extract, and 6% water soluble gummy fibers diets for 21 days led to a significant decline in reduced blood glucose and a rise in glucose tolerance [82]. The feeding of streptozotocin-induced Wistar rats with 250, 500, and 1000 mg/kg of Jamun seed powder daily for 15 days reduced fasting blood glucose, and the effect was most conspicuous in diabetic rats fed with 500, and 1000 mg/kg Jamun seed powder [83]. The alloxan-induced mild and severe diabetic rabbits daily administered with 100 mg/kg Jamun seeds/kernel ethanol extract for 15 days showed a significant depletion in the blood glucose [84]. Significant attrition in blood glucose, AST, ALT, urea, and cholesterol levels has been reported in streptozotocin-induced diabetic rats treated with 100 mg/kg ethanol extract of Jamun seed kernel for 30 days. This was followed by bringing the GSH, catalase, GPx, and SOD levels to normal and reduction in the lipid peroxidation in the liver and kidney of streptozotocin-induced diabetic rats [85-87]. The streptozotocin-induced diabetes rats after receiving 200 and 400 mg/kg of ethyl acetate and methanol extracts of Jamun seeds or 50 mg/kg of mycaminose, an isolated component from seeds daily for 15 days showed reduced blood glucose level in an earlier study [88].

The streptozotocin-induced Type-2 diabetic Long Evans rats fed with 1.25 g/kg Jamun seed powder and ethanol extract daily for 21 days showed attrition in the blood glucose level [89]. Oral administration with 10 mg/kg body weight active principles isolated from the ethanol fraction of seed extract of Jamun daily for 21 days resulted in an alleviation in the serum glucose in alloxan-induced mild and severe diabetes rats [90,91]. The streptozotocin-induced Type-2 diabetic rats orally given 100, 200, and 400 mg/kg aqueous seed extract of Jamun daily for 21 days brought blood glucose to almost normal level and increased peroxisome proliferator activated receptor (PPARγ) and PPARα gene expression in the diabetic rat liver [92]. Lowered blood glucose level was detected in alloxan-induced diabetic rabbits orally given 50, 100, and 200 mg/kg body weight of Jamun fruit pulp aqueous and ethanol extract or 25 mg of partially purified water extract where the aqueous extract was more effective than the ethanol extract [93]. The daily administration of 200 mg/kg for 15 days of aqueous extract of the Jamun fruit pulp led to a decline in serum glucose in the streptozotocin-induced diabetes female Wistar rats. The combination of the stem bark extract with Cinnamon zeylanicum in a ratio of 1:1 was more effective than a single treatment alone [94].

Attrition in serum glucose level was reported in alloxan-induced diabetic male Sprague Dawley rats fed with 50 or 100 mg/kg aqueous and methanol extracts of Jamun leaves, stem bark, root, and seeds once daily for 21 days. The highest reduction in serum glucose was reported for leaf extract which also restored the architecture of islets of Langerhans to the normal [95]. A significant reduction in serum glucose was reported in alloxan-induced diabetic mice intraperitoneally injected with 150 and 250 mg/kg body weight of aqueous Jamun seed extract once a day for 21 days [96]. An inhibition in porcine pancreatic α-amylase activity in vitro was detected by the methanol extracts of Jamun fruit pulp, seed, and kernel collected from different locations of Gujarat at a concentration of 0.1 to 300 µg and maximum inhibition of α-amylase activity was reported for the kernel extract in vitro [97]. Attrition in the serum glucose and a rise in insulin high sucrose-fed has been reported in Sprague Dawley rats daily fed with a diet mixed with 3% aqueous ethanol extract (50%) of Jamun fruits and seeds for 60 days [98]. Feeding various doses of methanol extract of Jamun seeds for 14 days in alloxan-induced diabetic Wistar albino rats resulted in reduced serum glucose significantly at 9, 11, and 14 days [99].

A reduction in the serum glucose, insulin, HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), and TNF-α levels and an increase in liver PPARγ and PPARα expression was reported in the streptozotocin-induced diabetic Wistar albino rats orally given 100, 200, and 400 mg/kg/day aqueous Jamun seed extract once daily for 21 days. Similarly, a rise in catalase, SOD, and GPx activities and a decline in streptozotocin-induced pancreatic β-cells damage and lipid peroxidation were detected in the rat pancreas [100]. The streptozotocin-induced diabetic C57BL/6 mice fed with 100 mg/kg body weight triterpenoids rich Jamun fruit extract daily for ten days caused significant reduction in the fasting serum glucose and to the pancreatic damage followed by a rise in insulin levels, and HOMA-β index. The triterpenoid-enriched Jamun fruit extract treated diabetic mouse liver showed increased A rise in phosphorylation of serine/threonine kinase (AKT) and p-AKT/AKT followed by a reduction in Forkhead box protein-1 (Foxo-1), phosphoenolpyruvate carboxykinase (PEPCK), peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC1α), and glucose-6-phosphatase (G6Pase) [101]. Streptozotocin-induced diabetic rats. The administration of 200 and 400 mg/kg Jamun root aqueous extract or 4-(2-amino-2-(2-(2-hydroxy-3 methyl butyl) octahydropyrrolo [1,2-a] pyrazin-7-yl) ethyl)-2-ethylphenol (isolated compound) daily for 15 days decreased the serum glucose [36]. Oral administration of streptozotocin-induced diabetic Sprague Dawley rats with 100 and 200 mg of ethanol Jamun seed extract for 2, 4, and 8 weeks significantly reduced blood glucose level and HbA1C, especially for 200 mg extract. The maximum decline was reported for 8 weeks post-administration [102]. The antidiabetic action of Jamun fruit pulp and seed was accessed by analyzing α-amylase and α-glucosidase activity in vitro by the n-hexane, ethyl acetate, and ethanol extracts of Jamun. Jamun pulp and seed extracts resulted in an IC_{50} value of α-amylase 75.85 and 74.72 mg/ml and 55.79 and 59.85 mg/ml α-glucosidase activity, respectively [103]. Oral feeding of streptozotocin-induced diabetic Wistar rats with 5% and 10% Jamun fruit powder for 15, 30, 45, and 80 days led to a time-dependent reduction in blood glucose level with a maximum reduction on 80 days post administration for 5% fruit powder [104]. Aqueous Jamun fruit extract inhibited α-amylase, α-glucosidase, lipase, and porcine pancreatic lipase activity in vitro [105].

Clinical studies

More than 130 clinical trials were conducted to control blood sugar levels in diabetes using Jamun in the Western world however; the results were inconclusive due to mixed responses of patients against Jamun therapy. In these trials, many patients responded well to the treatment, but others did not [8,11,15,23,72,106]. The diabetic patients given aqueous Jamun leaf extract showed a reduction in serum ADA activity and glucose levels [107]. Similarly, diabetic patients given 80% ethanol leaf extract showed a reduction in serum glucose, ADA, 5'-nucleotidase (5'NT), triglycerides, and lipid peroxidation levels followed by a rise in the catalase activity [108]. Attrition in the fasting and postprandial blood glucose levels was reported at 30 and 60 days in the serum of diabetic patients given 2 g Jamun seed powder for 60 days [109]. Feeding 99 diabetic patients with 5 g of seed powder before meals twice daily for 90 days led to a depletion of serum glucose and HbA1c in a randomized double-blind placebo-controlled clinical trial [110]. An almost similar effect was detected in another double-blind clinical study carried out between March 2018-March, 2019 in Type 2 diabetic patients given 5 g of seed powder before meals twice daily for 90 days [111]. Similarly, Type-2 diabetic patients administered orally with 2 g of roasted Jamun seed powder for sixty days showed a reduction in their serum glucose [112]. The aqueous and alcoholic Jamun seed extracts were given to Type 2 diabetic patients for six months in a clinically controlled trial where both extracts lowered blood glucose significantly. The aqueous and alcoholic Jamun seed extracts also cured glycosuria in patients [113]. The preclinical and clinical studies listed above indicate that Jamun is an effective treatment to control diabetes.

Antihyperlipidemic Activity

Hyperlipidemia and diabetes are linked to diabetes causes cardiovascular morbidity. The use of various parts of Jamun reduces serum cholesterol levels. Attrition in serum cholesterol/high-density lipoprotein cholesterol (HDL-c) ratio, serum low density lipoprotein cholesterol (LDL-c), and 3-hydroxy-3 methyl glutaryl CoA (HMG-CoA) reductase activity was reported in alloxan-induced diabetic rabbits fed with ethanol Jamun seed extract [84]. The Jamun seed kernel ethanol extract reduced LDL-c and very low density lipoprotein (VLDL) cholesterol ensued by an increase in HDL-c levels in the streptozotocin-induced diabetic rats [87]. Administration of 200 mg/kg aqueous Jamun fruit pulp extract caused a reduction in the serum total cholesterol, and triglycerides, and increased HDL-c levels in the streptozotocin-induced diabetic rats intraperitoneally [94].

Adminstration of alloxan-induced diabetic rabbits with 10 mg/kg of active principles isolated from the ethanol Jamun seed extract fraction daily for 21 days resulted in an alleviation in the triglycerides, and total cholesterol, accompanied by a rise in the HDL-c [91]. Alloxan-induced diabetic Swiss albino mice administered with 150 and 200 mg/kg body weight of Jamun seed aqueous extract decreased hyperlipidemia by restoring triglycerides and total cholesterol to normal and increased the amount of HDL-c level [96]. Treatment of high cholesterol diet (30 days) rats with 3% ethanol Jamun fruit or seed extract for 60 days caused reduction depletion in triglycerides, and LDL-c accompanied by a significant rise in HDL-c [114]. The administration of 100 mg/kg body weight of triterpenoid-enriched Jamun fruit extract once daily for ten days to streptozotocin-induced diabetic C57BL/6 mice has been reported to reduce triglyceride and free fatty acid (FFA) levels in the serum and liver of diabetic mice. The fruit extract also suppressed the mRNAs of acetyl-CoA carboxylase 1 (ACC1), cluster of differentiation 36 (CD36), stearoyl-CoA desaturase-1 (Scd1), and the fatty acid synthase (Fas). Jamun fruit extract inhibited the protein expression of ACC1 accompanied by an elevation in the p-ACC1 protein expression. The fruit extract normalized the expressions of extracellular signal-regulated kinase (Erk1/2) and p-Erk1/2 in diabetic mice [101]. High-fat diet-fed Charles foster rats treated with Jamun seed extract during induction of hyperlipidemia (49 days) and after hyperlipidemia (90 days) showed a significant decline in triglyceride and LDL-c and raided HDL-c at 49 days post-seed extract treatment. Similar results were recorded on day 139 i.e. 90 days after hyperlipidemia induction indicating the effectiveness of Jamun seed in treating hyperlipidemia [115]. Significant attrition in serum triglycerides, cholesterol, VLDL-c, and LDL-c has been reported in diabetic patients receiving 2 g of Jamun seed powder daily for 60 days [112]. The cholesterol and LDL-c levels declined significantly in diabetic patients given 4.5 g encapsulated Jamun seed powder once daily for 84 days [116].

Anti-obesity Activity

Body mass index > 30 kg/m2 is the hallmark of obesity. Obesity has emerged as one of the significant problems, the world is facing today. A rise of 39% in the obese population throughout the world between 1975 to 2020 has been registered and approximately 764 million individuals were obese in 2020 and it is poised to increase up to 1 billion obese individuals by 2030. Obesity is a risk factor for Type 2 diabetes as obesity is known to trigger diabetes and insulin resistance in humans [117,118]. Obesity can be tackled by using Jamun as numerous preclinical studies have reported; Jamun is a good paradigm for arresting obesity. The Wistar rats maintained on a high carbohydrate and fat diet and fed 2.5% Jamun seed powder mixed in the diet for 56 days exhibited a significant decline in blood glucose, body weight gain, accumulation of white adipose tissue (WAT), serum insulin, total cholesterol, LDL-c, triglycerides, and lipid peroxidation in the plasma. The Jamun seed powder also reduced the activity of AST, ALT, and ALP in obese rats to normal. Further, a restoration in HDL-c, GSH, SOD, and catalase levels in the plasma was reported in the obese rats fed with Jamun seed powder This was accompanied by a decrease in the nitric oxide generation, advanced protein oxidation products, myeloperoxidase, lipid peroxidation, and a rise in the levels of GSH, catalase, and SOD in the liver of obese rats fed with Jamun seed powder [119].

The ethanol and acetone Jamun fruit extracts fed C57BL/6 obese mice showed an arrest in body weight gain, WAT accumulation in epidydimal, visceral, and subcutaneous tissues and the ratio of Firmicutes to Bacteroidetes in the gut became normal. The feeding of ethanol and acetone Jamun fruit extracts to obese mice also reduced serum glucose and insulin levels. The analysis of molecular markers revealed that obese mice receiving both ethanol and acetone Jamun fruit extracts exhibited normal expression of p-AKT and phosphoinositide 3-kinase-PI3k (p85) protein and lowered the phosphorylation of p-IRS (insulin receptor substrate)-1 at Ser318, expression mRNAs of FAS, ACC1, SREBP1c (sterol regulatory element-binding protein), PPARγ, and CD36 in the liver. Both ethanol and acetone Jamun fruit extracts also reduced triglycerides, cholesterol, and FFA levels in the liver and plasma of obese mice except that the plasma cholesterol level remained unaltered [120].

Feeding of 0.5 or 1.0 g/kg/day of hydroalcoholic Jamun leaf extract daily for 8 weeks in obese newborn Wistar rats (monosodium L-glutamate-induced obesity) arrested the weight gain and WAT storage in their retroperitoneal and periepididymal area. Obese rats receiving Jamun leaf extract showed a significant reduction in serum glucose and FFA levels and normalization of total cholesterol and triglyceride. The extract also treated nonalcoholic fatty liver disease and reduced AST activity in the obese rats treated. The study at molecular levels indicated suppression of the G protein-coupled receptor (GPR98) expression, translation of the KDEL (endoplasmic reticulum protein retention receptor) chaperone, and GPR78 leading to mitigating of endoplasmic reticulum stress. Further, Jamun leaf hydroalcoholic extract also inhibited XBP-1s (X-box binding protein), unspliced XBP-1u, MTP (spliced microsomal triglyceride transfer protein), and expression of protein disulfide isomerase (PDI) in the obese rats hepatocytes [121].

Mechanism of Action

How Jamun can reduce diabetes, hyperlipidemia, and obesity is not well understood. All these diseases are often caused by excessive oxidative stress resulting from the accelerated generation of free radicals/reactive oxygen species (ROS) [122,123]. The passivation of free radicals by Jamun seems to be one of the putative mechanisms of action in treating diabetes, hyperlipidemia, and obesity [8,11,124-126]. The activation of molecular markers including PPARα, PPARγ and AKT accompanied by the downregulation of TNF-α, ACC1, Foxo-1, PGC1α, Scid 1, SREPB1c, endoplasmic reticulum protein retention receptor (KEDL), and GPR98 by Jamun are responsible for the attrition of ADA, 5’NTase, Fas, G6Pase, and PEPCK and reduce glucose level and other events of hyperlipidemia and obesity (Figure 7) [100,101,107,109]. The malfunctioning of the (Nuclear factor E2-related factor 2) Nrf2/Keap1/ARE (Antioxidant Response Element) signaling pathway is indicated in diabetes [123,127] and Jamun upregulates and restores this pathway by sequestration of Nrf2/Keap1 and translocation of Nrf2 into the nucleus, where it activates ARE and triggers heme oxygenase-1 (HO1) and NAD[P]H: quinone oxidoreductase-1 (NQO1) pathway which increases the antioxidants like GSH, catalase, glutathione reductase (GR), GPx, SOD, and glutathione-s-transferase (GST) and depletes lipid peroxidation in diabetic, hyperlipidemia and obesity (Figure 8) [128-130]. Apart from these Jamun may have activated other unknown mechanisms to treat diabetes, hyperlipidemia, and obesity.

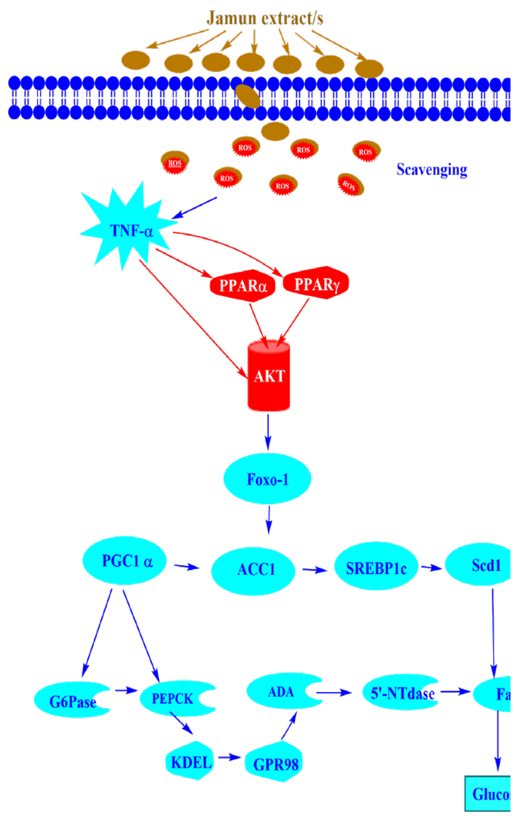

Figure 7: Jamun scavenges free radicals (reactive oxygen species ROS) that downmodulate TNF-α and upregulate protein kinase (AKT), peroxisome proliferator activated receptor (PPARγ) and PPARα that downregulates Forkhead box protein-1 (Foxo-1), peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC1α), (SREBP1c), Acetyl-CoA carboxylase (ACC1), stearoyl-CoA desaturase-1 (ACC1), 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).

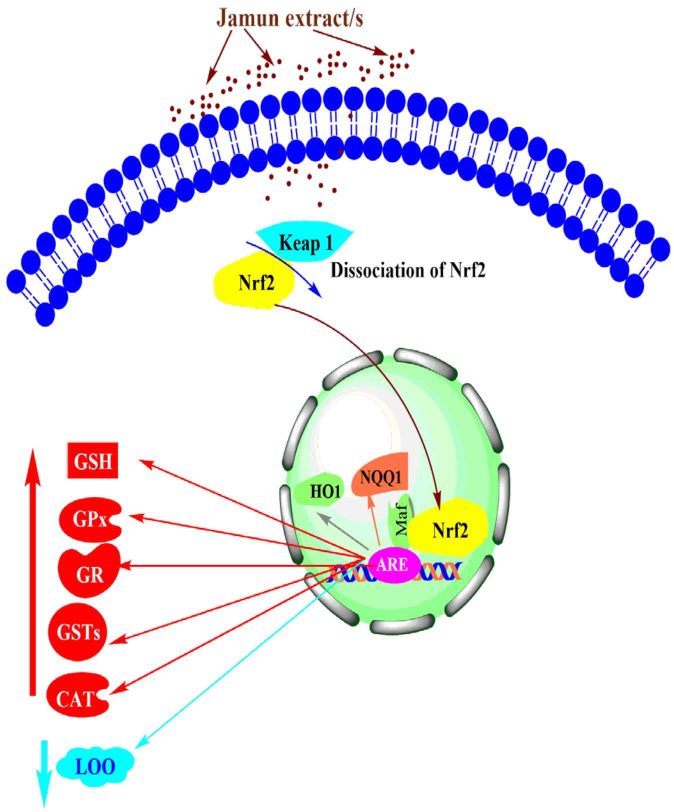

Figure 8: The antidiabetic action of Jamun is due to its ability to dissociate (nuclear factor E2-related factor 2) Nrf2/Keap1 that translocates Nrf2 into the nucleus. Once Nrf2 is in the nucleus it activates antioxidant response element (ARE), heme oxygenase-1 (HO1) and NAD[P]H: quinone oxidoreductase-1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

Conclusion

Traditionally, Jamun finds its extensive use in treating numerous diseases and in particular diabetes. The presence of alkaloids, anthraquinones, cardiac glycosides, catechins, flavonoids, glycosides, phenols, phytosterols, quinones, saponins, steroids, tannins, resins, terpenoids, and volatile oils, in various parts of Jamun may orchestrate its antidiabetic, antiobese and hypolipidemic action in synchrony with each other. Attrition in the 5'NTase, ADA, Fas, G6Pase, activities, and PEPCK by Jamun lower blood glucose. The activation of PPARα, PPARγ, and AKT and suppression of ACC1, Foxo-1, GPR98 PGC1α, Scid 1, and SREPB1c, and KEDL, expression exert antidiabetic, antiobesity, and hypolipidemic action. Activation of the Nrf2 signaling pathway by Jaumn elevates GSH, catalase, GST, GPx, and SOD and reduces lipid peroxidation in diabetic conditions. Extensive research has to be carried out to investigate the safety profile of Jamun and to clearly understand the molecular mechanisms of action in diabetic conditions in vitro and in vivo with a particular emphasis on humans.

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