CHAPTER 42

Antidiabetic and Hypoglycemic Effects of *Syzygium cumini* (Black Plum)

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ABBREVIATIONS

AGEs Advanced glycation end products
CAT Catalase
GSH Reduced glutathione
GST Glutathione S-transferase
H_2O_2 Hydrogen peroxide
LPO Lipid peroxidation
NIDDM Noninsulin-dependent diabetes mellitus
SOD Superoxide dismutase

1. INTRODUCTION

Diabetes mellitus, characterized by chronic hyperglycemia and disturbances in the carbohydrate, fat, and protein metabolism, results from either impaired insulin secretion (type 1 diabetes mellitus) or insulin action (type 2 diabetes mellitus) or at times both (Andrew, 2000). Diabetes is a disease as old as mankind, and ancient literatures dating back to first century BC have documented its existence in different civilizations. In spite of the tremendous progress achieved in medical sciences in the last century, the complete cure and the management of diabetes mellitus are still absent.

Recent information suggests that diabetes is today the world's largest endocrine disorder, and estimates are that it affects almost 10% of the population (WHO, 2009). Approximations are that worldwide, nearly 285 million people are suffering from diabetes and that annually around 3.2 million deaths are attributed to it. It is expected that the number will increase to more than 438 million by the year 2030, and with disproportionate numbers in the developing countries like India, China, Indonesia, Japan, Pakistan and Bangladesh, that have limited resources to treat (WHO, 2009).

The other worrying fact is that while most diabetics in the developed countries are above the age of retirement, in developing countries it is mostly the people between the 35 and 64 years of age that are affected (WHO, 2009). Additionally, the chronic nature

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of the disease and the severity of its complications require regular treatment, which affects not only the individuals and their families but also the health care systems of the world (WHO, 2009). In the milieu of these observations, the World Health Organization (WHO) has indicated that a global diabetic epidemic is underway (WHO, 2009).

Excess hyperglycemia causes glucotoxicity, and this leads to the potentially dangerous long-term side effects like the microvascular impediments that include retinopathy, nephropathy, and neuropathy, and the macrovascular complications like coronary artery disease, peripheral artery disease, and cerebrovascular disease. Nonvascular complications like gastroparesis, infections, and skin changes are also common (Andrew, 2000). These complications require regular medical attention and at times may require prolonged hospitalization. The mechanism by which hyperglycemia precisely causes the observed organ dysfunction is unknown; however, activation of protein kinase C, formation of advanced glycosylation end products, increased sorbitol production, activation of hexosamine pathway, and production of reactive oxygen species and reactive nitrogen species are observed to contribute toward endothelial dysfunction and cellular damage (Andrew, 2000).

2. CLINICAL MANAGEMENT OF DIABETES

Since its discovery in the early 1960s, the use of insulin has been the mainstay in the treatment of diabetes. Insulin is extremely useful in the treatment of type 1 diabetes, where its synthesis is compromised. It is also effective when combined with other hypoglycemic agents in the treatment of type 2 diabetes when other modalities are ineffective. However, the development of severe hypoglycemia and localized lipoatrophy at the site of injection complicates the management (Andrew, 2000).

On a comparative note, the clinical management of type 2 diabetes is complicated and is used either as monotherapy or in combination to achieve better glycemic regulation. The use of secretagogs like sulfonylureas and meglitanides is associated with hypoglycemia and weight gain; metformin to cause lactic acidosis and to aggravate renal failure; thiazolidonediones to cause fluid retention, cause weight gain, and increase the risk of fracture; alpha glucosidase inhibitors to cause abdominal discomfort, flatus, diarrhea, jaundice, and cholestasis; glucagon like peptide (GLP 1) analogs to cause nausea, pancreatitis, and severe allergic reactions; and amylin agonist to cause nausea and hypoglycemia (Andrew, 2000).

In view of these observations, discovering newer antidiabetic agents especially from herbal sources, used in the various alternative and complementary systems of medicines that recognize the disease condition and have medications subscribed, is useful

(Grover et al., 2000, 2002; Mukherjee et al., 2006). The advantages of these plants over modern medicines are that most of the traditional medicines are plant based and comparatively cheaper, orally administrable, possess fewer side effects, and have easy acceptability (Grover et al., 2002; Mukherjee et al., 2006).

3. AYURVEDA AND DIABETES

Ayurveda, which in Sanskrit means knowledge of life (*ayu* = longevity and *veda* = knowledge), is the traditional Indian medical system of medicine. It has been practiced for more than 5000 years in the Indian subcontinent and is still an integral part of the Indian culture and materia (Mukherjee et al., 2006). The early practitioners of Ayurveda were aware of diabetes mellitus and the renowned texts of Ayurveda like *Charaka Samhita* (1000 BC), *Sushruta Samhita* (600 BC), and subsequent works refer to this disease under the term Madhumeha or Ikshumeha ('madhu' meaning sweet/sweetness and 'meha' excessive urination). Detailed descriptions of pathogenesis, prevention, and management of diabetes are found in the ancient literatures of Ayurveda (Grover et al., 2002; Mukherjee et al., 2006).

Ayurveda treats diabetes by advocating a balanced and holistic multimodality approach consisting of change of life style, exercise (yoga), and administering medications made from various herbs like *Gymnema sylvestre*, *Momordica charantia*, *Aegle marmeloes*, *Swertia chirayita*, *Syzigium cumini*, and *Trigonella foenum graecum* that are now reported to possess antihyperglycemic and antidiabetic actions in various experimental systems of studies, validated and followed in the modern system of medicine (Grover et al., 2002; Mukherjee et al., 2006).

4. *SYZYGIUM cumini* AS ANTIDIABETIC PLANT OF IMPORTANCE

S. cumini Lam. Skeels (Syn. *Eugenia jambolana* Lam; *S. jambolanu* DC) (Figure 42.1), an evergreen tree belonging to family myrtaceae, is one of the most important medicinal plants used in the treatment of diabetes in Ayurveda and in the various folk systems of

Figure 42.1 Photograph of Jamun fruit, seed, and leaf.

medicine in Southeast Asia. Jamun is also used in the treatment of diabetes in the Unani, Siddha, Srilankan, and Tibetan and in the Homeopathy systems of alternative and complementary medicine (International Academy of Classical Homeopathy, 2010; Sagrawat et al., 2006). Additionally, Jamun is also a major constituent of many marketed antidiabetic formulations and some of the well-known formulations which contain Jamun include diabecon, diasulin, pancreatic tonic 180cp, dia-care, diabeta, hyponidd, and diashis (Subash Babu and Prince, 2004).

4.1 Botanical Aspects of Jamun

Historically, the Jamun tree was exclusive to the Indian subcontinent but is today found growing throughout the Asian subcontinent, Eastern Africa, South Africa, Madagaskar, and in the warmer regions of USA in states like Florida. The fruit of *E. jambolana* is called by different names such as Jamun, black plum, Indian blackberry, jambu, and jambool (Warrier et al., 1996). The tree grows up to a height of 50 ft and has sufficiently large canopy. The young barks are pale brown in color, while the mature are slightly dark brown, scaly and at times peel off. The leaves are elliptic to broadly oblong, smooth, glossy, leathery, and fibrous in nature (Warrier et al., 1996).

The tree flowers and fruits once a year, which in the Indian subcontinent is during the month of June–July. The flowers are sessile, small (7–12 mm), white in color, fragrant, and with thin membranous petals. They are arranged mostly in threes and appear usually from the scars of the fallen leaves (Warrier et al., 1996). The fruits are found in clusters of 4–20, and the process of fruiting from the flowering stage takes around 2 months to complete. The Jamun fruits present in a bunch, do not ripen all at once, and drop off when fully ripe. Each fruit is round, oblong, or ellipsoid, 1/2 to 2 in. long with a centrally placed large seed. The raw fruits are green in color and as they mature turn to light magenta and then to dark purple or black when fully ripe. The fully ripe fruit has a combination of sweet, mildly sour, and astringent flavor and imparts purple color to the tongue of the consumer (Warrier et al., 1996).

4.2 Phytochemistry of Jamun

Jamun plant is known to possess diverse phytochemicals, most of which are observed to be of beneficial effects to health. The stem bark is reported to possess friedelin, friedelan-3-α-ol, betulinic acid, β-sitosterol, kaempferol, β-sitosterol-D-glucoside, gallic acid, ellagic acid, gallotannin and ellagitannin, and myricetine (Sagrawat et al., 2006). The leaves are known to contain β-sitosterol, betulinic acid, mycaminose, crategolic (maslinic) acid, *n*-hepatcosane, *n*-nonacosane, *n*-hentriacontane, noctacosanol, *n*-triacontanol, *n*-dotricontanol, quercetin, myricetin, myricitrin, and the flavonol glycosides myricetin 3-O-(4″-acetyl)-α-L-rhamnopyranosides (Sagrawat et al., 2006). The flowers are observed to contain oleanolic acid, ellagic acids, isoquercetin, quercetin, kampferol, and myricetin (Sagrawat et al., 2006).

Studies have shown that the pulp of Jamun contains anthocyanins, delphinidin, petunidin, and malvidin-diglucosides. These compounds are responsible for their bright purple color (Sagrawat et al., 2006; Sharma et al., 2008a,b; Veigas et al., 2007). The seeds are the most studied plant part and are reported to contain jambosine, gallic acid, ellagic acid, corilagin, 3,6-hexahydroxy diphenoylglucose, 4,6-hexahydroxydiphenoylglucose, 1-galloylglucose, 3-galloylglucose, quercetin, and β-sitoterol (Sagrawat et al., 2006). The essential oil is reported to contain the phytochemicals pinocarveol, α-terpeneol, myrtenol, eucarvone, muurolol, α-myrtenal, 1, 8-cineole, geranyl acetone, α-cadinol, and pinocarvone. Some of the phytochemicals are depicted in Figure 42.2.

4.3 Traditional Uses

All parts of the Jamun and the seeds in particular have a long history of medicinal use in the various traditional and folk systems of medicines in countries where it grows. The fruits are considered to be tonic, astringent, carminative, and useful in spleen diseases. The fruits and seeds are also used to treat pharyngitis and ringworm infection. The fruits are acrid and sweet, cooling, dry, and astringent to bowels (Warrier et al., 1996). Seeds are astringent, diuretic, and stop urinary discharge (Warrier et al., 1996). The bark of the plant is astringent, sweet, refrigerant, carminative, antihelmintic, febrifuge, constipating, stomachic, antibacterial, diuretic, and digestive (Warrier et al., 1996). The leaves have been extensively used to treat diabetes, constipation, leucorrhoea, stomachalgia, fever, gastropathy, strangury, dermopathy and to inhibit blood discharges in the feces (Warrier et al., 1996). The leaves are considered to possess antibacterial effects and are used to strengthen the teeth and gums (Warrier et al., 1996).

In the Ayurvedic system of medicine, Jamun is considered good for treating sore throat, bronchitis, asthma, dysentery, and diabetes mellitus. In India, decoction of kernels Jamun is used as household remedy for diabetes. In the Siddha system of medicine, Jamun is recognized to be hematinic, semen promoting, and to reduce the excessive heat of the body (Warrier et al., 1996). According to the Unani system of medicine, it acts as liver tonic, enriches blood, strengthens teeth and gums, and forms good lotion for removing ringworm infection of the head. The ashes of the leaves are used as a dentrificant to strengthen the teeth and the gums (Warrier et al., 1996). The seeds are astringent, diuretic, stop urinary discharge, and are a remedy for diabetes. The barks also possesses wound-healing properties. The homeopathic system of medicine, originally native to Europe, also uses Jamun to treat various ailments, including diabetes.

5. ANTIDIABETIC EFFECTS OF JAMUN

Jamun has been thoroughly investigated for its antidiabetic effects during the last 127 years. Many experimental studies with rodents have shown that the seed, fruit, and bark of Jamun possess antidiabetic effects (Gohil et al., 2010; Helmstädter, 2007,

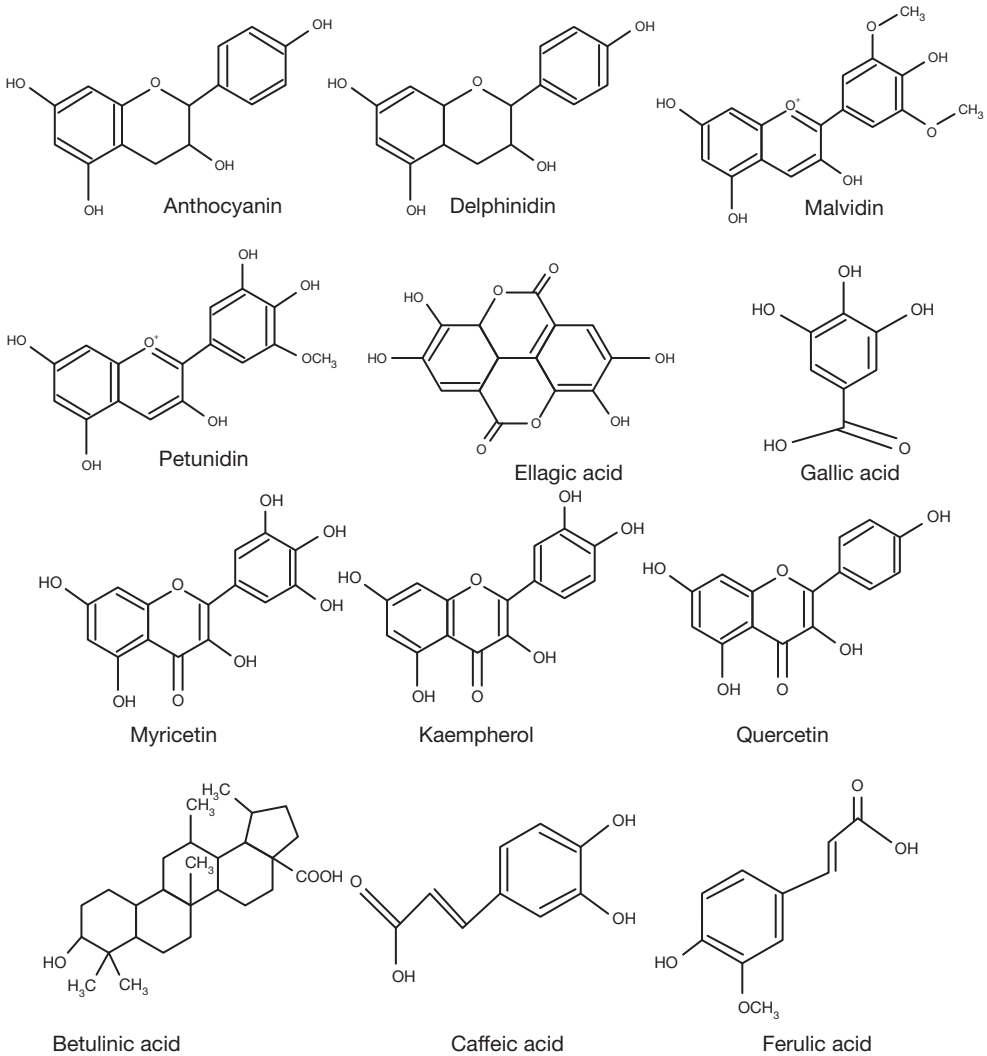

Figure 42.2 Important phytochemicals present in Jamun.

2008; Sharma et al., 2009), while the leaf is devoid of these effects (Pepato et al., 2001). Jamun exhibited hypoglycemic action similar or sometimes even better than the oral hypoglycemic drugs (Sahana et al., 2010; Saravanan and Pari, 2007; Subash Babu and Prince, 2004).

Administering Jamun is observed to decrease the fasting and postprandial blood glucose levels by about 30%, in these studies. Jamun seeds and their extracts, both polar and nonpolar, have been reported to be effective. Fruit pulps when administered as lyophilized powder too were proficient. Jamun was capable in preventing hyperglycemia and

diabetic complications in laboratory animals. The dosage in these studies ranged from 25 to 2000 mg kg^{-1}, and the duration of treatment was from a single administration to daily for up to 6 weeks. Consequently, a few studies also suggest that Jamun possesses antihyperglycemic action in humans suffering from diabetes (Gohil et al., 2010; Helmstädter, 2008; Sahana et al., 2010; Sharma et al., 2009).

6. USE OF JAMUN SEEDS IN THE TREATMENT OF DIABETES, PRECLINICAL STUDIES

Innumerable experimental studies in the past two decades have shown that the seed of Jamun possesses antihyperglycemic effects (Achrekar et al., 1991; Rathi et al., 2002; Ravi et al., 2004a,b,c, 2005; Sharma et al., 2003, 2008a,b; Sridhar et al., 2005). The Jamun seed, which is the ethnomedically recommended plant part, has been studied extensively, and the observations seen from the scientific studies validated the traditional observations.

Studies with alloxan-induced diabetic rabbits have shown that ethanolic extract of the seeds was effective in decreasing hyperglycemia in the subdiabetic and mildly diabetic rabbits, but it was ineffective against severely diabetic rabbits. Administering the extract (100 mg kg^{-1} body weight) orally to subdiabetic rabbits for 1 day, mildly diabetic for 7 days, and severely diabetic rabbits for 15 days showed significant decrease in the fasting blood glucose during glucose tolerance test. In addition, a significant decrease in the glycosylated hemoglobin levels and a concomitant increase in the concentration of serum insulin, and in the levels of liver and muscle glycogen were also observed. The histopathological studies of liver, pancreas, and aorta in alcoholic extract treated diabetic groups showed almost normal appearance (Sharma et al., 2003).

Sharma et al. (2009) purified hypoglycemic principles from Jamun seeds and one such principle named as LH II was shown to contain saturated fatty acid and sterol. Administration of LH-II orally at a dose of 10 mg kg^{-1} resulted in significant decrease in fasting blood glucose at 90 min, seventh day, and fifteenth day in diabetic rabbits. Glycosylated hemoglobin was significantly decreased in severely diabetic rabbits after 15 days of treatment. Plasma insulin levels were significantly increased. To further validate these observations, mechanistic studies in the *in vitro* systems with pancreatic islets have shown a threefold increase in insulin levels as compared with untreated animals. There was an increase in the activity of key enzymes of glycolysis and decrease in the activity of key enzymes of gluconeogenesis. Liver and muscle glycogen content were also increased (Sharma et al., 2009).

The flavonoid-rich extract obtained from seeds of Jamun is also observed to be an efficient antihyperglycemic agent in the streptozotocin-induced diabetic rats (Sharma et al., 2008a). *In vitro* study validated that the culturing pancreatic cells with flavonoids stimulated 16% release in insulin, thereby confirming its ethnomedicinally presumed

secretagog effects. The extract also possessed hypolipidemic action and decreased the levels of low-density lipoprotein (LDL) and triglycerides and increased the high-density lipoprotein (HDL) levels over untreated diabetic rats (Sharma et al., 2008a).

The rate of glycogen biosynthesis levels of glucose homeostatic enzymes (glucose-6-phosphatase, and hexokinase) was also enhanced when compared with the diabetic cohorts (Sharma et al., 2008b). Jamun seed and pulp extract stimulated the release of insulin from the cultured Langerhans cells from both normal and diabetic rats, with better effects seen in the cells from the normoglycemic animals (Achrekar et al., 1991). The pulp and seed extracts were also found to inhibit the hepatic and renal insulinase activity in a concentration-dependent manner (Achrekar et al., 1991).

In addition to decreasing hyperglycemia and hyperinsulinemia, animal studies have also shown that Jamun seeds prevented the diabetes-induced secondary complications like nephropathy, neuropathy (Grover et al., 2002), gastropathy (Grover et al., 2002), and diabetic cataract (Rathi et al., 2002) and also decreased peptic ulceration (Chaturvedi et al., 2009). These properties are useful in the management of the hyperglycemia-induced complications and in improving the quality of life of the patients.

The alcoholic extract of Jamun was shown to restore serum glutamic oxaloacetate transminase and serum glutamic pyruvate transminase activities and serum urea, total protein, and albumin concentrations in streptozotocin diabetic rats, in a dose- and duration-dependent manner. These observations suggest that Jamun is useful in preventing structural and functional impairment of liver and kidney, in diabetes. The beneficial effects of Jamun in 500 mg kg^{-1} dose in streptozotocin diabetic rats were comparable to that of glibenclamide (300 μg kg^{-1}), a standard oral hypoglycemic drug used in clinical practice (Sundaram et al., 2009). Studies have also shown that mycaminose (50 mg kg^{-1}), isolated from the seeds of Jamun, produced significant reduction in blood glucose level against streptozotocin-induced diabetes in rats (Kumar et al., 2008).

Administration of different doses of alcoholic and aqueous extracts of Jamun seed to fructose-induced type 2 diabetic rats was observed to cause concentration-dependent beneficial effects. Feeding fructose for 15 days increased the serum glucose, insulin levels, and the triglycerides levels marginally when compared with the normal controls (Vikrant et al., 2001). Treatment with 400 mg day^{-1} of aqueous extracts of Jamun for 15 days substantially prevented hyperglycemia and hyperinsulinemia induced by a diet high in fructose, suggesting it to be of use in type 2 diabetes (Vikrant et al., 2001).

7. USE OF JAMUN FRUIT PULP IN DIABETES TREATMENT

The fruits of Indian Jamun have been shown to have antihyperglyciemic properties (Achrekar et al., 1991; Sharma et al., 2006; Sundaram et al., 2009). The oral antihyperglycemic effect of water and ethanolic extracts of the fruit pulp of Jamun was investigated in alloxan-induced rabbits (Sharma et al., 2006). Water extract was found to be more

effective than the ethanolic extract in reducing the fasting blood glucose and improving blood glucose in the glucose tolerance test. Chromatographic purification of the water extract yielded two hypoglycemic fractions. Decrease in fasting blood glucose, improved glucose tolerance, and increase in the plasma insulin levels were seen in both moderately diabetic and severely diabetic rabbits. *In vitro* studies with pancreatic islets showed that the insulin release was nearly two and half times more than that in untreated diabetic rabbits (Sharma et al., 2006).

The mechanism of action of FIII fraction appears to be both pancreatic by stimulating release of insulin and extra pancreatic by directly acting on the tissue (Sharma et al., 2006). Pepato et al. (2005) investigated the antidiabetic effects of Brazilian Jamun fruit. They found that, when compared to the untreated controls, rats treated with the lyophilized fruit pulp showed no observable difference in body weight, food or water intake, urine volume, glycemia, urinary urea and glucose, hepatic glycogen, or on serum levels of total cholesterol, HDL cholesterol, or triglycerides. This lack of any apparent effect on diabetes was attributed to the regional ecosystem where the fruit was collected and to the severity of the induced diabetes (Pepato et al., 2005).

8. JAMUN BARK IN DIABETES TREATMENT

Dried bark at a dose of 5 mg/20 g mouse caused significant decrease in glucose levels after a glucose tolerance testing (Villasenor and Lamadrid, 2006). Oral or intraperitoneal administration of bark extract exhibited antidiabetic activity by significantly lowering blood glucose and urine sugar levels in diabetic rats and improving glucose tolerance. Additionally, diabetic rats treated with bark extract had elevated levels of plasma insulin and C-peptide. There was also a significant decrease in the level of sialic acid and elevated levels of hexose, hexosamine, and fucose in the liver and kidney of diabetic rats, which was reversed by bark extract treatment. As compared with glibenclamide, bark extract had better antidiabetic effects (Saravanan and Leelavinothan, 2006; Saravanan and Pari, 2007).

9. HUMAN TRIALS ON ANTIDIABETIC EFFECT OF JAMUN

There have been very few studies on human volunteers in the post-1945 era, but these studies have shown promising results. Srivastava et al. (1983) administered 4–24 g of the seed powder to 28 diabetic patients and observed a reduction in the mean fasting and postprandial blood sugar levels. Later, Kohli and Singh (1993) have also observed that administering 12 g of the Jamun seed powder in three divided doses for 3 months to 30 patients with 'uncomplicated' noninsulin-dependent diabetes mellitus (NIDDM) caused a moderate hypoglycemic effect. The effect of Jamun was comparable to that of chlorpropamide, and it caused considerable relief by ameliorating symptoms like polyurea, polyphagia, weakness, and weight loss. In this study, no side effects were observed,

and this may be possibly due to the fact that the powder was administered thrice a day (Kohli and Singh, 1993).

Recently, in an open labeled randomized parallel designed controlled study with freshly diagnosed, 15 type 2 diabetes mellitus patients, Sahana et al. (2010) observed that administering the standardized seed powder caused a significant decrease in the fasting blood sugar, insulin resistance, and increase in High-density lipoprotein (HDL) cholesterol at the end of the third month (when compared with the baseline). However, there was no significant reduction in the post-prandial blood sugar (PPBS) and glycated hemoglobin (hemoglobin A1c, HbA1c, A1C, or Hb1c) at the end of third and sixth month, when compared to the baseline. There was no change in the triglyceride, total cholesterol, and low-density lipoprotein (LDL) LDL levels (Sahana et al., 2010).

10. MECHANISMS OF ACTION

Diabetes mellitus is a multifactorial disorder involving genetic influence and effects of environmental factors. Type 1 diabetes mellitus involves genetic basis with autoimmune destruction of pancreatic islet beta cells triggered by viral infections. Type 2 diabetes mellitus has the involvement of many genes and multiple environmental factors. Insulin resistance, decreased insulin sensitivity, impaired glucose uptake, hyperglycemia, and dyslipidemia are the biochemical features of type 2 diabetes mellitus. The long-term complications of DM include retinopathy, neuropathy, and nephropathy.

Various mechanisms have been proposed for the antidiabetic actions of Jamun. These mechanisms include stimulation of pancreatic insulin secretion (Achrekar et al., 1991; Gohil et al., 2010; Saravanan and Leelavinothan, 2006; Sharma et al., 2006, 2009; Sridhar et al., 2005), restoration of beta cell architecture (Achrekar et al., 1991; Gohil et al., 2010; Sharma et al., 2003), reduction of oxidative stress and antioxidant action (Ravi et al., 2004a,c; Subash Babu and Prince, 2004), and amelioration of dyslipidemia (Gohil et al., 2010; Sharma et al., 2008a,b).

Other mechanisms suggested are inhibition of the human peroxisome proliferator-activated receptor (PPAR) gamma (Rau et al., 2006), upregulation of the glucose transporter type 4 (GLUT-4) (Anandharajan et al., 2006), rise in cathepsin-B activity (Achrekar et al., 1991), inhibition of extrahepatic insulinase activity, development of insulin positive cells from the pancreatic duct epithelial cells (Schossler et al., 2004), and increase in glycogen content in liver and muscle (Achrekar et al., 1991; Sharma et al., 2003, 2008a). Jamun also caused an increase in the activity of key enzymes of glycolysis and decrease in the activity of important enzymes of gluconeogenesis (Sharma et al., 2009).

10.1 Jamun Stimulates Pancreatic Insulin Secretion and Restores and Regenerates Beta Cell Architecture (Secretagog Effect)

Optimal pancreatic beta-cell function is essential for the regulation of glucose homeostasis, and its impairment leads to the development of diabetes. Insulin and C-peptide are the

products of the enzymatic cleavage of proinsulin and are secreted into the circulation in equimolar concentrations. Serum levels of insulin and C-peptide are indicators of beta cell function. Few studies have demonstrated that Jamun stimulates secretion of pancreatic insulin (Achrekar et al., 1991; Gohil et al., 2010; Ravi et al., 2004a,b; Sharma et al., 2006; Sridhar et al., 2005). Increased C-peptide on treatment with Jamun bark extract has been observed in diabetic rats (Saravanan and Leelavinothan, 2006; Saravanan and Pari, 2007).

Jamun administration is reported to restore the architecture of the pancreatic beta cell in diabetic experimental animal cells (Achrekar et al., 1991; Gohil et al., 2010; Sharma et al., 2003). Additionally, it also increases plasma insulin levels by converting proinsulin to insulin possibly through pancreatic cathapsin B and its secretion (Bansal et al., 1981). Jamun extract is also reported to inhibit the insulinase activity from the liver and kidney (which are the main sites for insulin extraction), thereby suggesting that its protective effects are also mediated by the extrapancreatic pathways (Achrekar et al., 1991; Gohil et al., 2010; Sharma et al., 2008a,b).

Phytochemical examinations have confirmed that Jamun contains flavonoids and other polyphenolics, and it is possible that these compounds could act separately or synergistically to cause the hypoglycemic effect. To substantiate this, flavonoids are shown to regenerate the damaged pancreatic beta cells in diabetic animals (Vessal et al., 2003). Anthocyanins, the natural colorants, have also been shown to stimulate insulin secretion from rodent pancreatic β-cells *in vitro* (Jayaprakasam et al., 2005).

10.2 Jamun Reduces the Oxidative Stress and Improves Antioxidant Status

Oxidative stress refers to a condition of increased generation of free radicals and depletion of antioxidant defense systems. Experimental evidence suggests the involvement of free radicals in the onset of diabetes and more importantly in the development of diabetic complications. Persistent hyperglycemia in the diabetic patients leads to generation of oxidative stress due to autooxidation of glucose, nonenzymatic glycosylation of body proteins, and polyol pathway. The autooxidation of glucose involves spontaneous reduction of molecular oxygen to superoxide and hydroxyl radicals, which are highly reactive and interact with all biomolecules. They also accelerate the formation of advanced glycation end products (AGEs) and impair synthesis, regeneration, and functioning of antioxidants. Together these mechanisms contribute to the secondary complications observed in diabetes (Yan et al., 2008).

Benherlal and Arumughan (2007) evaluated the antioxidant effects of the ethanolic extract of the fruit pulp, kernel, and seed coat in various *in vitro* assays (diphenyl-1-picryl-hydrazyl (DPPH), OH and $O_2\bullet^-$) with gallic acid, quercetin, and trolox as reference molecules. The authors observed that in the DPPH scavenging assay the kernel extract was better than the seed coat and pulp extract but less effective than the reference

molecules. However, in the superoxide radical scavenging activity the kernel extract was six times more effective than trolox and three times more than catechin.

In hydroxyl radical scavenging assay, the kernel extract was comparable to the effect of catechin (Benherlal and Arumughan, 2007). The methanol–formic acid (9:1) extract of the fruit (Reynertson et al., 2008), the hydroethanolic extract of the seed (Raquibul-Hasan et al., 2009), and anthocyanin-rich fruit peel extract (Veigas et al., 2008) have all been reported to be potent free radical scavengers in the DPPH scavenging assay. The hydrolyzable and condensed tannins in the fruit are also reported to possess antioxidant activity in the DPPH radical scavenging and fluorescence recovery after photobleaching assays (Zhang and Lin, 2009). The organic extract of the leaf (methanol-dichloromethane extract) as well as the hydroethanolic extract of the seed are reported to be a scavenger of nitric oxide *in vitro* (Jagetia et al., 2005).

Studies by Banerjee et al. (2005) have shown that the fruit skin of Jamun possesses antioxidant effects as confirmed by results from the hydroxyl radical-scavenging assay, superoxide radical-scavenging assay, DPPH radical-scavenging assay, and lipid peroxidation assay with egg yolk as the lipid-rich source. The anthocyanin-rich fruit peel extract is also observed to be an effective reducing agent (Veigas et al., 2008). Recently, Bajpai et al. (2005) have also observed that the hydromethanolic extract of the Jamun seed was effective in scavenging (90.6%) free radicals as evaluated in the autooxidation of β-carotene and linoleic acid assay. The authors observed that there was a direct correlation between the free radical scavenging effect and the presence of high total phenolic content in the extract and that this contributed to the observed effects (Bajpai et al., 2005).

Animal studies have also shown that administering Jamun decreased the levels of lipid peroxides in the stomach of animals subjected to ulcerogenic treatments (Chaturvedi et al., 2009) in the brain, liver, kidneys, and serum of diabetic animals (Ravi et al., 2004a,c; Subash Babu and Prince, 2004).

10.3 Jamun Improves Glucose Utilization and Maintains Glucose Homeostasis

In the postprandial state, insulin promotes the uptake of glucose by tissues, glycolysis, oxidation, and glycogenesis. Studies suggest that administering Jamun increases glycogen content in the liver and muscle cells of diabetic animals (Achrekar et al., 1991; Gohil et al., 2010; Ravi et al., 2003; Sharma et al., 2003, 2008a,b), increases the activities of enzymes crucial for glycogenesis and glycolysis, and concomitantly decreases enzymes involved in gluconeogenesis.

10.4 Jamun Prevents Alterations in Glycation Status and Formation of AGEs

The high incidence of vascular complications in patients with diabetes mellitus has prompted researchers to look for a relationship between vascular dysfunction and

diabetes mellitus. Several hypotheses relating to hyperglycemia have been proposed: the sorbitol hypothesis, the diacyl glycerol pathway, the nonenzymatic glycation of proteins, and an alteration of the redox potential. A long exposure to hyperglycemia leads to the glycosylation of proteins and lipoproteins by a nonenzymatic pathway called as Maillard reaction. The nonenzymatic glycosylation, or glycation, results in the formation of different classes of heterogeneous sugar–protein adduct collectively called AGEs (Yan et al., 2008).

AGEs generate reactive oxygen intermediates by autooxidation. They are responsible for diabetic microvascular and macrovascular complications. Blood levels of glycated proteins and their products such as glycated hemoglobin, glycated albumin, and fructosamine are used as indices of glycemic control in diabetics. Studies have shown that the blood levels of glycated hemoglobin in experimental diabetic animals decreased on administering Jamun (Sharma et al., 2006, 2008a,b, 2009). However, similar observation was unseen in glycated hemoglobin levels of humans administered with Jamun (Sahana et al., 2010).

Levels of glycoconjugates such as protein-bound sialic acid, protein-bound fucose, and protein-bound hexosamines are known to increase with progression of diabetic complications. Diabetic rats showed increased or decreased levels of sialic acid and increased levels of total hexoses, fucose, and hexosamines in plasma, liver, kidney, heart, and brain (Saravanan and Pari, 2007). Treatment with Jamun bark extract was effective in restoring the levels of sialic acid, hexose, hexosamine, and fucose in plasma, liver, and kidney of diabetic rats (Saravanan and Pari, 2007). The observed effect of Jamun bark extract on reversing the adverse effects of hyperglycemia provides an insight into the pathogenesis of diabetic complications and may be used to advantage in therapeutic approaches.

10.5 Jamun Has Ameliorating Effect on Dyslipidemia in Diabetes

Dyslipidemia characterized by increased levels of triglycerides, total cholesterol, and LDL and decreased level of HDL is an important biochemical abnormality of diabetes mellitus. Free radicals target lipoproteins, especially LDL, to cause their oxidation. Oxidized LDL is implicated in the etiopathogenesis of atherosclerosis and vascular complications of DM and cardiovascular diseases (Vikrant et al., 2001).

Preclinical studies have shown that administering Jamun seeds and fruits decreased LDL cholesterol, triglycerides, and total cholesterol and increased HDL cholesterol in diabetic rats or rabbits (Helmstädter, 2008; Sharma et al., 2006, 2008a,b; Vikrant et al., 2001). In the case of human studies, some observations suggest beneficial effects in amelioration of dyslipidemia (Helmstädter, 2008) while others have been contradictory (Sahana et al., 2010).

10.6 Jamun Inhibits Alpha-Glucosidases

Alpha-glucosidase inhibitors (acarbose, migitol, and voglibose), which inhibit the digestion of carbohydrates, are used to establish greater glycemic control over hyperglycemia in diabetes mellitus type 2, particularly with regard to postprandial hyperglycemia. They may be used as monotherapy in conjunction with an appropriate diabetic diet and exercise, or they may be used in conjunction with other antidiabetic drugs. These medications do not stimulate pancreas to produce insulin, and they lower blood sugar when used in combination with other oral medications for diabetes or with insulin.

Recently, *in vitro* studies by Ahmed et al. (2009) have shown that the Jamun extract significantly inhibited the α-amylase, α-glucosidase, and sucrase activities in a dose-dependent manner. The heat treatment of the sample resulted in a significant increase in the α-amylase inhibitory activity of the sample, while a marginal increase in the α-glucosidase and sucrase inhibitory activities was observed. These findings emphasize that inhibition of carbohydrate hydrolyzing enzymes is one of the mechanisms through which Jamun exerts its hypoglycemic effect *in vivo* (Ahmed et al., 2009).

10.7 Jamun Activates Peroxisomal Proliferator-Activated Receptors

The PPARs are a group of nuclear receptor proteins important in the regulation of carbohydrate, lipid, and protein metabolism. They are expressed highly in the adipose tissue, and activation of PPARγ induces adipocyte differentiation and lipid accumulation by modulating numerous genes regulating adipogenesis, lipid uptake, and lipid metabolism (Berger, 2005). The hypolipidemic fibrates activate PPARα, and the antidiabetic glitazones activate PPARγ. The fibrate-type hypolipidemic drugs can induce the expression of genes participating in lipid catabolism such as fatty acid uptake and binding, fatty acid oxidation in microsomes, peroxisomes, and mitochondria, and lipoprotein assembly and transport. Likewise, thiazolidinediones are PPARγ ligands, and the antidiabetic effects exerted by this type of drugs are believed to be mediated by PPARγ (Libby and Plutzky, 2007).

A growing body of evidence indicates that herbal compounds influence PPARs and mediate their protective effects (Rau et al., 2006). Rau et al. (2006) screened a variety of ethanolic extracts, obtained from traditionally used herbs including Jamun, for PPAR activation. They observed that Jamun activated both PPARα and PPARγ. Sharma et al. (2008a,b) observed that the hypoglycemic and hypolipidemic actions of Jamun were mediated through dual mechanisms (1) by upregulation of both the peroxisome proliferator-activated receptors (PPARα and PPARγ) up to about three- to fourfolds (over control) and (2) by their capacity to promote adipocyte differentiation. Together, these observations clearly suggest the beneficial effects of Jamun.

11. CONCLUSIONS

Jamun has been used to treat diabetes for centuries, and scientific studies carried out in the past few decades have confirmed that the seed is most effective and is useful in both insulin-dependent and noninsulin-dependent diabetes. Reports also suggest it to be effective in reducing the production of glucose, in inducing utilization of glucose, and of use in preventing/retarding diabetic complications. Mechanistic studies indicate that Jamun possesses free radical scavenging and antioxidant effects, prevents lipid peroxidation, regenerates the β-cells, prevents alterations in glycation status and formation of AGEs, improves glucose utilization and maintains glucose homeostasis, activates peroxisomal PPARs, inhibits alpha-glucosidases, and ameliorates dyslipidemia. These activities are beneficial in reducing hyperglycemia and in preventing/reducing the secondary complications of diabetes. Although Jamun has been propounded as an effective antidiabetic agent in both traditional and animal studies, the clinical trials performed with small sample size have been inconclusive. The antidiabetic action of Jamun includes the combined effect of acarbose, meglutude, insulin, lovastatin, and vitamin E. Future studies should be aimed at performing randomized double-blinded clinical studies with a large sample size and a standardized extract with suitable controls. The observation from these studies will help in understanding and validating the traditional observations.

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