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The therapeutic potential of *Syzygium cumini* seeds in diabetes mellitus

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Abstract
Diabetes mellitus (DM) type II is a long term endocrine metabolic disorder due to disturbances in metabolism of carbohydrate, fat, protein and characterized by hyperglycemia. It is a multi-factorial disease and the current strategy used for the treatment is a combination of an insulin secretagogue and an insulin sensitizer. These synthetic medicines generally target single pathway to control the blood glucose level. Therefore, despite of better result to control of diabetes mellitus, these synthetic therapeutic approaches have serious and several side effects. Due to low toxicities and cost effectiveness natural products are comparatively safe and good source of effective antidiabetic agents. *Syzygium cumini* and its seed a member of Myrtaceae family acquire potential role in regulating diabetes mellitus and its seeds are moderately rich in protein (6.3-8.5%) and contains so many other phytochemicals. It gives a new therapeutic paradigm as anti-hyperglycemic agent either due to a single component or combination of different components present in the seed. Present review gives an idea about the multiple mode of action by *S. cumini* seeds to control diabetes mellitus and its related complications clinically and pharmacologically.

Keywords: *Syzygium cumini*, antidiabetic, diabetes mellitus, pharmacological attributes, folk medicines

1. Introduction
A long term endocrine metabolic disorder characterized by hyperglycemia is commonly known as diabetes. This endocrine disorder is due to disturbances in metabolism of carbohydrate, protein and fat either in secretion and mode of action or both of insulin. Non-insulin dependent (type II) diabetes is more common and reaching 90–95% of the population [1]. It is a multi-factorial disease and the current strategy used for the treatment is a combination of an insulin secretagogue and an insulin sensitizer [2]. These synthetic therapeutic approaches have several side effects, such as severe hypoglycemia, digestive discomfort, lactic acidosis, hepatotoxicity, headache, dizziness, permanent neurological deficit and many more [3]. Therefore, focus on more effective oral hypoglycemic agents from natural sources with superior quality of therapeutic effect and minimum side effects become necessary. Natural hypoglycemic agents can hit multiple targets either by single component or mixture of active components in a single drug by multiple-target strategy [4, 5].
Plants are being used for the healing purpose of a variety of diseases from the beginning of civilization and we get so many currently available drugs directly or indirectly from them due to low toxicities and safety. According to the ethnobotanical survey report more than 25,000 plant based drug formulations from 800 plants may be a good source of effective antidiabetic agents in Indian folk medicines [6, 7]. *S. cumini* and its different parts are popular for its medicinal and nutritional value and traditionally utilized as anti-diabetic, antioxidant, anti-hyperlipidic and hepatoprotective [8, 11]. Seeds of *S. cumini* are moderately rich in protein (6.3-8.5%) and various phytochemicals along with flavonoids quercetin and, rutin a well-known antioxidants [12, 15]. These phytochemicals may provide versatile benefits by influencing biological pathways and improve the diabetic symptoms [16].

2. Materials and Methods
2.1 Morphology, Taxonomy & Distribution
S. cumini is a tropical fruit tree usually known as Jamun, Indian blackberry black plum and jambolana. This evergreen tree is large densely foliaceous up to height of 30 m and broadly distributed in forest of India, Bangladesh, Sri Lanka, Malaysia, Australia and many other tropical regions. Its leaves are 6-12 cm long pointed at tip, smooth, glossy, leathery oriented in

opposite direction and elliptical in shape. Greenish white flowers are small (7–12 mm) and sessile, found in cluster with cup shaped calyx at stem tip with four petals and many stamens are found in cluster with cup shaped calyx at stem tip.

The fruits are barriers dark–purple succulent, fleshy edible and having centrally placed single large seed [17]. Ripe fruits are very luscious, odorless, with a pleasant, slightly bitter and astringent taste [18]. Seed of *S. cumini* is thin walled mesophyll and parenchymatous cells packed with simple starch grains and isodiametric in shape. It contains single layered epidermis covering cotyledons and moderately rich in protein and contains 6.3-8.5% protein, 41% starch, 21.72% ash, 16.9% crude fiber, 6-19% tannin, 1.18% fat, 0.41% calcium, 0.17% phosphorus, fatty acids, 6.1% dextrin and phytosterol [12]. *S. cumini* seeds are rich source of phytochemicals and researchers are taking keen interest in exploring its role in different diseases. Flavonoids such as rutin and quercetin, well known antioxidants and monoterpenoids are present in the seeds, which accounts for the scavenging of free radicals and protective effect on antioxidant enzyme. Glucoside jamboline, a phenolic substance present in the seeds, halts the diastatic conversion of starch into sugar [13, 19]. Unfortunately, proteins remain neglected till date to check its curative role in different diseases. A proteomic study using phenol extraction method disclosed about the proteins present in the *S. cumini* seed and after two dimension gel electrophoresis brightly stained protein spots were identified. Along with other proteins being involved in several functions like carbohydrate metabolism, secondary metabolite transport, fruit ripening and softening, antifungal, hormone signaling, seed germination, defense and stress response, sulphur metabolism, nitrogen metabolism, lactoferrin also get identified [20]. Hence, proteins present in *S. cumini* seeds may have various roles in plant physiology and therapeutics. Lactoferrin is 80 kDa glycoprotein with high pharmaceutical and nutritious value found in milk and human biological fluid [21, 22]. The potential role of bovine lactoferrin in the management and treatment of diabetes is well known and has been already reported [23]. The protein constituents of *S. cumini* seed require more studies and intensive research *in vivo* and *in vitro* to establish their role in plant and human physiology.

Fig 1: Different stages of *S. cumini*; a: Flowering stage, b: Fruiting stage, c: Mature Fruit, d: Seeds of *S. cumini* (Figure Sources – Google Image)

Balance of insulin and glucagon to maintain blood glucose level in normal range depends on so many factors. *S. cumini* seeds as an anti-diabetic agent in folk medicine as well as in clinical and experimental studies is well versed. The wide spread medicinal uses of it fetches our attention to compile a review on its mode and classification of action. So far, this type of review hasn't been compiled on the basis of mode of action showing pharmacological attributes of *S. cumini* seeds. This review deals with the maintenance of blood glucose level by *S. cumini* seeds by different mode of action. We have used Pubmed, Google, and High wire search engines by using keywords: antidiabetic effect of *S. cumini*, *S. cumini* seed, *E. jambolana*, jambolan, Indian blackberry, jamun, and java plum.

3. Results and Discussion

3.1 Medicinal & Pharmacological Uses

S. cumini and its parts have been used as an alternative and complementary medicine to regulate diabetes all over the world. Each and every part of the plant stem bark, leaves, fruit, and seed shows its prospective role in regulating different diseases, as diabetes, cancer, mouth ulcer, colic diarrhea, dysentery, piles, pimples and indigestion [24]. The bark is acrid, sweet digestive astringent helps in blood purification and used for the treatment of the sore throat. The fruit is used to remove bad smell from the mouth, biliousness, stomachic, astringent, diuretic, anti-diabetic [25] also used for the treatment of chronic diarrhea and other enteric disorder [26]. Leaf ashes are used for strengthening teeth's and gums. The seed extract is used to treat cough, cold, fever, skin rashes and mouth throat, intestines and genitourinary infections due to *Candida albicans* by the native of Tamil Nadu [27] and very much effective as anti-oxidant, anti-inflammatory, anti-microbial, antibacterial anti-HIV, anti-fungal, anti-diarrheal, anti-fertility, gastro-protective antiulcerogenic and radio protective activities and many more [28]. The efficacy of *S. cumini* seeds for the treatment of diabetes has been tested in several clinical and experimental studies proposing various mode of action.

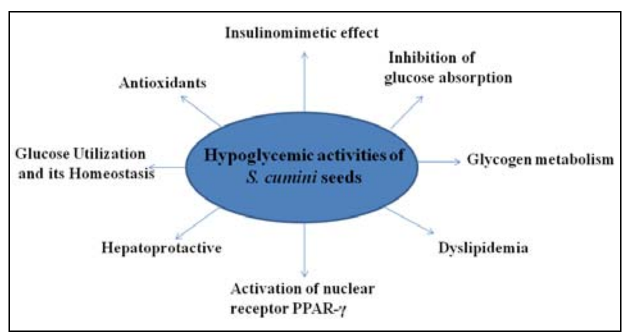

Fig 2: Different mode of action by which S. cumini seeds acts as anti-diabetic agent

3.1.1. Insulin Mimetic and Insulinotropic effect

Pancreatic β-cell acts as sensors in glucose-sensing mechanism to regulate glucose homeostasis [29]. Any kind of deterioration in these cells is the centre of development and progression of diabetes due to combined effects of genetic and acquired factors. Type 2 diabetes patients have either reduced islet number and/or reduced beta cells amount in the pancreas due to increased beta cell death. Therefore, more effective and targeted strategies for the avoidance and treatment of the non-insulin dependent diabetes should be focused [30]. *S. cumini* seeds are highly rich in phenolics and flavonoids having antioxidant activity [31]. Quercetin, a flavonoid helps in regeneration of the pancreatic β-cells and stimulates insulin release in streptozotocin -induced diabetic rats. An intraperitoneal injection of quercetin significantly decreases plasma glucose level, GTT, plasma cholesterol and triglycerides in diabetic rats, whereas, hepatic glucokinase activity was found significantly increased [32]. Bright colored fruit and vegetables are normally used as antidiabetic agents and this bright colour is due to anthocyanins a natural colorants. Anthocyanin has effective insulin secretagogues properties; it stimulates insulin secretion from rodent pancreatic b-cells and has been already reported [33]. Flavonoids rich *S. cumini* seed extracts were able to maintain glucose homeostatic and enhanced glycogen biosynthesis significantly by stimulating insulin secretion [10]. Restoration of normoglycemia, increase in G6PD and hepatic and muscle glycogens along with increase in c-peptide and plasma insulin levels supports antidiabetic property of chloroform extract of *S. cumini* seeds (SC2). Presence of neo islets also confirms the regenerative property and insulin secretagogue activity of SC2 after 21 days of treatment histologically [34]. Diabetic rabbits, which were in different stages of diabetes mild and severe respond significantly after 15 days treatment of *S. cumini* seeds ethanolic extract and showed their hypoglycemic behavior by significant fall in glycosylated haemoglobin (GHb) levels and fasting blood glucose levels, while serum insulin level were noticed significantly increased [35]. Another study showed that levels of serum insulin shoots up in both diabetic and euglycemic rats by oral administrated of aq. extract of *S. cumini* pulp and seed in streptozotocin-induced diabetic rats [36]. Seeds of *S. cumini* may help to convert proinsulin in to insulin either by pancreatic cathepsin B and its secretion or both and also help to increase plasma insulin level [37]. In diabetic condition formation of glycosylated haemoglobin increases and total haemoglobin level normally falls down [38]. But oral administration of alcoholic extract of *S. cumini* seeds showed significant improvement in diabetic rats by increasing total haemoglobin and decreasing sugar level in blood and urine at a dose of 100 mg/ kg body weight [39]. Ethanolic extract of seed kernel also gives similar effect in diabetic rats, significantly increases glucose tolerance tests, liver glycogen and levels of total proteins whereas, blood glucose, blood urea and cholesterol were found to decrease, when given orally at a concentration of 100 mg/kg of body weight [40]. The probable mode of action by which these extracts of *S. cumini* seeds brings about its hypoglycaemic action is; either it directly increases insulin secretion from β-cells or help to release as Proinsulin, which is finally converted in to insulin and C-peptide. It also increases the effect of insulin output to the existing blood glucose level [41, 42].

3.1.2. Activation of nuclear receptor PPAR-γ

PPARs are a group of nuclear receptor proteins, which regulates carbohydrate and lipid metabolism by managing energy homeostasis as a transcription factors. This nuclear receptor super family is of three types: PPARα, PPARβ/δ and PPARγ. Among them PPARγ are mainly present in adipose tissue and regulates insulin resistance, lipid storage and adipocyte differentiation. Anti -diabetic thiazolidinediones activate PPARγ and due to their insulin receptor sensitizing activity used in treatment of non insulin dependent diabetes [43]. Insulin secretion from pancreatic islets was found to be increased in a streptozotocin induced diabetic rats after oral administration of flavonoid rich extract of *S. cumini* seeds. This flavonoid rich extracts significantly established a dual regulator function for both PPARα and PPARγ in a dose dependent manner and found to increased up to 3-4 folds over the control and helps in the differentiation of adipocytes from preadipocytes. These observations clearly suggest the upregulation of PPARα and PPARγ and its beneficial effects as hypoglycemic [10]. Up-regulation of PPARγ and PPARα protein expressions in hepatic tissue was also noticed by aqueous extract of *S. cumini* seed in streptozotocin induced diabetic rat at a dose of 400mg/kg [44]. PPARγ agonists activate PPARγ and increases Glut-4 transcription and glucose uptake [45]. The methanolic extracts of *A. marmelos* and *S. cumini* increases the up-regulation of glucose uptake with increase in PPARγ Glut-4, and PI3 kinase by the activation of glucose transport system [46].

3.1.3. Up-regulation of glucose transporters and Enhancement of glucose uptake

During carbohydrate ingestion stimulating the peripheral glucose uptake is highly required to maintain glucose homeostasis, GLUT-4 in adipocytes and skeletal muscles and GLUT-2 in liver stimulates glucose uptake process [3]. The lipid bilayer of cell membrane requires specific transporters, carbohydrate-transport systems to make it permeable for carbohydrates. These cellular transporters are of two types; sodium linked GLUT in kidney and intestine and another group of transporters are made up of five homologous transmembrane proteins encoded by different genes, GLUT-1 to GLUT -5 and convey glucose by the facilitated transmission down the glucose-concentration gradient [47]. Due to reduced metabolism in skeletal muscle and adipocytes, a decreased expression of GLUT-4 mRNA and insulin-stimulated glucose transport may be a causative factor for insulin resistance in type II diabetes mellitus [48]. *S. cumini* seed extracts were found to be involve in the increment of expression of Glut-4 in adipose tissues and muscle. After oral administration of a flavonoid-rich extract of *S. cumini* seeds in diabetic mice expression of Glut-4 in adipose tissue and muscle were found to be elevated, this supports glucose uptake [23]. Similarly, increased in expression of Glut-4, PPARγ and PI3 kinase in glucose transport system by methanolic extracts of *S. cumini* supports the up-regulation of glucose uptake [45].

3.1.4. Glycogen metabolism

Glucose homeostasis is maintained by hepatic output which is associated with liver metabolic functions lipogenesis and glycogenesis. Insulin inhibits glycogen phosphorylase and stimulates glycogen synthase for deposition of glycogen [49] which acts as energy storage in liver and skeletal muscle. In gluconeogenic pathway glucose-6-phosphatase and fructose-1,6-bisphosphatase acts as a regulatory and rate limiting enzymes [50] and insulin behaves abolish of gluconeogenic enzymes [51] Due to insulin insufficiency activities of these enzymes increases in the liver of diabetic patients [52]. Diabetes mellitus is coupled with a obvious diminish in the level of liver glycogen [53, 54] hepatic and skeletal glycogen, but LH II purified from *S. cumini* increases the level of glycogen in liver and skeletal muscles may be due to increased glycogen synthase and decreased glycogen phosphorylase activity. It has shown both pancreatic [37] and extra-pancreatic mechanism of action by inhibiting insulinase activity in both kidney and liver [36] and proved that it can be an excellent antidiabetic agent.

3.1.5. Inhibition of glucose absorption

Absorption of glucose monomers after breakdown of complex carbohydrate in to simple sugar glucose by alpha-glucosidase and alpha-amylase by the gut causes postprandial hyperglycemia [55]. Risk of chronic complexity of secondary complications increases in postprandial hyperglycemia due to non-enzymatic glycosylation of proteins [3] and it becomes difficult to manage in initial stage. Inhibition of intestinal α-glucosidases in the small intestine during carbohydrate metabolism and its absorption helps to manage postprandial hyperglycemia. Inhibition of α-amylase and α-glucosidase, which are carbohydrate-hydrolyzing enzymes for slowing down starch digestion and its absorption in the gastrointestinal tract, will be a good curative approach for controlling of postprandial hyperglycemia in diabetes mellitus [56]. In hyperglycemic conditions pancreatic α-amylase inhibitors controls glucose formation due to blockage of normal pathway of conversion of complex carbohydrate into monomers in the gut and glucose finally get absorbed in the blood [7]. Concentration-dependent HPA inhibitory activity and significant porcine pancreatic α- amylase inhibition was observed in presence of aqueous extract of *S. cumini* seeds [57]. Hypoglycemic effect of various extracts of *S. cumini* seed kernel were evaluated against different alpha-glucosidase, such as *B. stearothermophilus* (bacterial), *S. cerevisiae* (yeast), and mammalian (rat intestine) for their α-glucosidase inhibition activity in Goto–Kakizaki (GK) rats. Among them mammalian alpha-glucosidase from rat intestine were found to be more effective in inhibiting maltase, in comparison with acarbose, a positive control. So many α-glucosidase and α-amylase inhibitors have been identified from the different extract of *S. cumini* seed [58, 59]. Therefore, α-glucosidase and pancreatic α-amylase inhibitors can be used to check the initiation and progression of type II diabetes mellitus and will be an important strategy to manage this disease [60].

3.1.6. Anti-hyperlipidemic activity

Dyslipidemia, a consistent metabolic disorder of lipoprotein with diabetes mellitus and about 40% of diabetic patients are suffering from it. In diabetic condition atherogenic lipid profiles are common which initiates or accelerates formation and deposition of fatty deposits in the arteries and increases risk of ischemic heart disease [61, 62]. Circulation of free fatty acids increases in the adipose tissue due to excessive lipolysis and forms triglycerides in liver. It causes hypertriglyceridemia, which is responsible for vascular complications in diabetic patients due to decreased HDL cholesterol [63, 65]. Plasma lipid abnormalities are a low concentration of HDL cholesterol and high concentration of TG and low density of LDL [66]. In diabetes-induced hyperlipidaemia increase in deposition of glucagon in skeletal muscle is most common due to insufficient supply of insulin and low amount of glucose is utilized [67] *S. cumini* seed showed anti-hyperlipidemic activity in streptozotocin (STZ)-induced diabetic rats by normalizing the alterations in lipid profiles and restored them to near normal levels either by hydrolysis and selective uptake of lipoproteins or due to the presence of different phytochemicals present in it [68]. In diabetic animals cholesterol level increases due to active hydroxymethyl glutaryl coenzyme A reductase (HMG CoA) which helps in the production of cholesterol [69]. Level of cholesterol and serum triglycerides considerably found decreased after the administration of flavonoid rich extract of *S. cumini* seeds as compared to their control. This hypolipidemic activity of the seed extract may be due to presence of either some stimulator of insulin, which reduces lipid peroxidation [70] or inhibits lipoprotein lipase activity or presence of some hypocholesterolemic compounds [68]. These compounds behave like inhibitors for the enzymes hydroxyl methyl glutaryl CoA reductase, and cholesterol absorption from intestine get reduces in presence of HMG CoA [29, 10]. Lipid metabolism and membrane composition of the brain are highly impacted in diabetes mellitus [71, 72]. The level of phospholipids, brain cholesterol and free fatty acids are highly increased the in the brain of a diabetic mice. Brain of diabetic mice becomes highly susceptible to lipid peroxidation due to increased level of phospholipid content with polyunsaturated fatty acid along with high oxygen consumption [73]. Due to activation of lipid peroxidation system thiobarbituric acid reactive substances (TBARS), a byproduct of lipid peroxidation also get increased. Aqueous extract of *S. cumini* seed decreases the level of free fatty acids cholesterol, phospholipids and TBARS after oral administration in diabetic brain and restore them to normal value [74].

3.1.7. Antioxidants

Oxidative stress is an imbalance between free radical generation and elimination due to depletion of antioxidant scavenger systems and characterized by increased lipid peroxidation and number of chronic complications of diabetes [75, 77]. In diabetes mellitus reactive oxygen species (ROS) normally founds in increased stage due to intracellular metabolism of glucose oxidation which constantly produce superoxide radicals (O_2) and hydrogen peroxide (H_2O_2) [78]. These free radicals (O2 & H_2O_2) generate hydroxyl radical for the acceleration of lipid peroxidation and decrease the activities of superoxide dismutase (SOD) and catalase (CAT) [73]. SOD reduces the toxic effects of superoxide radicals and CAT protects tissues from highly reactive hydroxyl radicals [79, 80]. Activities of these enzymes in diabetic brain increase after oral administration of aq. extract of *S. cumini* seed and alcoholic extract help to restore them to normal level. Seed kernel plays a protective role due to the antioxidative effect of highly present flavonoids in *S. cumini* acts as singlet oxygen quenchers and strong superoxide radical [70]. The flavonoid quercetin had shown its ability as antioxidant by reversing oxidative stress in streptozotocin-induced diabetic Sprague-Dawley rats [81]. Quercetin modify antioxidant defense pathways and inhibits lipid peroxidation either by scavenges free radicals directly or inhibits biomolecule oxidation [82].

3.1.8. Hepatoprotective activity

Injury of liver due to exposure of exogenous and endogenous substances coupled with impaired liver function is hepatotoxicity. Oxidative stress and free radicals has important role to causes injury and plant materials having antioxidant activities are used to treat liver injury or hepatic stress [83, 8]. Carbon tetrachloride (CCl_4) frequently used to induce liver injury in rodents and produces trichloromethyl ($\bullet CCl_3$) free radicals, which further reacts with oxygen and form trichloromethyl peroxy ($\bullet CCl_3O_2$) radical with the help of enzyme Cytochrome P450 2E1. Trichloromethyl proxy free radicals cause lipid peroxidation in membrane and ultimately cell death of adipose tissue [84, 85]. *S. cumini* and its different part such as, seeds, leaves and bark used as folklore to treat gastrointestinal and liver diseases and significant hepatoprotective effect was observed by aqueous extract of *S. cumini* seed in diabetic rats [8, 86]. Methanolic extract of *S. cumini* seeds downs SGPT, SGOT, ALP and total bilirubin level in CCl4-Induced stressed Sprague-Dawley rats and this decrease level of SGOT and SGPT gives an idea about repair of hepatic tissue damage and stabilization of plasma membrane caused by CCl4 [11]. Therefore, methanolic extracts of *S. cumini* seed can intensify hepatotoxic free radicals and antioxidant defense activities by altering liver cytochrome P-450 enzymes [87].

4. Conclusion

Syzygium cumini has been widely used by the traditional practitioner for diabetes and its related complications from centuries. It has been confirmed by numerous clinical and experimental studies that *S. cumini* and its different part, especially seed is very much effective for the management of diabetes mellitus. Different active constituents present in the seeds control glucose homeostasis by attacking on the pathways of the hyperglycemic process through different-modes of action. *S. cumini* seeds are widely used as an antidiabetic drug for the management of diabetes mellitus type II and hypoglycemic behavior of this seed is due to its Insulin mimetic and insulinotropic effect. It acts as antidiabetic drug either by stimulation of insulin release from beta cells or by lowering glucose absorption of intestine, hepatic glucose production and boosting sensitivity of insulin by enhancement of peripheral glucose uptake and utilization, activation of nuclear receptor PPAR-γ**.** These activities to maintain glucose homeostasis also reduce the chance of other complications associated with diabetes. Therefore, it can be used as valuable therapeutic agents with higher safety profile and also cost effective. Further research work is required to reveal the exact mechanism of action to show their hypoglycemic effect with standardized extract with large sample size with randomized double-blinded clinical studies and suitable controls. Identified proteins from *S. cumini* seeds definitely have panorama of action and opens the door for more extensive research to demonstrate their role as an antidiabetic agent and any other different beneficial aspects.

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