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Antihyperglycemic Potential of *Syzygium cumini*: Current Pharmacological Insights and Future Perspectives

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Abstract:

Syzygium cumini (L.) Skeels, commonly known as jamun, Indian blackberry, or black plum, is a tropical fruit tree belonging to the Myrtaceae family and is widely found in the Indian subcontinent. It has gained considerable attention for its potential role in managing hyperglycemia associated with diabetes mellitus, a metabolic disorder characterized by inadequate insulin production or impaired glucose regulation.This review focuses on the antihyperglycemic activity of *S. cumini*, particularly its seeds, which are an important by-product rich in various bioactive compounds. Phytochemical studies have identified the presence of several secondary metabolites such as flavonoids, polyphenols, terpenoids, and alkaloids including jambosine and jamboline, which are believed to contribute to its therapeutic effects.The antidiabetic action of *S. cumini* is associated with multiple mechanisms, including improvement of glucose homeostasis, stimulation of pancreatic β-cell function, enhancement of insulin secretion, and inhibition of carbohydrate-digesting enzymes like α-amylase and α-glucosidase. Experimental studies in streptozotocin-induced diabetic animal models have demonstrated a dose-dependent reduction in blood glucose levels and HbA1c. Furthermore, computational studies suggest that compounds such as kaempferol and gallic acid exhibit strong interactions with key enzymes involved in carbohydrate metabolism.Clinical findings also indicate that the administration of standardized seed powder can significantly reduce fasting as well as postprandial blood glucose levels. Although *S. cumini* is generally considered safe, further research is needed to standardize extraction methods and develop advanced drug delivery systems to enhance its bioavailability and therapeutic effectiveness.

Keywords: nutraceuticals, phytochemicals, antioxidants, jamun seed, Syzygium cumini, and antidiabetic.

Introduction:

Medicinal plants have long been recognized as valuable sources of therapeutic agents due to the presence of natural compounds that help maintain health and prevent diseases. Among these, *Syzygium cumini* (L.) Skeels, commonly known as jamun, Indian blackberry, or Java plum, has gained significant scientific interest because of its wide range of pharmacological and nutritional benefits. This evergreen tropical plant, belonging to the Myrtaceae family, is widely used in traditional systems of medicine such as Ayurveda and Unani for the management of diabetes, inflammatory conditions, gastrointestinal disorders, and cardiovascular diseases.

The global burden of diabetes is rapidly increasing, largely driven by factors such as sedentary lifestyles, obesity, and unhealthy dietary habits. It is estimated that the number of diabetic individuals may rise from 425 million in 2017 to approximately 629 million by 2045. Although conventional antidiabetic drugs like biguanides and sulfonylureas are effective, they are often associated with adverse effects including hypoglycemia, fatigue, and weight gain. This has led to a growing interest in safer and more affordable plant-based alternatives. *S. cumini* is widely distributed across tropical and subtropical regions, including India, Southeast Asia, parts of Africa, and Latin America. Notably, its seeds—comprising about 10–47% of the fruit weight—are often discarded as waste despite being rich in bioactive compounds, highlighting their potential as an underutilized resource for therapeutic applications.

Phytochemistry of *Syzygium cumini*

1.Phenolic Acids

Major compounds: Gallic acid, Ellagic acid, Ferulic acid, Chlorogenic acid, Syringic acid, Caffeic acid

Phenolic acids are one of the most important groups of bioactive compounds present in *Syzygium cumini* seeds. These compounds are well known for their strong antioxidant potential, as they help neutralize harmful free radicals and reduce oxidative stress in the body. Oxidative stress is a key factor involved in the progression of diabetes and its complications. In addition to their antioxidant activity, phenolic acids also exhibit hepatoprotective effects by protecting liver cells from damage. Some of these compounds, particularly gallic acid and chlorogenic acid, are known to help regulate glucose metabolism and reduce blood sugar levels. Therefore, phenolic acids play a crucial role in the overall antihyperglycemic and protective effects of the plant.

2. Flavonoids

Major compounds: Quercetin, Kaempferol, Myricetin, Rutin, Catechin

Flavonoids are another major class of phytochemicals found in *S. cumini* seeds and are widely recognized for their diverse biological activities. These compounds possess strong antioxidant and anti-inflammatory properties, which help in reducing cellular damage and inflammation associated with chronic diseases like diabetes. Flavonoids such as quercetin and kaempferol have been reported to improve insulin sensitivity and enhance glucose uptake by cells. They may also help in protecting pancreatic β-cells from damage, thereby supporting insulin production. Additionally, flavonoids contribute to cardiovascular protection by improving blood vessel function and reducing oxidative stress. Their multifunctional role makes them an important contributor to the therapeutic potential of *S. cumini*.

3. Alkaloids

Major compounds: Jambosine, Jamboline, Gallicin

Alkaloids present in *Syzygium cumini* seeds are known to exert significant effects on glucose metabolism. Compounds such as jambosine and jamboline are particularly important due to their hypoglycemic properties. These alkaloids are believed to regulate blood sugar levels by influencing insulin secretion and improving the body's ability to utilize glucose effectively. They may also interfere with the breakdown and absorption of carbohydrates in the digestive system, thereby preventing sudden spikes in blood glucose levels. In addition, alkaloids can modulate various metabolic pathways, contributing to their overall antidiabetic effect.

4. Glycosides

Major compound: Jamboline

Glycosides, especially jamboline, play a vital role in maintaining blood glucose levels. This compound is known to delay the conversion of starch into glucose, which helps in reducing the rate at which sugar enters the bloodstream after meals. By slowing down carbohydrate digestion, glycosides help prevent postprandial hyperglycemia, a common problem in diabetic patients. Moreover, glycosides may also contribute to improving overall glucose utilization in the body. Their ability to regulate carbohydrate metabolism makes them an important component of *S. cumini*'s antidiabetic action.

5. Terpenoids

Major compounds: Lupeol, Betulinic acid, Oleanolic acid

Terpenoids found in *S. cumini* seeds contribute significantly to its medicinal properties. These compounds are known for their anti-inflammatory effects, which help reduce chronic inflammation

associated with metabolic disorders. In addition, terpenoids exhibit antioxidant activity, protecting cells and tissues from oxidative damage. They also possess hypolipidemic properties, meaning they help lower cholesterol and triglyceride levels in the body. This is particularly beneficial for individuals with diabetes, as they are more prone to cardiovascular diseases. Some terpenoids may also enhance insulin sensitivity and support better glucose metabolism, further strengthening the plant's therapeutic potential.

6. Saponins

Major compounds: Various saponins

Saponins are another important group of phytochemicals present in *Syzygium cumini* seeds. These compounds are known for their ability to lower cholesterol levels and improve lipid metabolism. They also exhibit antioxidant properties, helping to protect the body against oxidative stress. In addition, saponins have immune-modulating effects, which may help in strengthening the body's defense system. Some studies suggest that saponins may also contribute to glucose regulation by influencing metabolic pathways related to carbohydrate and lipid metabolism. Overall, they play a supportive role in enhancing the therapeutic effectiveness of the plant.

Table: Phytochemicals of *Syzygium cumini* Seeds and Their Pharmacological Activities

Phytochemical Class	Major Compounds	Pharmacological Activities
Phenolic Acids	Gallic acid, Ellagic acid, Ferulic acid, Chlorogenic acid, Syringic acid, Caffeic acid	Antioxidant, hepatoprotective, antihyperglycemic, free radical scavenging
Flavonoids	Quercetin, Kaempferol, Myricetin, Rutin, Catechin	Antioxidant, anti-inflammatory, antidiabetic, improves insulin sensitivity
Alkaloids	Jambosine, Jamboline, Gallicin	Hypoglycemic activity, regulation of insulin secretion, modulation of carbohydrate metabolism
Glycosides	Jamboline	Inhibits conversion of starch to glucose, helps in blood glucose regulation
Terpenoids	Lupeol, Betulinic acid, Oleanolic acid	Anti-inflammatory, hypolipidemic, antioxidant
Saponins	Various saponins	Antioxidant, cholesterol-lowering, immune-modulating effects

Pharmacological Mechanisms of Antihyperglycemic Activity

1 Insulin Secretion and Pancreatic β-Cell Protection

Extracts of *Syzygium cumini* have been reported to enhance insulin secretion from pancreatic β-cells, which play a central role in maintaining glucose homeostasis. Bioactive compounds such as jamboline help reduce the conversion of starch into glucose, thereby lowering the glucose load and indirectly supporting insulin release. In addition, these extracts may stimulate the residual or functional β-cells in a manner similar to sulfonylurea drugs, leading to increased insulin output. Flavonoids present in the seeds also contribute to the regeneration and protection of β-cells by reducing oxidative stress and cellular damage. This dual action—stimulating insulin secretion and preserving β-cell integrity—plays a key role in controlling hyperglycemia.

2 Enhancement of Peripheral Glucose Uptake

Syzygium cumini extracts, particularly methanolic extracts, have been shown to improve glucose uptake in peripheral tissues such as skeletal muscle and liver. This effect is mainly mediated through the activation of insulin signaling pathways, including phosphoinositide 3-kinase (PI3K). Activation of this pathway promotes the translocation of glucose transporter type 4 (GLUT4) to the cell membrane, allowing greater glucose entry into cells. Phytochemicals like kaempferol and gallic acid are known to enhance this process, thereby improving glucose utilization. As a result, there is a reduction in circulating blood glucose levels and improved o**3**

3 Inhibition of Carbohydrate-Digesting Enzymes (α-Amylase and α-Glucosidase)

Another important mechanism of *S. cumini* involves the inhibition of key digestive enzymes responsible for carbohydrate breakdown, namely α-amylase and α-glucosidase. Bioactive compounds such as jambosine, jamboline, ellagic acid, and gallic acid interfere with the activity of these enzymes, slowing the conversion of complex carbohydrates into simple sugars. This leads to a gradual release of glucose into the bloodstream and helps prevent postprandial hyperglycemia. Computational studies have further supported this mechanism, showing that compounds like gallic acid and kaempferol have strong binding affinity toward α-glucosidase, even demonstrating better inhibitory potential compared to standard drugs like acarbose. This enzyme inhibition strategy is highly beneficial in managing blood glucose spikes after meals.

4 Anti-Inflammatory and Antioxidant Effects

Chronic hyperglycemia is often associated with increased oxidative stress and inflammation, both of which contribute to the progression of type 2 diabetes mellitus. *Syzygium cumini* seeds are rich in antioxidant compounds such as phenolics, anthocyanins, and ascorbic acid, which help neutralize reactive oxygen species (ROS) and reduce oxidative damage. These antioxidants also prevent lipid peroxidation

and protect cellular structures. In addition, the plant exhibits anti-inflammatory activity by modulating key signaling pathways, including NF-κB and COX-2. This leads to a reduction in pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Together, these effects help in slowing disease progression and improving metabolic health.

Specific Preclinical Findings from In Vitro and In Vivo Studies

Experimental studies have provided strong evidence supporting the antidiabetic potential of *Syzygium cumini*. In streptozotocin-induced diabetic rat models, administration of seed extract at doses of 100 mg/kg and 200 mg/kg resulted in a significant reduction in blood glucose levels from the second week onward. At higher doses, a marked decrease in both blood sugar levels and HbA1c was observed by the end of the eighth week, indicating improved long-term glycemic control.

Similarly, studies in alloxan-induced diabetic rabbits demonstrated that oral administration of ethanolic seed extract effectively reduced fasting blood glucose levels. Histopathological examination further revealed improvement in pancreatic and liver tissue structure, suggesting protective and regenerative effects of the extract on vital organs involved in glucose metabolism

Molecular Docking and Computational Evidence

Computational approaches have been used to further validate the interaction between *S. cumini* phytochemicals and key enzymes involved in glucose metabolism. Molecular docking studies have shown that compounds such as gallic acid and kaempferol form stable complexes with α-glucosidase. In molecular dynamics simulations, these compounds maintained stable binding over extended periods, indicating strong interaction and inhibitory potential.

Kaempferol, in particular, demonstrated high binding affinity by interacting with important amino acid residues such as Asp547, Asp327, and His600 within the enzyme's active site. These findings support the experimental evidence and highlight the potential of these natural compounds as effective inhibitors of carbohydrate-digesting enzymes.

Clinical Evidence of Antihyperglycemic Activity

Although extensive preclinical studies support the antidiabetic potential of *Syzygium cumini*, clinical evidence remains relatively limited. However, the available studies provide encouraging results.

In one clinical investigation, the administration of encapsulated seed powder in doses ranging from 4 to 24 g per day resulted in a significant reduction in both fasting and postprandial blood glucose levels in patients with severe diabetes. Similarly, another study reported that daily intake of 12 g of seed powder for a period of three months led to nearly a 30% decrease in serum glucose levels in individuals with type

2 diabetes mellitus. This treatment also helped in reducing common diabetic symptoms such as excessive hunger (polyphagia) and excessive thirst (polydipsia).

In a separate clinical observation, a patient receiving a combination of Ayurvedic formulations containing jamun showed a remarkable reduction in HbA1c levels from 11.1% to 5.6% within 12 weeks, which eventually eliminated the need for daily insulin therapy. However, not all plant parts demonstrated similar efficacy. For example, a study using leaf decoction (2 g in 250 mL water) did not show any significant effect on blood glucose levels in either diabetic or non-diabetic individuals. These findings suggest that the seed is the most pharmacologically active part of the plant for glycemic control.

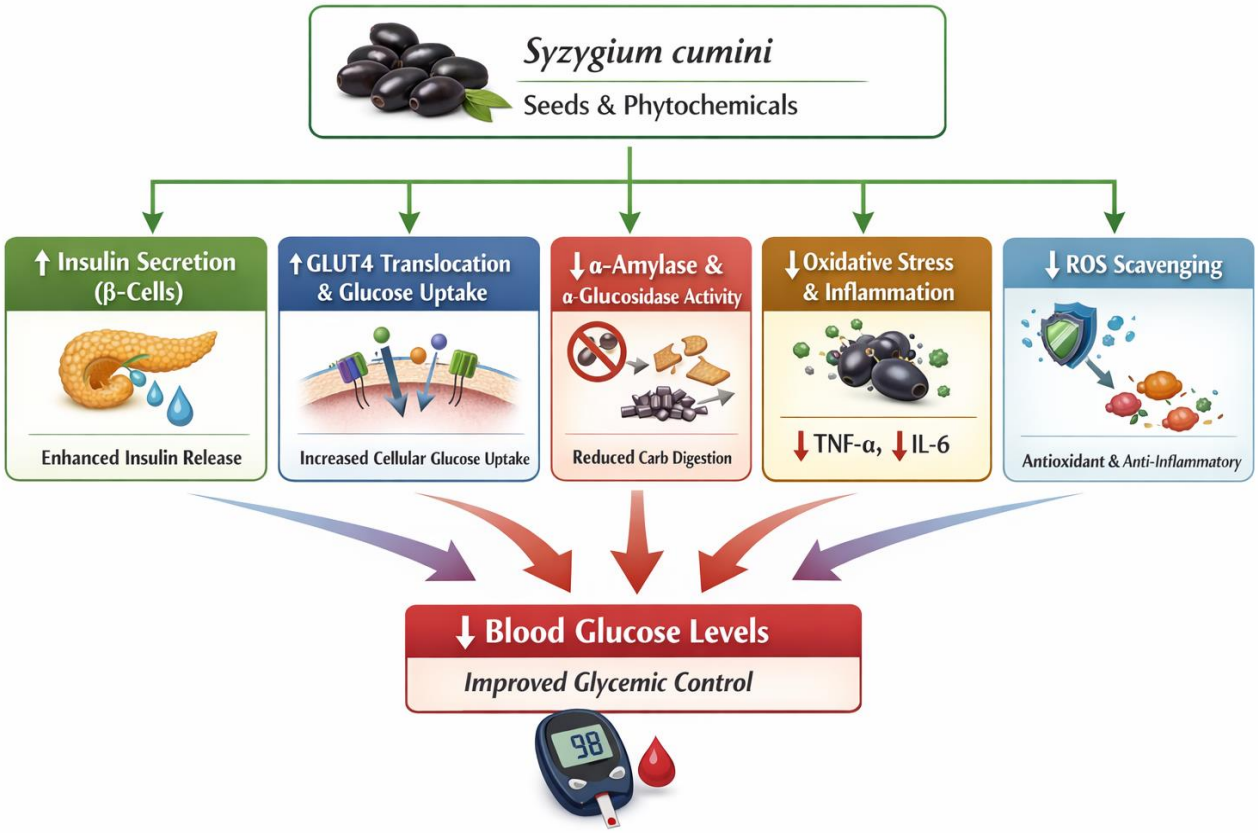

Diagram: Antihyperglycemic Acitivity

Safety and Toxicological Profile

Studies evaluating the safety of *Syzygium cumini* extracts indicate a favorable toxicological profile. In acute toxicity experiments, extracts prepared from different plant parts such as roots, seeds, bark, and leaves were found to be non-toxic in mice at doses of 2000 mg/kg (ethanolic extract) and 200 mg/kg

(methanolic extract). Similarly, oral administration of hydroalcoholic extracts in rats, even at high doses up to 6 g/kg, did not produce any mortality or noticeable behavioral abnormalities.

Long-term toxicity assessments also suggest good safety. Continuous administration of the extract at doses up to 0.25 g/kg for a duration of 180 days did not lead to any significant structural or histopathological alterations in tissues. Furthermore, ADMET analysis has demonstrated that important phytoconstituents such as kaempferol and gallic acid are non-cardiotoxic and considered safe for human use.

However, excessive intake of *Syzygium cumini* may lead to mild adverse effects in humans, including fever, body aches, cough, and accumulation of mucus in the respiratory tract. Therefore, consumption should be maintained within recommended limits.

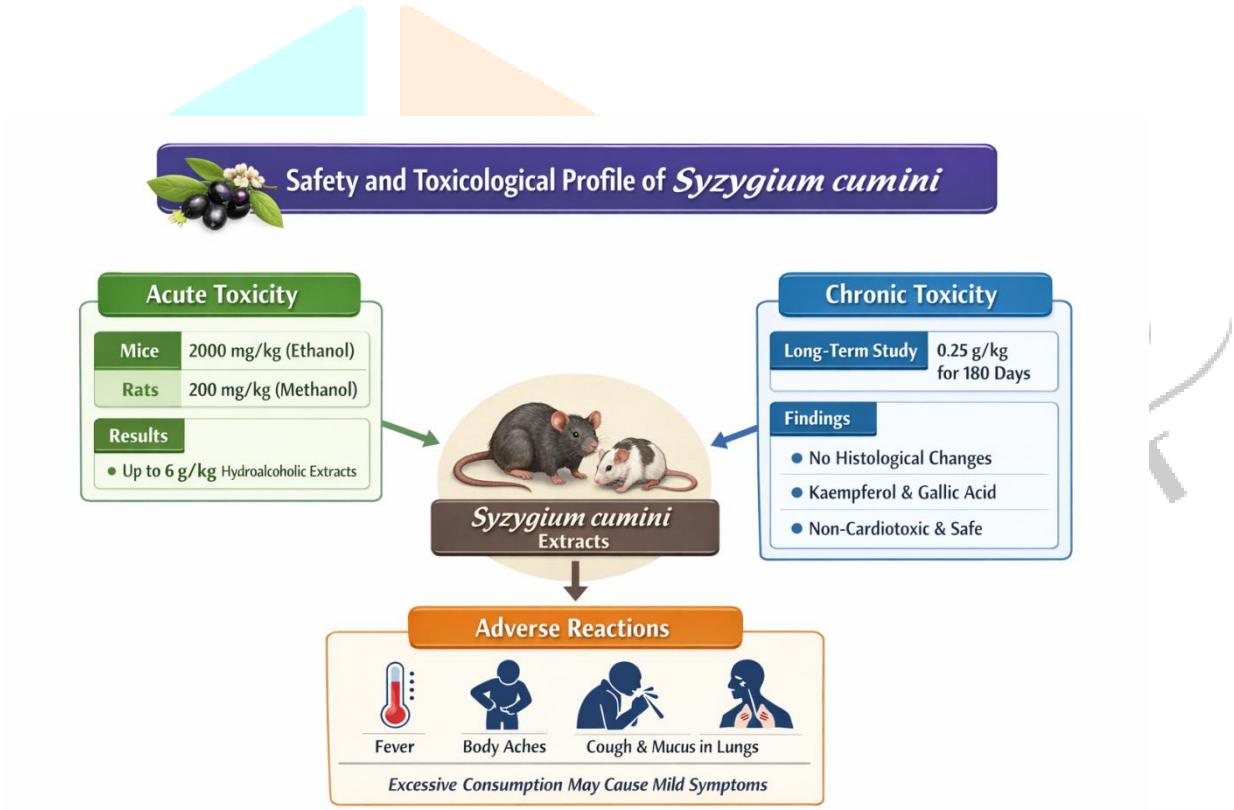

Diagram: Safety and Toxicological Profile

Prospective Views and Research Gaps

To properly understand the therapeutic potential of *Syzygium cumini* in humans, more carefully designed clinical studies are required. At present, there is a need to clearly identify and standardize the key phytochemical constituents responsible for its activity, along with improving extraction methods to ensure consistency and effectiveness.

Future research should also focus on advanced drug delivery approaches, such as nanoformulations, phytosomes, and nanoemulsions, which can improve the solubility, bioavailability, and targeted action of jamun seed bioactive compounds. These modern techniques may enhance its overall therapeutic efficiency.

In addition, further studies are needed to explore nutrigenetic and nutrigenomic aspects, which will help in understanding how *Syzygium cumini* interacts with genes and metabolic pathways at the molecular level. This could provide deeper insight into its role in disease prevention and treatment.

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