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REVIEW

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Antidiabetic Potential of *Syzygium* sp.: An Overview

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Diabetes, characterized by hyperglycemia, is one of the most significant metabolic diseases, reaching alarming pandemic proportions. It can be due to the defects in insulin action, or secretion, or both. The global prevalence of diabetes is estimated at 425 million people in 2017, and expected to rise to 629 million by 2045 due to an increasing trend of unhealthy lifestyles, physical inactivity, and obesity. Several treatment options are available to diabetics, however, some of the antidiabetic drugs result in adverse side effects such as hypoglycemia. Hence, there has been a proliferation of studies on natural products with antidiabetic effects, including plants from the Myrtaceae family, such as *Psidium guajava*, *Eucalyptus globulus, Campomanesia xanthocarpa,* and more significantly, *Syzygium* sp. Previous studies have shown that a number of *Syzygium* species had potent antidiabetic effects and were safe for consumption. This review aims to discuss the antidiabetic potential of *Syzygium* sp., based on *in vitro* and *in vivo* evidence.

INTRODUCTION

Diabetes, characterized by hyperglycemia, is one of the most significant metabolic diseases, reaching alarming pandemic proportions. It can be due to the defects in insulin action, or secretion, or both. It is a chronic, non-communicable disease that can result in blindness, renal failure, and limb amputations [1]. The latest estimates show that in 2017, the total global prevalence of diabetes is 425 million. Incidence rates are expected to rise to 629 million by year 2045 as the prevalence of unhealthy behaviors, physical inactivity, and obesity increases [2]. Diabetes can occur due to genetic disorders, obesity, drugs, and as a pregnancy-related complication. Symptoms of diabetes are polyuria, polyphagia, slow-wound healing, and polydipsia. Furthermore, diabetes can lead to a host of complications such as neuropathy, glaucoma, ischemic heart disease, nephropathy, and ketoacidosis [1].

The two major types of diabetes are categorized as type 1 and type 2. Type 1 diabetes, commonly known as insulin-dependent diabetic mellitus (IDDM), is a pancreatic islet autoimmune disorder resulting in absolute insulin secretion deficiency by β cells. In contrast, type 2 diabetes, also known as non-insulin-independent diabetic mellitus (NIDDM), is caused by inadequate insulin se-

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Abbreviations: IDDM, insulin-dependent diabetic mellitus; NIDDM, insulin-independent diabetic mellitus; GLUT, glucose transporter; OGTT, oral glucose tolerance test; HbA1c, hemoglobin A1c; STZ, streptozotocin; COB, *Cleistocalyx operculatus* flower buds; LD_{50}, median lethal dose; OA, oleanolic acid; MA, maslinic acid; SGLT, sodium-glucose linked transporter.

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cretion and also insulin resistance action of various target tissues or cells [3,4]. IDDM is due to chronic autoimmune destruction of the insulin-producing pancreatic β-cells. In patients with IDDM, uncontrolled lipolysis that leads to increasing levels of free fatty acids in the plasma occur as a result from the insulin deficiency. This will suppress glucose metabolism that takes place in the peripheral tissues. In type 2 diabetes, pathological defects leading to impairment in insulin secretion and resistance manifests as hyperglycemia in patients. The genetic association of disease in type 2 diabetes is greater than in type 1 [4].

The most clinically significant complication from either types of diabetes is diabetic ketoacidosis, which is a major cause of morbidity and mortality among diabetic patients. Long-term complications of diabetes include retinopathy, nephropathy, and neuropathy [1]. Diabetes can be diagnosed through fasting plasma glucose assessment or oral glucose tolerance test (OGTT). Besides, the use of hemoglobin A1c (HbA1c) has been recommended by American Diabetes Association to diagnose diabetes [5].

Conventional treatments of diabetes include insulin injections, oral glucose-lowering drugs, and nutritional therapy [6]. For patients who fail to achieve an acceptable level of glycemic control, oral therapy is usually indicated. However, oral hypoglycemic drugs have the potential to lose their efficacy despite providing a good initial response. Administration of drugs such as sulfonylurea, thiazolidinedione, and biguanide gives rise to various undesirable side effects which include weight gain, fatigue, and increased low-density lipoprotein cholesterol levels [7,8]. Additionally, the use of oral drugs usually leads to hypoglycemia [9-11]. Nonetheless, supplementation of chromium may improve glucose control in diabetic patients [12-27]. Supplementation of vitamin D and vanadium treatment was also presumed to be beneficial for alleviating diabetes, however, no randomized controlled trials had demonstrated their benefit on glycemic control [28-42].

Currently, the use of modern medicines for glycemic control has caused numerous adverse side effects, resulting in an increasing demand for safe and cost-effective measures [43,44]. Medicinal plants contain phytoconstituents, some showing mild-to-potent antihyperglycemic activity. As an example, alkaloids are known to interact with proteins involved in glucose homeostasis, hence exhibiting excellent antidiabetic effect. Recent evidence showed that alkaloids might act as potent α-glucosidase inhibitors and could be alternatively used in the treatment of diabetes, although further evaluation is necessary to validate their efficacy [45]. Bioactive compounds isolated from plants may lower blood glucose levels by improving beta cell function, promoting glucose reabsorption, reducing insulin resistance, or regulating glucagon-like peptide-1 homeostasis [46]. Accessibility is one of the main reasons herbal medicines are widely used in the treatment of diabetes, especially in rural communities [47]. Hence, the antidiabetic potential of a wide repertoire of medicinal plants has been widely reviewed in the last few decades [48].

Recently, some highly effective biomolecules with potential antidiabetic effects have been isolated from plants [49]. Medicinal plants with mild-to-potent antidiabetic activity include those from the families Cucurbitaceae, Apocynaceae, Asclepiadaceae, Malvaceae, Acanthaceae, Anacardiaceae, Meliaceae, Amaranthaceae, Rutaceae, Poaceae, Menispermacea, and Myrtaceae (Table 1) [50-139]. Several species from the family Myrtaceae have shown potential antidiabetic effects, for example, *Psidium guajava*, of which its leaf aqueous extract has proven to be able to lower blood glucose. The extract contains flavonoid glycosides which have been used in the treatment of diabetes to improve insulin sensitivity. Other active antidiabetic components such as glycoproteins were identified in the leaf extract [51]. The aqueous extract of *Eucalyptus globulus* leaves was found to contain a high level of manganese which is highly efficient in diabetes management. In a study by Pinto *et al.* (2007), the extract reduced blood glucose levels more drastically than the reference drug, glibenclamide [52]. Several studies focused on the antidiabetic activity of *Campomanesia xanthocarpa* leaf decoction. In one study, streptozotocin (STZ)–induced diabetic rats which were treated with a leaf decoction of *C. xanthocarpa* experienced reduced blood glucose levels, reduced loss of liver glycogen and minimal pancreas and kidney histopathological alterations [53-56]. Another study evaluated the efficacy of aqueous extract of *Cleistocalyx operculatus* flower buds (COB) in diabetic patient management. In the trial, patients drank 150 mL of COB tea before and while having a meal of 170 g cooked rice. Results showed suppression of postprandial blood glucose, overall blood glucose and HbA1c levels in the COB tea group [57]. Schumacher *et al.* (2015) studied the effect of *Eugenia uniflora* aqueous leaf extract in type 1 diabetic mice, and concluded that the extract had antioxidant activity due to its high phenol content and may even reduce the risk of diabetes [58]. Another study on alloxan-induced diabetic rats showed a decrease in blood glucose levels after 500 mg/kg of *Eucalyptus citriodora* aqueous extract was administered orally [59]. The findings are summarized in Table 2 [51-59].

The antidiabetic potential of *Syzygium*, another genus of the family Myrtaceae, has also been widely researched with promising findings. This article aims to review the antidiabetic potential of various *Syzygium* species based on current *in vivo* and *in vitro* evidence.

Table 1. Families of medicinal plant with antidiabetic activity.

Family	Active compounds	Reference
Acanthaceae	Tannins, flavonoids, alkaloids, sterols, phenolics, triterpenoids	[60-67]
Amaranthaceae	Sterols, glycosides, flavonoids, carbohydrates, tannins, alkaloids, glycosides, terpenes, phytosterol	[68-72]
Anacardiaceae	Phenolic compounds	[73-77]
Apocynaceae	Alkaloids, tannins, saponins, phytosterols, flavonoids, glycosides, carbohydrates, steroids, triterpenoids	[78-85]
Asclepiadaceae	Alkaloids, flavonoids, glycosides, saponins, terpenes, steroids, proteins, coumarins, tannins, phenols	[86-94]
Cucurbitaceae	Glycosides, triterpenoids, alkaloids, flavonoids, resins, polyphenolics, saponins, carbohydrates, alkaloids, fatty acids, steroids, terpenoids, tannins, terpenes	[95-104]
Malvaceae	Flavonoids, carbohydrates, proteins, tannins, phenols, terpens, saponins	[105-113]
Meliaceae	Limonoids	[114-117]
Menispermaceae	Alkaloids, saponins, terpenoid compound, anthraquinones, flavonoids, tannins, cardiac glycosides	[118-121]
Poaceae	Phytosterols, carbohydrates, tannins, alkaloids, phytosterols, glycosides, flavonoids, triterpenoids, saponins, phenolic compounds	[122-125]
Rutaceae	Flavonoids, alkaloids, saponins, tannins	[126-130]
Myrtaceae[1]	Alkaloids, catechin, coumarin, tannins, saponins, steroids, flavonoids, phenols, sugar, glycosides, xanthoprotein	[51-59,131-139]

[1]Examples: leaf of *Eucalyptus globulus* Labill., flower bud of *Cleistocalyx operculatus* (Roxb.) Merr and Perry, leaf of *Eucalyptus citriodora* Hook., leaf of *Campomanesia xanthocarpa* Berg, leaf of *Eugenia operculata* Roxb., leaf and unripe fruit peel of *Psidium guajava* L., leaf of *Eugenia uniflora* L.

ANTIDIABETIC POTENTIAL OF *SYZYGIUM* SPECIES

Syzygium is a flowering plant belonging to the myrtle (Myrtaceae) family and is named after the Greek word "coupled," alluding to the paired leaves and branches. There are 1200 to 1800 species of *Syzygium* and most of them are shrubs and evergreen trees. The biggest diversity of these plants is found in Malaysia and north-eastern Australia. Generally, the lower part of the tree trunk of *Syzygium* is rough, flaking, and cracked while its bark is dark gray in color, becoming smoother and lighter higher up. Its wood is resistant to water. Furthermore, its leaves are dark-green and glossy, turpentine-scented, evergreen, elliptic, and either blunt or tapering with pointed apexes. Besides, its fruits are usually astringent, sometimes unpalatable, and the flavor varies from acidic to fairly sweet. Each fruit contains a single, green or brown and oblong-shaped seed [139,140].

The *Syzygium* species reported to have antidiabetic potential, and discussed herein, are *S. cumini, S. polyanthum, S. samarangense, S. calophyllifolium, S. aqueum, S. aromaticum, S. malaccense, and S. alternifolium*.

Syzygium cumini

S. cumini is alternatively named as *Syzygium jambolanum*, *Syzygium jambolana*, *Eugenia jambolana*, *Eugenia cumini*, *Myrtus cumini*, *Eugenia caryophyllifolia*, *Calyptran jambolana,* or *Eugenia djovant*. Its common names are jambolan, Indian blackberry, jamun, Portuguese plum, java plum, black plum, Malabar plum, Jamaica plum, damson plum, and purple plum [141,142]. This species can be found in India, Philippines, Thailand, Madagascar, Africa, Tropical America, and the Caribbean. It commonly grows in evergreen forests, damp places, and along streams. The tree can also be planted in gardens and along the roadside, as it is large and densely foliaceous. It grows slowly and can reach a height of up to 30 meters, with a life span of more than 100 years. The bark at the lower part of the tree is grayish-brown which exfoliated in woody scales, becoming lighter in shade and smoother higher up. It has whitish, close-grained, and durable wood. Its leaves are pinkish when young, later changing to a glossy dark green, leathery surface with yellow midribs as they get older and emit an aroma similar to turpentine. The length of its leaves is about 6 to 12 cm long and are variable in shape, broad and few acum-

Table 2. Examples of plants exhibiting antidiabetic potential.

Plant species	Part of the plant	Active compounds	Findings	Reference
Psidium guajava	Leaf	Flavonoids, glycoproteins	Improves insulin sensitivity	[51]
Eucalyptus globulus	Leaf	Manganese	Reduces blood glucose levels	[52]
Campomanesia xanthocarpa	Leaf	Gallic acids, chlorogenic acids, quercetins, rutins	Reduces blood glucose levels, reduces loss of liver glycogen	[53-56]
Cleistocalyx operculatus	Flower bud	Flavonoids	Suppresses blood glucose and HbA1c levels	[57]
Eugenia uniflora	Leaf	Phenolic compounds	Reduces inflammation of pancreatic islets, maintains insulin levels and hepatic glutathione, reduces lipid peroxidation	[58]
Eucalyptus citriodora	Leaf	Triterpenes, tannins, flavonoids, anthocyanins, phenolic compounds	Decreases blood glucose levels	[59]

inate tips. Its panicles are borne from branchlets under the leaves, axillary or terminal, at 4 to 6 cm in length. Its flowers are scented, present in clusters of 10 to 40, greenish-white in color, round or oblong-shaped with dichotomous paniculate cymes. It has a flannel-shaped calyx that is toothed and about 4 mm long. The petals are cohered and fall together as a disk. It has numerous stamens that are also about 4 mm long. Its fruits, commonly developed in May or June, resemble berries, have single seed with various colors and sizes bearing from purple to white or violet-colored flesh [70]. They are oblong, dark-purple to black colored, 1.5 to 3.5 cm long, fleshy, and luscious [143-145]. Unripe fruits are green and change to pink, to shining crimson red and black color as they mature [146]. The fruits taste sweet and sour and also has an astringent flavor [143].

S. cumini leaves, seeds and fruits are used in various medicinal applications [147]. The hydroethanolic leaf extract has been shown to reverse reproductive dysfunction in obese female rats [148] as well as revert hypertriglyceridemia [149]. Chagas *et al*. (2015) adequately summarized the use of the plant in the treatment of cardiometabolic diseases [150]. A study by Gowri *et al.* (2010) showed that the leaves of *S. cumini* contain phytochemicals such as flavonoids, glycosides, alkaloids, terpenoids, steroids, tannins, phenols, and cardiac glycosides which are important for medical applications (Table 3) [151]. Myricetin, found in *S. cumini* leaves, strongly inhibits platelet function, hence could be used in the treatment of thrombotic disorders [152]. An *in vitro* study showed that *S. cumini* extracts are more effective in inhibiting maltase when compared to acarbose. Furthermore, the extracts are more potent against α-glucosidase derived from *Bacillus stearothermophilus* [153].

In a study evaluating the antidiabetic effect of *S. cumini* leaf and seed extracts, researchers prepared teas from the seeds and leaves of *S. cumini* with a concentration ranging from 1 to 64 g/L. These teas were used as a substitution of water for 14 to 95 days and administered to STZ-induced diabetic and normal rats. The levels of post-prandial blood glucose were then determined by the glucose oxidase method. However, no determinable effect was determined in normal or STZ-induced diabetic rats. Hence, this study suggested that *S. cumini* that was prepared as the form of tea (a method commonly consumed by people) lacks the purported antihyperglycemic effect [154]. In another study, the antidiabetic effect of crude ethanolic extract as well as aqueous and butanolic fractions of *S. cumini* leaves was evaluated. Likewise, the extracts (200 or 2000 mg/kg) did not exert any effect on the mice (both diabetic and non-diabetic) after short-term administration. When treatments were given twice a day for 7 days, there was a reduction in glycemia in non-diabetic mice, although this may be attributed to factors such as food intake and body weight. The researchers concluded that there was no strong evidence on the antidiabetic activity by both the extract and fractions of *S. cumini* leaves [155].

Nevertheless, the inhibitory activity of *S. cumini* seed extract on α-glucosidase, an enzyme involved in carbohydrate metabolism, was evaluated. The study, performed on Goto-Kakizaki rats, showed that the acetone extract was a potent inhibitor of α-glucosidase. These findings suggest that the inhibition of α-glucosidase may be a possible mechanism for antidiabetic agents [153]. Similar findings have shown that the treatment of diabetic rats with *S. cumini* seed extracts exerted a hypoglycemic effect [147,156,157]. Antihyperglycemic activity of

Table 3. Phytochemical screening results for *S. cumini* leaves extract.

Phytochemical Constituents	Aqueous extract	Methanol extract
Resins	Present	Present
Terpenoid	Moderately present	Present
Saponins	Present	Present
Phenols	Appreciable amount	Moderately present
Flavonoids	Appreciable amount	Appreciable amount
Steroids	Present	Appreciable amount
Alkaloids	Appreciable amount	Moderately present
Glycosides	Moderately present	Moderately present
Tannins	Present	Present
Cardiac glycosides	Moderately present	Present

S. cumini was proven in diabetic animals through OGTT [158-160]. Another study on alloxan-induced diabetic rabbits showed that reduced hyperglycemia was noted in sub-, mild, and severely diabetic rabbits by oral administration of 100 mg/kg ethanolic seed extract. Results had shown a significant reduction in fasting blood glucose in all the treated groups. Histopathological studies of the pancreas, liver, and aorta of treated animals revealed a normal morphology [158]. In addition, the flavonoid-rich *S. cumini* extract was observed to be an effective anti-hyperglycemic agent in STZ-induced diabetic rats [159-166]. *S. cumini* ethanolic extract was able to increase the activity of key enzymes involved in glycolysis and reduce the activity of gluconeogenesis-associated enzymes. Additionally, it increased glycogen content in the liver and muscle and stimulated the release of insulin from Langerhans cells [167]. *S. cumini* extracts also prevented or alleviated diabetes-induced secondary complications including neuropathy, nephropathy, gastropathy, and peptic ulcer [168,169].

Sanches *et al.* (2016) tested the polyphenol-rich extract of *S. cumini* leaves in monosodium L-glutamate-induced obese rats. Rats that received 500 mg/kg of extract for 30 days showed partial reversal of glucose intolerance, reduced hyperinsulinemia, and insulin resistance, a direct result of improved pancreatic function. An *in vitro* study using isolated rat islets and INS-1E β-cells demonstrated that the extract stimulated insulin secretion in the cells [170]. In similar study using alloxan-induced rats, *S. cumini* extract was found to decrease fasting glycaemia, triglycerides, and total cholesterol [171].

In a clinical study by Srivastava *et al.* (1983), 4 to 24 g of *S. cumini* seed powder was administered to 28 diabetic patients and reduction in mean fasting as well as post-prandial blood glucose levels was observed [172]. Correspondingly, another group of researchers observed a moderate hypoglycemic effect by administration of 12 g of *S. cumini* seed powder for 3 months in 30 patients with mild NIDDM [173]. Fifteen patients with known type 2 diabetes mellitus and freshly diagnosed patients were given standardized seed powder of *S. cumini* in a separate clinical trial, resulting in a significant reduction in fasting blood glucose as well as insulin resistance. However, post-prandial blood glucose and glycosylated hemoglobin showed no reduction at the end of the third and sixth months of treatment compared to baseline [174].

To assess whether the methanol and ethanol extracts of *S. cumini* root, seed, bark, and leaf were safe for consumption, an acute toxicity study was performed on albino mice. All subjects survived the dose of 2000 mg/kg of ethanol and 200 mg/kg of methanol extract, and potential side effects such as depression, weight loss, and mild diarrhea were not observed. Furthermore, an acute oral toxicity study on the methanol extract from the leaves revealed that the extract was safe to be consumed up to 3500 mg/kg. Correspondingly, a sub-acute toxicity was studied on ethanolic leaf extract in Wistar rats, which revealed increase in body weight and no mortality observed within 14 days [175]**.** Another acute toxicity study was conducted on hydroalcoholic extracts of *S. cumini* in both mice and rats for 14 days through the determination of median lethal dose (LD_{50}). Six g/kg of the extract was administered orally to mice, and the dose proved to be safe. However, when the extract was administered intraperitoneally, mortality was observed (LD_{50}: 0.489 g/kg). Chronic toxicity in rats was also assessed at treatment concentrations of 0.05, 0.1, and 0.25 g/kg; administered orally and daily. Although there were changes in certain biochemical parameters at 30, 90, or 180 days of treatment, histological examination revealed no morphological disturbances. Collectively, these findings suggest that the extract does not have significant acute or chronic toxicity when administered orally [176]**.**

Syzygium polyanthum

S. polyanthum or *Eugenia polyantha* is known to

Malaysians as "salam," "samak kelat," or "serai kayu;" while in Indonesia, "ubar serai," "manting," "meselengan," Indonesia bay leaf, or Indonesia laurel are common names [177,178]. *S. polyanthum* is endemic to several Southeast Asian countries, inhabiting forests and hilly areas or planted in gardens or fields near rural residential areas [179-183]. The plant can reach a height of 25 m, has straight roots and a rounded trunk with lush branches, and grow elliptical-shaped leaves measuring between 5 to 15 cm in length and 3 to 8 cm in width. The leaves have petioles of 0.5 to 1 cm, pointy bases and tips, and are dark or light green at the superior or inferior surfaces respectively. Its small, white, and fragrant flowers give rise to round, dark red fruits measuring 8 to 9 mm in diameter with tiny round brown seeds [184].

Widyawati *et al*. (2015) studied the antidiabetic effect of *S. polyanthum* leaf extracts in male Sprague Dawley rats. In the study, petroleum ether, chloroform, methanol, and water extracts were administered to normal rats and intraperitoneal glucose tolerance test was performed after an hour. Results showed only the water extract reduced the blood glucose levels. Additionally, administration to STZ-induced diabetic rats revealed that the methanol extract reduced blood glucose levels significantly. These findings demonstrated that the methanol extract of *S. polyanthum* leaves possesses a antihyperglycemic effect [177]. Another study by Widharna *et al*. (2015) on the antidiabetic potential of an aqueous extract mixture of *S. polyanthum* and *Andrographis paniculata* leaves was performed on male Wistar rats. Using the OGTT, 200 mg/kg of mixture exerted a more significant hypoglycemic effect after 14 days of treatment compared to single extracts. Islet morphology was improved with an absence of toxic symptoms in treated rats. Hence, the researchers suggested that the extract mixture had antidiabetic potential without toxicity [185]. Subsequently, Wahjuni *et al.* (2017) studied the antioxidant as well as hypoglycemic effects of *S. polyanthum* ethanolic leaf extract on alloxan-induced diabetic Wistar rats. It was shown that the extract significantly reduced blood glucose levels with the effective dose of 5 mg/kg [186]. An *in vitro* study of *S. polyanthum* leaf extract suggested that the antidiabetic effect of the plant may be due to its ability to inhibit α-glucosidase [187].

An acute toxicity study was performed using oral infusions of 2000 mg/kg *S. polyanthum* and *A. paniculata* extract mixture on male Wistar rats. The rats were observed after 0.5, 1, 2, 4, and 24 hours after treatment for behavioral changes. As postulated, surviving rats recovered and gained weight, restored their pancreatic islet cells, and exhibited no behavioral changes. No toxicity or mortality was observed throughout the experiment [185]. As for sub-chronic toxicity, a study was conducted using *S. polyanthum* ethanolic leaf extract on Wistar rats treated with 2% Arabic gum suspension (PGA) or 100, 400, and 1000 mg/kg of the ethanol extract. Similarly, increased body weight and white blood cell count was observed, while treated male rats showed decreased red blood cell counts in a dose-dependent manner. No histological alteration was determined [188]. In another study, toxicity of *S. polyanthum* aqueous leaf extract was assessed using the brine shrimp lethality test. Results suggested that the extract possessed very low toxicity on brine shrimp larvae (LD_{50} > 1000 μg/mL) [187].

Syzygium samarangense

S. samarangense, also known as wax apple, water apple, samarang rose apple, and wax jambu, is a popular fruiting plant in Southeast Asia. An evergreen tree that can grow up to 15 m high, it has a short trunk with a slightly crooked base with flaky, pinkish-gray bark. The tree produces pear-shaped, 5 to 12 cm green, pink, and red fleshy fruits with four calyx lobes and harbors up to four 8-mm seeds. Its white flesh is spongy, aromatic, juicy, and has a sweet-sour taste. Its leaves are elliptical to oblong, opposite, and pellucid-dotted, with a thick petiole about 3 to 5 mm long. The yellow-white flowers, which usually bloom either in the dry season, are 3 to 4 cm in diameter, with lobes 3 to 5 mm long and have 4 orbicular to spatulate petals. The tree grows in moist tropical lowland with an elevation up to 1200 m and is often planted along streams, small rivers, or ponds [189,190].

Resurreccion-Magno *et al.* (2005) studied the antidiabetic effect of flavonoids isolated from *S. samarangense* leaves by conducting OGTT in mice. They demonstrated that 2',4'-dihydroxy-3',5'-dimethyl-6'-methoxychalcone and 5-O-methyl-4'-desmethoxymatteucinol reduced blood glucose levels if administered 15 minutes after a glucose load. Co-administration of 2',4'-dihydroxy-3',5'-dimethyl-6'-methoxychalcone with glucose showed a significant decrease in blood glucose levels after 45 minutes. However, when the compounds were administered before glucose load, the flavonoids showed no positive effect. This finding suggested that the timing of treatment administration is important [191]. In a separate, but similar, study on diabetic mice, various doses of leaf extract were administered one hour before glucose load and the blood glucose levels were measured after two hours through the glucose oxidase method. Results showed a significant decrease in the levels of blood glucose after treatment. Hence, it was proven that the methanolic extract of *S. samarangense* leaves exerted antihyperglycemic effect [192]. Vescalagin, an active component in *S. samarangense* fruit, enhances the glucose uptake ability in hepatocytes. A study conducted by Shen *et al*. (2013) demonstrated the hypoglycemic effect of vescalagin *in vivo* by feeding it to high-fructose diet-induced diabetic rats. A reduction in fasting blood glucose

levels and increase in high-density lipoprotein cholesterol were observed [193].

Methanol extract of *S. samarangense* leaves was tested for acute toxicity in female albino Swiss and healthy nulliparous mice. Up to concentrations of 1000 mg/kg, there was no mortality over the period of two days, although slight changes in behavior, weight loss, diarrhea, and locomotor ataxia were observed [194]. Experiments were also conducted on zebrafish embryos to determine the toxicity of triterpenes and sterols isolated from *S. samarangense*. In the study, a mixture of compounds (cycloartenyl stearate, lupenyl stearate, sitosteryl stearate and 24-methylenecycloartanyl stearate) were found to be relatively toxic to non-dechorionated and dechorionated embryos [195].

Syzygium calophyllifolium

S. calophyllifolium, also known as the pretty-leaved plum, is an evergreen tree that can grow up to 20 m in height. It has thick, rough, brown bark with blaze pink and round branchlets. The leaves are opposite, simple, decussate, carried on stalks about 2 to 3 mm, hairless, and stout. Its leaf has a blade of 2 to 5 x 1.5 to 3 cm, almost circular, obtuse, or round base, slightly notched, pellucid dotted, hairless, and leathery. Its white flowers are bisexual, has four sepals and are arranged in dense corymbs. The sepal tube of its flower is about 3 mm long and ovoid-shaped. Its 1 to 1.2 cm long oblong or ovoid-shaped dark-purple fruits resemble berries. This species can be found mainly in Sri Lanka and the Western Ghats [196,197].

Gurusamy *et al*. (2007) evaluated the antidiabetic effect of a 30-day oral administration of *S. calophyllifolium* aqueous seed extract to alloxan-induced diabetic rats, based on changes in the levels of enzymes such as aspartate transaminase, alanine transaminase, lactate dehydrogenase, acid phosphatase, and alkaline phosphatase in rat tissue and serum. Upon alloxan induction, increased levels of enzymes in serum signal tissue injury caused by diabetes. The extract suppressed the elevated levels of serum enzymes in diabetic rats, indicating that *S. calophyllifolium* extract may protect against lysosomal rupture and leakage of enzymes owing to the presence of secondary metabolites [198]. In a separate study on *S. calophyllifolium* bark methanol extract administered to STZ-nicotinamide-induced diabetic rats, body weight was recovered and blood glucose levels were reduced at doses of 100 and 200 mg/kg with no observable alteration in hematological parameters. Results suggested that 200 mg/kg dose was effective as the histological architecture of the liver, kidney, and pancreas was preserved at this concentration [199].

Chandran *et al.* (2015) conducted an acute toxicity study on fasted Swiss albino male mice using *S. callophyllifolium* bark methanol extract, based on the Organization for Economic Co-operation and Development guidelines. Up to 2000 mg/kg of extract was administered orally to observe the animals' behavioral changes, diarrhea, piloerection, tremors, sedation, muscle relaxation, and skin color for 3 days. This study justified that the extract may be safe for consumption, at least by a murine model, with no adverse effects [200].

Syzygium aqueum

S. aqueum, known locally as watery rose apple or water guava, is widely found in tropical forest habitats in Malaysia, Queensland, New Guinea, and Indonesia [201,202]. The tree is farmed for its wood and edible fruit, which are fleshy red or yellow berries that are waxy, crisp, and bell-shaped. This species needs heavy rainfalls and thrive in a tropical habitat up to 1600 m above the sea level [103]. Its characteristically hard wood makes useful for tool-making, its bark used in herbal medicine preparations, while its leaves are turned into food wrappers. The fruits taste slightly sweet, resembling apples and have a crisp watery texture that resembles watermelon [203,204].

In a study done by Manaharan *et al.* (2012), six bioactive compounds (flavonoids) were found in the *S. aqueum* ethanolic leaf extract, namely myrigalone-B, myrigalone-G, phloretin, europetin-3-O-rhamnoside, myricetin-3-O-rhamnoside and 4-hydroxybenzaldehyde. Myricetin-3-O-rhamnoside and europetin-3-O-rhamnoside were found to inhibit α-glucosidase, an enzyme involved in carbohydrate metabolism [205]. Plant-derived flavonoids are known to exhibit antidiabetic properties [206,207], perhaps *via* a reduction of insulin resistance through adipocyte differentiation and adiponectin secretion [208].

In a separate study, acute and sub-chronic toxic effects of *S. aqueum* ethanolic leaf extract were evaluated on Sprague-Dawley rats. For acute toxicity, a single dose (2000 mg/kg) of the extract was administered through oral-gavage and the effects were observed for 14 days. On the other hand, for sub-chronic toxicity, a range of doses from 50 to 200 mg/kg were orally administered daily for 28 days. No visible signs of toxicity nor significant differences in water and food intake, organ and body weight, biochemical parameters, and histological changes were observed, suggesting that the extract may be minimally or non-toxic [209].

Syzygium aromaticum

S. aromaticum is a medium-sized evergreen tree reaching 20 m in height. It originates from Indonesia, Madagascar, Zanzibar, Sri Lanka, and the Caribbean. This species grows the best in tropical forests, especial-

ly at lower elevations of mountain slopes. It has simple, glossy, and bright green leaves with aromatic oil glands on the lower surface. The leaf stalks can grow until 13 cm long with numerous branches. Its flowers develop in small clusters with pale, fleshy, and glossy flower buds at the beginning and becoming green and bright red when mature. The flowers consist of four triangular sepals with a long ovary about 15 to 20 mm in length. The fruits are oblong-shaped, with one to two seeds [210-221].

An *in vitro* study by Adefegha *et al.* (2012) on *S. aromaticum* polyphenol-rich extract revealed that it dose-dependently inhibited α-glucosidase better than α-amylase, and exhibited potent antioxidant activities [212]. In another study on the hypoglycemic activity of *S. aromaticum* ethanolic flower bud extract in diabetic KK-A^y mice, the extract was orally administered at 0.5 g/100g diet for three weeks. Compared to the pioglitazone positive control, mice fed with the extract developed lower blood glucose levels after 3 weeks [214]. Therefore, the researchers suggested that the extract may elicit a therapeutic effect on type 2 diabetes. Furthermore, the antidiabetic effect of oleanolic acid (OA) derived from *S. aromaticum* was evaluated in STZ-induced diabetic rats, which were treated with either OA, deionized water (negative control), or standard hypoglycemic drugs for 5 weeks. Diabetes-induced depletion in glycogen and glycogenic enzyme levels in hepatic tissues and muscles was restored to near normalcy after the administration of OA. However, there was no alteration in hexokinase and glucokinase activities in the diabetic rats when OA was given in combination with insulin. This suggested that glycogen synthesis could take place from precursors like fructose, lactate, and amino acids. Hence, reduction in glycogenic enzymes associated with increasing glycogen concentrations may be a potential strategy to treat diabetes [215]. Similarly, researchers who assessed the hypoglycemic effects of *S. aromaticum*-derived OA and maslinic acid (MA) found that α-glucosidase, sucrose, α-amylase, glucose transporter (GLUT2), and sodium-glucose linked transporter (SGLT) 1 expression was reduced in the small intestines of STZ-induced diabetic rats treated with MA/OA for 5 weeks. The results suggested that MA and OA could be used as supplements in post-prandial hyperglycemia treatment [216].

An α-amylase assay was performed to determine the antidiabetic effect of up to 100 µg/mL *S. aromaticum* bud essential oil *via* inhibition of α-amylase. The results revealed that inhibitory action against the enzyme increased dose-dependently and was stronger than the effect of *Cuminum cyminum* essential oil, yet much weaker when compared to the standard antidiabetic compound, acarbose. The antidiabetic activity of *S. aromaticum* essential oil may be due to the presence of mimetic agents of insulin [217]. In a separate study, *S. aromaticum* extract reduced phosphoenolpyruvate carboxykinase and glucose-6-phosphate gene expression in hepatic cells due to the presence of an insulin-like compound. The repression was reversed by N-acetylcysteine and phosphoinositide 3-kinase inhibitors, and DNA microarray analysis revealed that the extract and insulin regulated the expression of many genes in a similar manner. Collectively, the evidence suggests that consumption of *S. aromaticum* extract had a potential in treating diabetes due to its content of insulin-like compounds [218].

In an acute toxicity study of polyphenolic clove bud extracts in Wistar rats, 5 g/kg of the extract was administered orally for 14 days. In contrast, extract with doses of 0.25, 0.5, and 1 g/kg were orally administered for 90 days for sub-chronic toxicity evaluation. Results showed no toxicological changes observed through behavioral, ophthalmic, body and organ weight, urinalysis, feed consumption, biochemistry parameters, hematology, and histopathology examination in treated rats [219]. Similarly, an acute toxicity study on *S. aromaticum* ethanolic extract (up to 500 mg/kg) performed on male Swiss mice revealed no adverse effect [220]. Another acute toxicity study was conducted on a decoction of *S. aromaticum* cloves on fasted mice. Doses ranging from 100 to 520 mg/kg were intraperitoneally administered, whilst higher doses (500 to 5000 mg/kg) were administered orally. Changes in behavior, respiration, gastrointestinal tract, and central nervous system symptoms as well as mortality were recorded, however only abdominal cramps were observed as a toxic manifestation. The lethal dose (LD_{50}) of the extract for oral administration was 2500 mg/kg, and 263 mg/kg for the intraperitoneally-administered extract. A sub-chronic toxicity study was performed with up to 700 mg/kg clove decoction in rats for 90 days. Hematological parameters and liver enzymes were observed to be affected significantly with the long term treatment of extract, along with histopathological changes in the organs. Thus, prolonged use of the clove extract should be avoided [221].

Syzygium malaccense

Another member of the *Syzygium* genus is *S. malaccense*, also known as the Malay-apple and wax jambu. It is an evergreen tree with a height up to 25 m, with flaky, grayish-brown bark. Its leaves are oblong-obovate to elliptic, subcoriaceous, 5 to 20 cm wide, and 14 to 38 cm long. The leaves have 8 to 15 lateral veins which is about 10 to 25 mm apart, apex short acuminate, sub-marginal vein sinuate, and petioles 8 to 15 mm long. The 2 to 5 mm-long flowers are in axillary cymes on trunks and older branches. The peduncles are 0.5 to 1 cm long, while the bracts are 1 to 1.5 mm long and it has four sepals with bright purplish-red. Moreover, its 5 to 7 cm long/10 to 20 mm thick, obovoid, maroon fruits resemble berries with

juicy flesh and a single subglobose 1.5 to 2 cm seed. This species can be found in tropical regions including Malaysia, China, India, Indonesia, Japan, Brazil, and South America [222,223].

Studies on the antihyperglycemic effect of *S. malaccense* leaf extract involved the isolation of a myricetin derivative, myricitrin, which was found to inhibit α-glucosidase and α-amylase activities by exhibiting insulin-like effects – including enhancement of glucose uptake, adiponectin secretion, and lipid accumulation through activation of the insulin signaling pathway. The compound upregulated glucose transporters, protein kinase B, adiponectin, and peroxisome proliferator activated receptor (PPAR) gamma genes and stimulated the glucose uptake [224,225]. Bairy *et al.* (2005) assessed the effect of *S. malaccense* aqueous and alcoholic bark extracts, which contain tannins, triterpenoids, glycosides, and flavonoids, in STZ-induced diabetic rats. Chronic oral administration of the extracts caused a hypoglycemic effect similar to the standard drug, glibenclamide [226].

A sub-acute toxicity study was performed on albino rats using *S. malaccense* ethanolic leaf extract with doses up to 500 mg/kg, administered orally for 28 days. Results revealed that LD_{50} of the extract was 1224.75 mg/kg, and no alterations in organ weight and kidney histopathology were observed in the treated animals. However, changes in biochemical and hematological parameters were noted. Thus, this study concluded that the extract might affect the hematological elements and also alter liver tissue integrity if ingested at higher doses [227].

Syzygium alternifolium

S. alternifolium is a dominant species found on the uplands of Tirumala with an altitude of 930 m. It can grow up to 12 m of height, with a grayish and slightly fissured bark. The dark-green, glossy leaves measure 10 to 12.3 by 7 to 9 cm. Its dark-purple, globose fruits resemble berries, which vary in shape, size, and taste [228-231].

Rao *et al.* (2001) conducted a study on the antihyperglycemic activity of hexane, ethanolic, and aqueous fractions of *S. alternifolium* seed extracts in alloxan-induced diabetic rats. Blood glucose levels were measured immediately after, and at 1, 3, 5, and 7 hours of treatment. The findings revealed that 0.75 g/kg of aqueous seed extract exerted the maximum glucose-reducing effect in both diabetic and normal rats, compared to hexane and ethanolic fractions. Antihyperglycemic activity of the extract was comparable to glibenclamide [228]. Another study on STZ-induced diabetic rats administered with 50 mg/kg *S. alternifolium* aqueous seed extract showed that there was a maximum reduction in blood glucose levels of (83%) after 6 hours of treatment. When the fraction was administered daily for 30 days, the results revealed significant reduction in blood glucose, glycosylated hemoglobin and creatinine levels, accompanied with an increase in plasma insulin. This indicated that the fraction also had a protective role against kidney damage, and suggested that its effect was more prominent compared to glibenclamide at 20 mg/kg [232]. Oral administration of 50 mg/kg cinnamic acid, an active compound found in the aqueous seed extract of *S. alternifolium*, to STZ-induced diabetic rats revealed an alteration in enzymes involved in carbohydrate metabolism in the kidney and liver. After fraction administration, elevated enzymes and blood glucose levels were reverted to normal levels. The treatment also caused glibenclamide-like modulatory effects on glucose homeostasis after 30 days of treatment, indicating the potent antidiabetic effect of cinnamic acid [233].

An analogous study on STZ-induced diabetic rats with a 30-day oral administration with 50 mg/kg of fraction obtained from *S. alternifolium* aqueous seed extract demonstrated decreased serum levels of glutamic-oxaloacetic transaminase, glutamic-pyruvate transaminase, alkaline phosphatase, and creatinine, indicating the non-toxic property of the fraction [232].

MECHANISMS OF ACTION AND BIOACTIVE COMPOUNDS OF *SYZYGIUM* SPECIES

A commonly reported antidiabetic mechanism of medicinal plants is the inhibition of enzymes involved in carbohydrate metabolism, such as α-glucosidase, maltase, and α-amylase. Glycosidase is an enzyme that breaks the glycosidic bonds of polysaccharides while maltase cleaves maltose, hence both hold critical roles in carbohydrate digestion [234,235]. α-Amylase also cleaves the glycosidic bonds of starch at random sites, subsequently forming the oligosaccharides or disaccharides. Excess activity of amylase enzymes usually leads to hyperglycemia [236].

Syzygium species reported to have enzymatic inhibitory activity include *S. cumini*, *S. polyanthum*, *S. aqueum*, *S. aromaticum,* and *S. malaccense*. *S. cumini* extract was found to inhibit maltase and α-glucosidase [153], while *S. polyanthum* inhibited α-glucosidase [187]. Similarly, active compounds isolated from *S. aqueum* (myricetin-3-O-rhamnoside and europetin-3-O-rhamnoside) were found to inhibit α-glucosidase [205], while polyphenols found in *S. aromaticum* attenuated both α-glucosidase and α-amylase [212]. Several studies also showed that *S. aromaticum* extracts were potent α-amylase inhibitors [216,217]. Myricitrin, the active compound of *S. malaccense*, was found to inhibit α-glucosidase and α-amylase [224,225]. On the other hand, cinnamic acid isolated from *S. alternifolium* was found to alter hexokinase, glucose-6-phosphatase, fructose-1,6-bisphosphatase, and glucose-6-phosphate dehydrogenase involved in carbohydrate metabolism [233].

Table 4. Bioactive compounds of *Syzygium* species.

Syzygium species	Bioactive compounds	Reference
S. cumini	Flavonoids, glycosides, alkaloids, terpenoids, steroids, tannins, phenols, cardiac glycosides	[151]
S. polyanthum	Tannins, flavonoids, glycosides, alkaloids, squalene	[241]
S. samarangense	Flavonoids (2',4'-dihydroxy-3',5'-dimethyl-6'-methoxychalcone and 5-O-methyl-4'-desmethoxymatteucinol)	[191]
S. calophyllifolium	Phenolics, tannins, flavonoids	[249]
S. aqueum	Flavonoids (myrigalone-B, myrigalone-G, phloretin, europetin-3-O-rhamnoside, myricetin-3-O-rhamnoside and 4-hydroxybenzaldehyde)	[205]
S. aromaticum	Oleanolic acid, maslinic acid	[215,216]
S. malaccense	Tannins, triterpenoids, glycosides, flavonoids (myricitrin)	[224-226]
S. alternifolium	Cinnamic acid	[233]

In addition to oral hypoglycemic agents, type 2 diabetic patients might require therapeutic insulin [237]. Hence, medicinal plants which stimulate insulin secretion would be useful in the diabetes management. Sharma *et al*. (2011) [167] and Sanches *et al.* (2016) [170] found that *S. cumini* extracts were able to stimulate insulin secretion of pancreatic beta cells. On the other hand, Sahana *et al*. (2010) [174] and Sharma *et al*. (2012) [238] reported that *S. cumini* extract exerted antidiabetic activities through reduction of insulin resistance. Other *Syzygium* sp. that may ameliorate insulin resistance include *S. aqueum* [208] and *S. samarangense* [239,240]. Besides, *S. malaccense* ethanolic extract was found to activate the insulin signaling pathway [224,225].

Medicinal plants that promote glucose uptake in cells may also benefit diabetic patients. Vescalagin from *S. samarangense* fruit [193] and myricitrin from *S. malaccense* leaf [224,225] had been shown to enhance this mechanism. *S. polyanthum* also stimulated cellular glucose uptake by muscle tissue [241] *via* upregulation of GLUT4 [242]. Another study provided evidence that the methanolic extract of *S. cumini* improved glucose uptake *via* activation of phosphoinositide 3-kinase [243]. On the other hand, a number of *Syzygium* species exerted antidiabetic effect by inhibiting glucose absorption. For example, the purported antihyperglycemic effect of *S. polyanthum* methanol leaf extract was evident through reduced glucose absorption from intestinal tissue [241]. Likewise, Saravanan and Pari (2008) suggested that the hypoglycemic effect of *S. cumini* in STZ-induced rats occur *via* the same mechanism [244].

Oxidative stress caused by the formation of reactive oxygen species and reactive nitrogen species is associated with the pathogenesis of diabetes [46]. Hence, compounds with antioxidant properties harbor a significant potential to complement antidiabetic treatment regimes. Several plants in the *Syzygium* genus were found to neutralize reactive oxygen or nitrogen species, and hence exhibit antidiabetic effect. The myriad of *Syzygium* species that are reported to have antioxidant properties include *S. cumini* [171], *S. polyanthum* [186], *S. samarangense* [245], *S. calophyllifolium* [199], *S. malaccense* [224], *S. aromaticum* [212], *S. densiflorum* [246], *S. mundagam* [247], and *S. paniculatum* [248]. Other antidiabetic mechanisms of *Syzygium* species include reduction of gluconeogenesis-associated enzymes by *S. cumini* [167] and reduction of glycogenic enzymes by *S. aromaticum* [215].

The antidiabetic effects of the plants are attributed to the presence of bioactive compounds. Table 4 summarizes bioactive compounds present in the various species of the *Syzygium* genus [151,191,205,215,216,224-226,233,241,249].

CONCLUSION

Evidence from current literature highlights the potential of seed, leaf, and fruit extracts from various *Syzygium* species in improving blood glucose and insulin regulation. This promising antidiabetic effect is compounded by its general non-toxic nature at moderate doses, bringing focus to a possible role in clinical therapy for type 1 or 2 diabetes. Nonetheless, available data is mostly based on extracts or fractions, and very few studies have isolated or identified bioactive compound derivatives. Furthermore, evidence from large-scale clinical trials and toxicology studies are crucial to verify the plants' antidiabetic potential. Future work delineate a need to isolate and develop bioactive compounds derived from *Syzygium* species into antidiabetic agents, and their effects should be validated *in vivo* and in clinical studies. In addition, the antidiabetic potential of a few rather elusive *Syzygium* species, such as *S. densiflorum* and *S. mundagam*, could be explored further.

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