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; LD50, 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 tis-
sues. 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 ei-
ther 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 assess-
ment 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 indicat-
ed. However, oral hypoglycemic drugs have the poten-
tial to lose their efficacy despite providing a good initial
response. Administration of drugs such as sulfonylurea,
thiazolidinedione, and biguanide gives rise to various un-
desirable 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 pa-
patients [12-27]. Supplementation of vitamin D and va-
nadium 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, result-
ing in an increasing demand for safe and cost-effective
measures [43,44]. Medicinal plants contain phytoconsti-
tuents, 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 improv-
ing 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 reper-
toire 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 ant-
diabetic activity include those from the families Cu-
curbitaceae, Apocynaceae, Asclepiadaceae, Malvaceae,
Acanthaceae, Anacardiaceae, Meliaceae, Amaranthace-
ae, Rutaceae, Poaceae, Menispermaceae, and Myrtaceae
(Table 1) [50-139]. Several species from the family Myrt-
aceae have shown potential antidiabetic effects, for exam-
ple, 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 glycopro-
teins were identified in the leaf extract [51]. The aqueous
extract of Eucalyptus globulus leaves was found to con-
tain 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 stud-
ies 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 alter-
ations [53-56]. Another study evaluated the efficacy of
aqueous extract of Cleistocalyx operculatus flower buds
(COB) in diabetic patient management. In the trial, pa-
tients 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 Euc-
alyptus 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.
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, Jamaican 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-
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]. Simpler findings have shown that the treatment of diabetic rats with *S. cumini* seed extracts exerted a hypoglycemic effect [147,156,157]. Antihyperglycemic activity of

| 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]      |
| *Camponanies 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]      |

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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 antihyperglycemic 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 (LD₅₀). 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 (LD₅₀: 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,” “meselen-gan,” 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 an antihyperglycemic effect [177]. Another study by Widiharma *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.* (2015) 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 (LD₅₀ > 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 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-methylene cycloartenyl 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. callo-

**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-Ay 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 (SGLT1) 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 (LD₅₀) 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
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 LD₅₀ 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 potential 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 glumatic-oxaloacetate 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* (myricitin-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]. Myricitin, 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].
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'-desmethoxymateucinol)
[191]

S. calophyllifolium
Phenolics, tannins, flavonoids
[249]

S. aqueum
Flavonoids (myrigalone-B, myrigal-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]

**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.
REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013 Jan;36 Suppl 1:S67–74.
2. Forouhi NG, Wareham NJ. Epidemiology of Diabetes. Medicine (Baltimore). 2010;38(11):602–6.
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010 Jan;33 Suppl 1:S62–9.
4. Ozouguw JC, Obimba KC, Belonwu C, Unakalamba CB. The Pathogenesis and Pathophysiology of Type 1 and Type 2 Diabetes Mellitus. J Physiol Pathophysiol. 2013;4(4):46–57.
5. Kahanovitz L, Sluss PM, Russell SJ. Type 1 Diabetes - A Clinical Perspective. Point Care. 2017 Mar;16(1):37–40.
6. Bregu A, Toçi E, Muja H, Çanaku D, Roshi E. Diabetes Management: A Literature Review. Alban Med J. 2012;4:86–92.
7. Dorababu M, Prabha T, Priyambada S, Agrawal VK, Aryya NC, Goel RK. Effect of Bacopa monniera and Azadirachta indica on gastric ulceration and healing in experimental NIDDM rats. Indian J Exp Biol. 2004 Apr;42(4):389–97.
8. Halim EM. Lowering of blood sugar by water extract of Azadirachta indica and Abroma augusta in diabetes rats. Indian J Exp Biol. 2003 Jun;41(6):636–40.
9. Singh S, Kumar R, Pal R, Kumar N, Dixit RK, Nath R. Switch Over to Alternative Therapy for Diabetes Mellitus - A Life Style Disease. Curr Res Diabetes Obes J. 2016;1(2):555557.
10. Ribes G, Sauvare Y, Da Costa C, Baccou JC, Loubatieres-Mariani MM. Antidiabetic effects of subfractions from fenugreek seeds in diabetic dogs. Proc Soc Exp Biol Med. 1986 Jun;182(2):159–66.
11. Abdel-Barry JA, Abdel-Hassan IA, Al-Hakiem MH. Hypoglycaemic and antihyperglycaemic effects of Trigonella foenum-graecum leaf in normal and alloxan induced diabetic rats. J Ethnopharmacol. 1997 Nov;58(3):149–55.
12. Landman GW, Bilo HJ, Houweling ST, Kleefstra N. Chromium does not belong in the diabetes treatment arsenal: current evidence and future perspectives. World J Diabetes. 2014 Apr;5(2):160–4.
13. Lewicki S, Zdanowski R, Krzyżowska M, Lewicka A, Dębski B, Niemiecwick M, et al. The role of Chromium III in the organism and its possible use in diabetes and obesity treatment. Ann Agric Environ Med. 2014;21(2):331–5.
14. McIver DJ, Grizales AM, Brownstein JS, Goldfine AB. Risk of Type 2 Diabetes Is Lower in US Adults Taking Chromium-Containing Supplements. J Nutr. 2015 Dec;145(12):2675–82.
15. Althuis MD, Jordan NE, Ludington EA, Wittes JT. Glucose and insulin responses to dietary chromium supplements: a meta-analysis. Am J Clin Nutr. 2002 Jul;76(1):148–55.
16. Martin J, Wang QZ, Zhang XH, Wachtel D, Volaufova J, Matthews DE, et al. Chromium picolinate supplementation attenuates body weight gain and increases insulin sensitivity in subjects with type 2 diabetes. Diabetes Care. 2006 Aug;29(8):1826–32.
17. Kleefstra N, Houweling ST, Jansman FG, Groenier KH, Gans RO, Meyboom-de Jong B, et al. Chromium treatment has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese Western population: a randomized, double-blind, placebo-controlled trial. Diabetes Care. 2006 Mar;29(3):521–5.
18. Ghosh D, Bhattacharya B, Mukherjee B, Manna B, Sinha M, Chowdhury J, et al. Role of chromium supplementation in Indians with type 2 diabetes mellitus. J Nutr Biochem. 2002 Nov;13(11):690–7.
19. Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. J Am Coll Nutr. 2001 Jun;20(3):212–8.
20. Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, et al. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. Diabetes. 1997 Nov;46(11):1786–91.
21. Kleefstra N, Houweling ST, Bakker SJ, Verhoeven S, Gans RO, Meyboom-de Jong B, et al. Chromium treatment has no effect in patients with type 2 diabetes in a Western population: a randomized, double-blind, placebo-controlled trial. Diabetes Care. 2007 May;30(5):1092–6.
22. Balk EM, Tatsioni A, Lichtenstein AH, Lau J, Pittas AG. Effect of chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled trials. Diabetes Care. 2007 Aug;30(8):2154–63.
23. Albarracin CA, Fuqua BC, Evans JL, Goldfine ID. Chromium picolinate and biotin combination improves glucose metabolism in treated, uncontrolled overweight to obese patients with type 2 diabetes. Diabetes Metab Res Rev. 2008 Jan-Feb;24(1):41–51.
24. Albarracin C, Fuqua B, Geohas J, Juturu V, Finch MR, Komorowski JR. Combination of chromium and biotin improves coronary risk factors in hypercholesterolemic type 2 diabetes mellitus: a placebo-controlled, double-blind randomized clinical trial. J Cardiometab Syndr. 2007;2(2):91–7.
25. Lai MH. Antioxidant effects and insulin resistance improvement of chromium combined with vitamin C and supplementation for type 2 diabetes mellitus. J Clin Biochem Nutr. 2008 Nov;43(3):191–8.
26. Abdollahi M, Farshchi A, Nikfar S, Seyedin M. Effect of chromium on glucose and lipid profiles in patients with type 2 diabetes: a meta-analysis review of randomized trials. J Pharm Pharm Sci. 2013;16(1):99–114.
27. Paiva AN, Lima JG, Medeiros AC, Figueiredo HA, Andrade RL, Uruhy MA, et al. Beneficial effects of oral chromium picolinate supplementation on glycemic control in patients with type 2 diabetes: a meta-analysis review of randomized trials. J Pharm Pharm Sci. 2013;16(1):99–114.
ciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. Eur J Nutr. 2009 Sep;48(6):349–54.
31. Nasri H, Behradmanesh S, Maghsoudi AR, Ahmadi A, Nasri P, Rafieian-Kopaei M. Efficacy of supplementary vitamin D on improvement of glycemic parameters in patients with type 2 diabetes mellitus; a randomized double blind clinical trial. J Renal Inj Prev. 2013 Nov;3(1):31–4.
32. Nigil Haroon N, Anton A, John J, Mittal M. Effect of vitamin D supplementation on glycemcic control in patients with type 2 diabetes: a systematic review of interventional studies. J Diabetes Metab Disord. 2015 Feb;14:3.
33. Nwosu BU, Maranda L. The effects of vitamin D supplementation on glycemic control and cardiometabolic risk among people at risk of type 2 diabetes: results of a randomized double-blind placebo-controlled trial. Diabetes Obes Metab. 2016 Apr;18(4):392–400.
34. Ghavamzadeh S, Mobasser M, Mahdavi R. The Effect of Vitamin D Supplementation on Adiposity, Blood Glycated Hemoglobin, Serum Leptin and Tumor Necrosis Factor-α in Type 2 Diabetic Patients. Int J Prev Med. 2014 Sep;5(9):1091–8.
35. Krull-Poel YH, Westra S, ten Boekel E, ter Wee MM, van Schoor NM, van Wijland H, et al. Effect of Vitamin D Supplementation on Glycemic Control in Patients With Type 2 Diabetes (SUNNY Trial): A Randomized Placebo-Controlled Trial. Diabetes Care. 2015 Aug;38(8):1420–6.
36. Schoor NM, van Wijland H, et al. Vitamin D deficiency and either type 1 or type 2 diabetes mellitus: a systematic literature review. Clin Endocrinol. 2016 Mar;84(3):385–9.
37. Elkassaby S, Harrison LC, Mazzitelli N, Wentworth JM, Colman PG, Spelman T, et al. A randomised controlled trial of high dose vitamin D in recent-onset type 2 diabetes. Diabetes Obes Metab. 2014 Dec;16(12):1362–70.
38. Strobel F, Reusch J, Penna-Martinez M, Ramos-Lopez E, Klahold E, Klepzig C, et al. Effect of a randomised controlled vitamin D trial on insulin resistance and glucose metabolism in patients with type 2 diabetes mellitus. Horm Metab Res. 2014 Jan;46(1):54–8.
39. Jeleh S, Lardi A, Felix B, Hulter HN, Stettler C, Krupf P. Effect of large doses of parenteral vitamin D on glycemic control and calcium/phosphate metabolism in patients with stable type 2 diabetes mellitus: a randomised, placebo-controlled, prospective pilot study. Swiss Med Wkly. 2014 Mar;144:w13942.
40. Ryu OH, Lee S, Yu J, Choi MG, Yoo HJ, Mantero F. A prospective randomized controlled trial of the effects of vitamin D supplementation on long-term glycemic control in type 2 diabetes mellitus of Korea. Endocr J. 2014;61(2):167–76.
41. Al-Sofiani ME, Jannah A, Racz M, Khawaja RA, Hasanato R, El-Fawal HA, et al. Effect of Vitamin D Supplementation on Glucose Control and Inflammatory Response in Type II Diabetes: A Double Blind, Randomized Clinical Trial. Int J Endocrinol Metab. 2015 Jan;13(1):e22604.
42. Autier P, Boniol M, Pizot C, Mullie P, Vitamin D. Vitamin D status and ill health: a systematic review. Lancet Diabetol. 2014 Jan;2(1):76–89.
43. Widyawati T, Pane YS, Yusoff NA. Effect of Lawsonia inermis Lim. Extracts on Blood Glucose Level in Normal and Streptozotocin-induced Diabetic Rats. Pak J Nutr. 2019;18(7):671–6.
44. Peesa JP. Herbal Medicine for Diabetes Mellitus: A Review. Int J Phytopharm. 2013;3(1):1–22.
45. Rasouli H, Yaran R, Pociot F, Popović-Djordjević J. Anti-diabetic potential of plant alkaloids: revisiting current findings and future perspectives. Pharmocol Res. 2020 May;155:104723.
46. Unuofin JO, Lelbo SL. Antioxidant Effects and Mechanisms of Medicinal Plants and Their Bioactive Compounds for the Prevention and Treatment of Type 2 Diabetes: An Updated Review. Oxid Med Cell Longev. 2020 Feb;2020:1356893.
47. Arya V, Gupta V, Ranjeet K. A Review on Fruits Having Anti-diabetic Potential. J Chem Pharm Res. 2011;3:204–12.
48. Salehi B, Ata A, V Anil Kumar N, Sharopov F, Ramirez-Alarcon K, Ruiz-Ortega A, et al.; Atta-ur-Rahman. Antidiabetic Potential of Medicinal Plants and Their Active Components. Biomolecules. 2019 Sep;9(10):E551.
49. Bnouham M, Ziyyat A, Mekhfi H, Tahri A, Legssyer A. Medicinal Plants with Potential Anti-diabetic Activity - A Review of Ten Years of Herbal Medicine Research (1990-2000). Int J Diabetes Metab. 2006;14(1):1–25.
50. Sidhu MC, Sharma T. A Database of Antidiabetic Plant Species of Family Asteraceae, Euphorbiaceae, Fabaceae, Lamiaeae and Moraceae. Int J Herb Med. 2013;1(2):187–99.
51. Chauhan A, Sharma PK, Srivastava P, Kumar N, Dudhe R. Plants Having Potential Anti-diabetic Activity: A Review. Pharm Lett. 2010;2(3):369–87.
52. Pinto G, Coutinho J, Araujo C, Neves L, Santos C. Importance of Media Mineral Composition on the Induction of Somatic Embryogenesis in Eucalyptus globulus Labill. Boletin de CIDEU. 2007;3:83–90.
53. Vinagre AS, Rönnau AD, Pereira SF, da Silveira LU. Willd EdF, Suyenaga ES. Anti-diabetic effects of Campomanesia xanthocarpa (Berg) leaf decoction. Braz J Pharm Sci. 2010;46(2):169–77.
54. Biavatti MW, Farias C, Curtis F, Brasil LM, Hort S, Schuster L, et al. Preliminary studies on Campomanesia xanthocarpa (Berg.) and Cuphea carthaginesis (Jacq.) J.F. Macbr. aqueous extract: weight control and biochemical parameters. J Ethnopharmacol. 2004 Aug;93(2-3):385–9.
55. Sánchez-Salgado JC, Ortiz-Andrade RR, Aguirre-Crespo F, Vergara-Galicia J, León-Rivera I, Montes S, et al. Hypoglycemic, vasorelaxant and hepatoprotective effects of Cochlospermum vitifolium (Willd.) Sprengel: a potential agent for the treatment of metabolic syndrome. J Ethnopharmacol. 2007 Feb;109(3):400–5.
56. Cardozo CM, Inada AC, Marcelino G, Figueiredo PS, Arakaki DG, Hiane PA, et al. Therapeutic Potential of Brazilian Cerrado Campomanesia Species on Metabolic Dysfunctions. Molecules. 2018 Sep;23(9):2336.
57. Mai TT, Ishiwaki A, Nomiy H, Hop LT, Lam NT, Thuy NT, et al. Efficacy of an Aqueous Extract from Flower Buds of
Cleistocalyx Operculatus on Type 2 Diabetic Patients in Vietnam. J Home Econ Jpn. 2013;64(1):3–9.
58. Schumacher NS, Colomeu TC, de Figueiredo D, Carvalho VC, Cazarin CB, Prado MA, et al. Identification and Antioxidant Activity of the Extracts of Eugenia uniflora Leaves. Characterization of the Anti-Inflammatory Properties of Aqueous Extract on Diabetes Expression in an Experimental Model of Spontaneous Type 1 Diabetes (NOD Mice). Antioxidants (Basel). 2015 Oct;4(4):662–80.
59. Patra A, Jha S, Sahu AN. Antidiabetic activity of Aqueous Extract of Eucalyptus citriodora Hook. in Alloxan Induced Diabetic Rats. Pharmacogn Mag. 2009;5(19):51–4.
60. Bhatt M, Gahlot M, Juyal V, Singh A. Phytochemical Investigation and Antidiabetic Activity of Adhatoda zeylanica. Asian J Pharm Clin Res. 2011;4(2):27–30.
61. Rao NK. Anti-Hyperglycemic and Renal Protective Activities of Andrographis paniculata Roots Chloroform Extract. Iranian Journal of Pharmacology and Therapeutics. 2006;5(1):47–50.
62. Dheer R, Bhatnagar P. A study of the antidiabetic activity of Barleria prioritis Linn. Indian J Pharmcol. 2010 Apr;42(2):70–3.
63. Marathakam A, Kannappan N, Jasemine S, Santhiagu A, Sreejith M, Ajith MP. Studies on Phytochemical and In-vitro Antioxidant Potential of Justicia beddomei (Clarke) Bennett. Free Radic Antioxid. 2012;2(4):26–31.
64. Padee P, Nualkaew S, Talubmook C, Sakuljaitrong S. Hypoglycemic effect of a leaf extract of Pseuderanthemum palatiferum (Nees) Radlk. in normal and streptozotocin-induced diabetic rats. J Ethnopharmacol. 2010 Nov;132(2):491–6.
65. Visweswara Rao P, Madhavi K, Dhananjaya Naidu M, Gan SH. Rhinacanthus nasutus Improves the Levels of Liver Carbohydrate, Protein, Glycogen, and Liver Markers in Streptozotocin-Induced Diabetic Rats. Evid Based Complement Alternat Med. 2013;2013:102901.
66. Shahwar D, Ullaha S, Ahmad M, Ullah S, Ahmad N, Khan MA. Hypoglycemic Activity of Ruellia tuberosa Linn (Acanthaceae) in Normal and Alloxan-Induced Diabetic Rabbits. Iran J Pharm Sci. 2011;7(2):107–15.
67. Arirajat S, Wutteerapol S, Saenphet K. Anti-diabetic effect of Thunbergia laurifolia Linn. aqueous extract. Southeast Asian J Trop Med Public Health. 2004;35 Suppl 2:53–8.
68. Vidhya R, Gandhi GR, Jothi G, Radhika J, Brindha P. Evaluation of antidiabetic potential of Achyranthes aspera Linn on alloxan induced diabetic animals. Int J Pharm Pharm Sci. 2012;4(5):577–80.
69. Geetha G, Kalavalarasariel Gopinathapillai P, Sankar V. Anti diabetic effect of Achyranthes rubrofusca leaf extracts on alloxan induced diabetic rats. Pak J Pharm Sci. 2011 Apr;24(2):193–9.
70. Deshmukh TA, Yadav BV, Badole SL, Bodhankar SL, Dhaneshwar SR. Antihyperglycaemic Activity of Alcoholic Extract of Aerva lanata (L.) A. L. Juss. Ex J. A. Schultes Leaves in Alloxan Induced Diabetic Mice. J Appl Biomed. 2008;6:81–7.
71. Pandhare R, Balakrishnan S, Mohite P, Khanage S. Antidiabetic and Antihyperlipidaemic Potential of Amaranthus viridis (L.) Merr. in Streptozotocin Induced Diabetic Rats. Asian Pac J Trop Dis. 2012;2(1):S180–5.
72. Vetrichelvan T, Jegadeesan M, Devi BA. Anti-diabetic activity of alcoholic extract of Celosia argentea Linn. seeds in rats. Biol Pharm Bull. 2002 Apr;25(4):526–8.
73. Sokeng SD, Lomtis D, Moundipa PF, Jatsa HB, Watcho P, Kamthoucing P. Hypoglycemic Effect of Anacardium occidentale L. Methanol Extracts and Fractions on Streptozotocin-induced Diabetic Rats. Glob J Pharmacol. 2007;1(1):1–5.
74. Basha DP, Kumar KP, Teja BB, Subbarao M. Anti diabetic Activity on Extracts of Mangifera indica in Alloxan Monohydrate Induced Diabetic Rats. Drug Invent Today. 2011;3(7):165–8.
75. Ojewole JA. Hypoglycemic effect of Sclerocarya birrea [(A. Rich.) Hochst.] [Anacardiaceae] stem-bark aqueous extract in rats. Phytomedicine. 2003 Nov;10(8):675–81.
76. Arul B, Kothai R, Christina AJ. Hypoglycemic and anti hyperglycemic effect of Semecarpus anacardium Linn in normal and streptozotocin-induced diabetic rats. Methods Find Exp Clin Pharmacol. 2004 Dec;26(10):759–62.
77. Adediwura F, Kio A. Antidiabetic Activity of Spondias mombin Extract in NIDDM Rats. Pharm Biol. 2009;47(3):215–8.
78. Bandawane D, Juvekar AR, Juvekar M. Anti diabetic and Antihyperlipidaemic Effect of Alstonia scholaris Linn. Bark in Streptozotocin Induced Diabetic Rats. Indian J Pharm Educ. 2011;45(2):114–20.
79. Jayanthi M, Sowbala N, Rajalakshmi G, Kanagavalli U, Sivakumar V. Study of Antihyperglycaemic Effect of Catharanthus roseus in Alloxan Induced Diabetic Rats. Int J Pharm Sci Pharm. 2010;2 Suppl 4:114–6.
80. Shende VS, Sawant VA, Turuskar AO, Chatap VK, Vijaya C. Evaluation of Hypoglycaemic and Antihyperglycaemic Effects of Alcoholic Extract of Chonemorpha fragrans Root in Normal and Alloxan Induced Diabetic Rats. Pharmacogn Mag. 2009;5 Suppl 2:36–41.
81. Mana S, Singhal S, Sharma NK, Singh D. Hypoglycaemic Effect of Holarrhena antidysenterica Seeds on Streptozotocin Induced Diabetic Rats. Int J Pharm Tech Res. 2010;2(2):1325–9.
82. Adeney A, Adayemi OM. Hypoglycaemic Effects of Aqueous Seed Extract of Hunteria umbellata in Normoglycaemic and Glucose and Nicotine-induced Hyperglycaemic Rats. Int J Appl Res Nat Prod. 2009;2(1):9–18.
83. Barik R, Jain S, Qwatra D, Joshi A, Tripathi GS, Goyal A. Antidiabetic activity of aqueous root extract of Ichnocarpus frutescens in streptozotocin-nicotinamide induced type-II diabetes in rats. Indian J Pharmacol. 2008 Jan;40(1):19–22.
84. Azmi MB, Qureshi SA. Methanolic Root Extract of Rauwolfia serpentina Benth Improves the Glycemic, Antiatherogenic, and Cardioprotective Indices in Alloxan-Induced Diabetic Mice. Adv Pharmacol Sci. 2012;2012:376429.
85. Raj RA, Kumar S, Gandhimathi R. Hypoglycaemic and Hypolipidaemic Activity of Wrightia tinctoria L. in Alloxan Induced Diabetes in Albino Wistar Rats. Pharmacologyonline. 2009;3:550–9.
86. Rathod NR, Chitme HR, Irchhaiya R, Chandra R. Hypoglycaemic Effect of Calotropis gigantea Linn. Leaves and Flowers in Streptozotocin-Induced Diabetic Rats. Oman Med J. 2011 Mar;26(2):104–8.
87. Bhaskar VH, Ajay SS. Evaluation of Antihyperglycaemic Activity Of Extracts of Calotropis procera (Ait.) R. Br. on Streptozotocin Induced Diabetic Rats. Glob J Pharmacol. 2009;3(2):95–8.

88. Abdel-Sattar E, Harraz FM, Ghareib SA, Elberry AA, Gabr S, Suliman MF. Antihyperglycaemic and hypolipidaemic effects of the methanolic extract of Caralluma tuberculata in streptozotocin-induced diabetic rats. Nat Prod Res. 2011 Jul;25(12):1171–9.

89. Akah PA, Uzodinma SU, Okolo CE. Antidiabetic Activity of Aqueous and Methanol Extract and Fractions of Gongronema latifolium (Asclepiadaceae) leaves in alloxan induced diabetic rats. J Appl Pharm Sci. 2011;1(9):99–102.

90. Ananthan R, Baskar C, NarmathaBai V, Pari L, Latha M, Akah PA, Uzodinma SU, Okolo CE. Antidiabetic Activity of Gymnema sylvestre leaves: effect on lipid peroxidation induced oxidative stress in experimental diabetes. Pharmacol Res. 2003 Dec;48(6):551–6.

91. Mall GK, Mishra PK, Prakash V. Antidiabetic and Hypolipidaemic Activity of Gymnema sylvestre in Alloxan Induced Diabetic Rats. Global J Biotech & Biochem. 2009;4(1):37–42.

92. Mahalingam G, Kannabiran K. Hemidesmus indicus root Extract Ameliorates Diabetes-mediated Metabolic Changes in Rats. Int J Green Pharm. 2009;3(4):314–8.

93. Saba AB, Oyagbemi AA, Azeez OI. Antidiabetic and haematinc effects of Parquetina nigrescens on alloxan induced type-1 diabetes and normocytic normochromic anaemia in Wistar rats. Afr Health Sci. 2010. Sep;10(3):276–82.

94. Maruthupandian A, Mohan VR. Antidiabetic, Antihyperlipidaemic and Antioxidant Activity of Pterocarpus marsupium Roxb. in Alloxan Induced Diabetic Rats. Int J Pharm Tech Res. 2011;3(3):1681–7.

95. Agarwal V, Sharma AK, Upadhyay A, Singh G, Gupta R. Hypoglycemic effects of Citrullus colocynthis roots. Acta Pol Pharm. 2012 Jan-Feb;69(1):75–9.

96. Dhanabal SP, Koate CK, Ramanathan M, Elango K, Suresh B. The Hypoglycemic Activity of Coccinia indica Wight and Arn. and Its Influence on Certain Biochemical Parameters. Indian J Pharmacol. 2004;36(4):249–50.

97. Xia T, Wang Q. Antihyperglycemic effect of Cucurbita ficifolia fruit extract in streptozotocin-induced diabetic rats. Fitoterapia. 2006 Dec;77(7-8):530–3.

98. Sediqheh A, Jamal MS, Mahbubeh S, Somayeh K, Mahmoud R, Azadeh A, et al. Hypoglycaemic and Hypolipidaemic Effects of Pumpkin (Cucurbita pepo L.) on Alloxan-induced Diabetic Rats. Afr J Pharm Pharmacol. 2011;5(23):2620–6.

99. Saha P, Mazumder UK, Haldar PK, Sen SK, Naskar S. Antihyperglycaemic Activity of Lagerania siceraria Aerial Parts on Streptozotocin Induced Diabetes in Rats. Diabetol Croat. 2011;40(2):49–60.

100. Chaurasia S, Saxena RC, Chaurasia ID, Shrivastav R. Antidiabetic Activity of Luffa aegyptica (Mill.) in Alloxan Induced Diabetic Rats. J Chem Pharm Res. 2011;3(2):522–5.

101. Kannan VR, Mathan M, Rajesh P, Sumathi CS, Balasubramanian V, Ramesh N, et al. Phytochemical Screening and Anti-Diabetic Efficacy in Fruit Extracts of Momordica charantia L. by Using Alloxan Induced Wistar Albino Diabetic Rats. J Pharm Res Clin Pract. 2011;1(3):88–93.

102. Reddy GT, Kumar BR, Mohan GK. Antihyperglycaemic Activity of Momordica dioica Fruits in Alloxan-induced Diabetic Rats. Niger J Nat Prod Med. 2005;9:33–4.

103. Eseyin OA, Ebong P, Ekpo A, Igboasoiyi A, Oforah E. Hypoglycemic effect of the seed extract of Telfaria occidentalis in rat. Pak J Biol Sci. 2007 Feb;10(3):498–501.

104. Adiga S, Bairy KL, Meharban A, Punitha IS. Hypoglycemic effect of aqueous extract of Trichosanthes dioica in normal and diabetic rats. Int J Diabetes Dev Ctries. 2010 Jan;30(1):38–42.

105. Sabitha V, Ramachandran S, Naveen KR, Panneerselvam K. Antidiabetic and antihyperlipidemic potential of Abelmoschus esculentus (L.) Moench. in streptozotocin-induced diabetic rats. J Pharm Bioallied Sci. 2011 Jul;3(3):397–402.

106. Seetharam YN, Chalageri G, Setty SR, Bheemachar. Hypoglycemic activity of Abutilon indicum leaf extracts in rats. Fitoterapia. 2002 Apr;73(2):156–9.

107. Kumar TR, Udaykumar E, Sekar M, Kumar MK. Antidiabetic Activity of Methanolic Extract of Hibiscus cannabinus in Streptozotocin Induced Diabetic Rats. Int J Pharma Bio Sci. 2011;2(1):125–30.

108. Saravanand D, Lakshami IA, Gobinath M, Kumar BG, Priya S, Syamala E, et al. Potential Antioxidant, Hypoglycemic and Hypolipidaemic Effect of Leaves of Hibiscus platanifolius Linn. Int J Pharm Sci Drug Res. 2011;3(3):236–40.

109. Sankaran M, Vadivel A. Antioxidant and Antidiabetic Effect of Hibiscus rosasinensis Flower Extract on Streptozotocin Induced Experimental Rats - A Dose Response Study. Not Sci Biol. 2011;3(4):13–21.

110. Kumar S, Kumar V, Prakash O. Antidiabetic and Hypolipidaemic Activities of Hibiscus tiliaceus (L.) Flowers Extract in Streptozotocin Induced Diabetic Rats. Pharmacologyonline. 2010;2:1037–44.

111. De D, Chatterjee K, Ali KM, Mandal S, Barik B, Ghosh D. Antidiabetic and Antioxidative Effects of Hydro-methanolic Extract of Sepals of Salmalia malabarica in Streptozotocin-induced Diabetic Rats. J Appl Biomed. 2010;8:23–33.

112. Dhalwal K, Shinde VM, Singh B, Mahadik KR. Hypoglycaemic and Hypolipidaemic Effect of Sida rhombifolia ssp. retusa in Diabetic Induced Animals. Int J Phytomed. 2010;2:160–5.

113. Parthasarathy R, Illavarasan R, Karrunakaran CM. Antidiabetic Activity of Thespesia populnea Bark and Leaf Extract Against Streptozotocin Induced Diabetic Rats. Int J Pharm Tech Res. 2009;1(4):1069–72.

114. Bisht S, Sisodia SS. Anti-hyperglycemic and Antidyslipidemic Potential of Azadirachta indica Leaf Extract in STZ-induced Diabetes Mellitus. J Pharm Sci & Res. 2010;2(10):622–7.

115. Susheela T, Balaravi P, Theophilus J, Reddy TN, Reddy PU. Evaluation of Hypoglycaemic and Antidiabetic Effect of Melia dubia CAV Fruits in Mice. Curr Sci. 2008;94(9):1191–5.

116. Georgewill UO, Georgewill OA. Effect of Extract of Pseudocedrela kotschyi on Blood Glucose Concentration of Alloxan Induced Diabetic Albino Rats. East J Med. 2009;14:17–9.
117. Maiti A, Dewanjee S, Jana G, Mandal S. Hypoglycaemic effect of Swietenia macrophylla seeds against type II diabetes. Int J Green Pharm. 2008;2(4):224–7.

118. Panda SP, Haldar PK, Bera S, Adhikary S, Kandar CC. Antidiabetic and antioxidant activity of Swietenia mahagomi in streptozotocin-induced diabetic rats. Pharm Biol. 2010 Sep;48(9):974–9.

119. Sangameswaran B, Jayakar B. Antidiabetic and Spermatogenic Activity of Cocculus hirsutus (L.) Diels. Afr J Biotechnol. 2007;6(10):1212–6.

120. Godwin M, Olufunmilayo A, Abraham O, Crescie N, Abayomi O. The Effect of Aqueous Root Extract of Sphe- nocentrum jollyanum on Blood Glucose Level of Rabbits. J Med Plants Res. 2009;3(11):870–4.

121. Sharma U, Sahu R, Roy A, Golwala D. Anti-hyperglycaemic potential of Psidium guajava raw fruit peel. Indian J Pharm. 2011 Dec;3(1):235–40.

122. Rajalakshmi M, Eliza J, Priya CE, Nirmala A, Daisy P. Antidiabetic Properties of Tinospora cordifolia Stem Extracts on Streptozotocin-induced Diabetic Rats. Afr J Pharm Pharmacol. 2009;3(5):171–80.

123. Mai TT, Chuyen NV. Anti-hyperglycaemic activity of an aqueous extract from flower buds of Cleistocalyx operculatus (Roxb.) Merr and Perry. Biosci Biotechnol Biochem. 2007 Jan;71(1):69–76.

124. Ismail SM. The Effect of Aqueous Extract of the Leaves of Eucalyptus globulus on the Blood Glucose Level in Fasted Rats. Iranian Journal of Pharmacology and Therapeutics. 2007;6(2):239–40.

125. Jelastin KS, Tresina PS, Mohan VR. Antioxidant, antihyperlipidaemic and antidiabetic activity of eugenia floccosa bedd leaves in alloxan induced diabetic rats. J Basic Clin Pharm. 2011 Dec;3(1):235–40.

126. Rai PK, Jaiswal D, Mehta S, Watal G. Antidiabetic Effect of Aqueous Extract in Euglycaemic and Hyperglycaemic Rats. Pharmaceutics. 2007;6(2):239–40.

127. Ahmad B, Baider C, Bernardini B, Biffin E, Brambach F, Burslem D, et al. Syzygium (Myrtaceae): Monographing A Taxonomic Giant Via 22 Coordinated Regional Revisions. PeerJ Preprints. 2016;4:e1930v1.

128. Stephen Irudayaraj S, Sunil C, Duraiapandiyan V, Ignacimuthu S. Antidiabetic and antioxidant activities of Tod-dalba asiatica (L.) Lam. leaves in streptozotocin induced diabetic rats. J Ethnopharmacol. 2012 Sep;143(2):515–23.

129. Syzygium [Internet]. cited 30 Nov 2019. Available from: https://www.revolve.com/page/Syzygium

130. Lawal HA, Atiku MK, Khelpai DW, Wannang NN. Hypoglycaemic and hypolipidaemic effect of aqueous leaf extract of Murraya koenigii in normal and alloxan-diabetic rats. Niger J Physiol Sci. 2008 Jun-Dec;23(1-2):37–40.

131. Kundu S, Roy A, Mazumder UK, Saha P, Bala A, et al. Evaluation of Antihyperglycaemic Activity of Citrus limetta Fruit Peel in Streptozotocin-Induced Diabetic Rats. ISRN Endocrinol. 2011;2011:869273.

132. Kundu S, Gupta M, Mazumder UK, Halder PK, Saha P, Bhattacharya S, et al. Antihyperglycaemic Effect and Antioxidant Property of Citrus maxima Leaf in Streptozotocin-induced Diabetic Rats. Diabetol Croat. 2011;40(4):113–20.

133. Joshi RK, Patil PA, Mujawar MH, Kumar D, Khoklate SD. Hypoglycemic Activity of Bambusa arundinacea Leaf Aqueous Extract in Euglycaemic and Hyperglycaemic Wistar Rats. Pharmacologyonline. 2009;3:789–95.

134. Kumar MS, Kumar PS, Changanakkattil F, Rajesh V, Perumal P. Evaluation of Antidiabetic Activity of Bambusa vulgaris Leaves in Streptozotocin Induced Diabetic Rats. Int J Pharm Sci Drug Res. 2011;3(3):208–10.

135. Kumar AS, Gnananath K, Kiran D, Reddy AM, Ch R. Antidiabetic Activity of Ethanolic Extract of Cynodon dac-tylon Root Stalks in Streptozotocin Induced Diabetic Rats. Int J Adv Pharm Res. 2011;2(8):418–22.
Hepatic XBP-1s/PDI/MTP Axis in Monosodium L-Glutamate-Induced Obese Rats. Oxid Med Cell Longev. 2019 Mar;2019:417498.

150. Chagas VT, França LM, Malik S, Paes AM. Syzygium cumini (L.) Skeels: a prominent source of bioactive molecules against cardiometabolic diseases. Front Pharmacol. 2015 Nov;6:259.

151. Gowri SS, Vasantha K. Phytochemical Screening and Antibacterial Activity of Syzygium cumini (L.) (Myrtaceae) Leaves Extracts. Int J Pharm Tech Res. 2010;2(2):1569–73.

152. Gaspar RS, da Silva SA, Stapleton J, Fontelles JL, Sousa HR, Chagas VT, et al. Myricetin, the Main Flavonoid in Syzygium cumini Leaf, Is a Novel Inhibitor of Platelet Thiol Isomerases PDI and ERp5. Front Pharmacol. 2020 Jan;10:1678.

153. Shinde J, Taldone T, Barletta M, Kunaparaju N, Hu B, Kumar S, et al. α-glucosidase inhibitory activity of Syzygium cumini (Linn.) Skeels seed kernel in vitro and in Goto-Kakizaki (GK) rats. Carbohydr Res. 2008 May;343(7):1278–81.

154. Teixeira CC, Pinto LP, Kessler FH, Knijnik L, Pinto CP, Gastaldo GJ, et al. The effect of Syzygium cumini (L.) skeels on post-prandial blood glucose levels in non-diabetic rats and rats with streptozotocin-induced diabetes mellitus. J Ethnopharmacol. 1997 May;56(3):209–13.

155. Oliveira AC, Endringer DC, Amorim LA, das Graças L Brandão M, Coelho MM. Effect of the extracts and fractions of Baccharis trimera and Syzygium cumini on glycemia of diabetic and non-diabetic mice. J Ethnopharmacol. 2005 Dec;102(3):465–9.

156. Proma NM, Naima J, Islam MR, Papel JA, Rahman MM, Hossam MK. Phytochemical Constituents and Antidiabetic Properties of Syzygium cumini Linn. Seed. Int J Pharm Sci Res. 2018;9(5):1806–14.

157. Baliga MS, Fernandes S, Thilakechand KR, D’ soupa R, Rao S. Scientific validation of the antidiabetic effects of Syzygium cumulianum DC (black plum), a traditional medicinal plant of India. J Altern Complement Med. 2013 Mar;19(3):191–7.

158. Sharma SB, Nasir A, Prabhu KM, Murthy PS, Dev G. Hypoglycaemic and hypolipidemic effect of ethanolic extract of seeds of Eugenia jambolana seed on streptozotocin induced diabetic rats and rats with streptozotocin-induced diabetes mellitus. J Ethnopharmacol. 2003 Apr;85(2-3):201–6.

159. Ravi K, Sekar DS, Subramanian S. Hypoglycemic activity of inorganic constituents in Eugenia jambolana seed on streptozotocin-induced diabetes in rats. Biol Trace Elem Res. 2004;99(1-3):145–55.

160. Ravi K, Sivagnanam K, Subramanian S. Anti-diabetic activity of Eugenia jambolana seed kernels on streptozotocin-induced diabetic rats. J Med Food. 2004;7(2):187–91.

161. Ravi K, Ramachandran B, Subramanian S. Effect of Eugenia Jambolana seed kernel on antioxidant defense system in streptozotocin-induced diabetes in rats. Life Sci. 2004 Oct;75(22):2717–31.

162. Ravi K, Rajasekaran S, Subramanian S. Antihyperlipidemic effect of Eugenia jambolana seed kernel on streptozotocin-induced diabetes in rats. Food Chem Toxicol. 2005 Sep;43(9):1433–9.

163. Rath SS, Grover JK, Vikrant V, Biswas NR. Prevention of experimental diabetic cataract by Indian Ayurvedic plant extracts. Phytother Res. 2002 Dec;16(8):774–7.

164. Sridhar SB, Sheetal UD, Pai MR, Shastri MS. Preclinical evaluation of the antidiabetic effect of Eugenia jambolana seed powder in streptozotocin-diabetic rats. Braz J Med Biol Res. 2005 Mar;38(3):463–8.

165. Sharma B, Balomajumder C, Roy P. Hypoglycemic and hypolipidemic effects of flavonoid rich extract from Eugenia jambolana seeds on streptozotocin induced diabetic rats. Food Chem Toxicol. 2008 Jul;46(7):2376–83.

166. Sharma B, Viswanath G, Salunke R, Roy P. Effects of Flavonoid-Rich Extract from Seeds of Eugenia jambolana (L.) on Carbohydrate and Lipid Metabolism in Diabetic Mice. Food Chem. 2008;110(3):697–705.

167. Sharma SB, Rajpoot R, Nasir A, Prabhu KM, Murthy PS. Ameliorative effect of Active Principle Isolated from Seeds of Eugenia jambolana on Carbohydrate Metabolism in Experimental Diabetes. Evid Based Complement Alternat Med. 2011;2011:789871.

168. Grover JK, Rathi SS, Vats V. Amelioration of experimental diabetic neuropathy and gastropathy in rats following oral administration of plant (Eugenia jambolana, Mucuna pruriens and Tinospora cordifolia) extracts. Indian J Exp Biol. 2002 Mar;40(3):273–6.

169. Chaturvedi A, Bhawani G, Agarwal PK, Goel S, Singh A, Goel RK. Antidiabetic and antinocer effects of extract of Eugenia jambolana seed in mild diabetic rats: study on gastric mucosal oxidative acid-pepsin secretion. Indian J Physiol Pharmacol. 2009 Apr-Jun;53(2):137–46.

170. Sanches JR, França LM, Chagas VT, Gaspar RS, Dos Santos KA, Gonçalves LM, et al. Polyphenol-Rich Extract of Syzygium cumini Leaf Dually Improves Peripheral Insulin Sensitivity and Pancreatic Islet Function in Monosodium L-Glutamate-Induced Obese Rats. Front Pharmacol. 2016 Mar;7:48.

171. Chagas VT, Coelho RM, Gaspar RS, da Silva SA, Mastrogiavanni M, Mendonça CJ, et al. Protective Effects of a Polyphenol-Rich Extract from Syzygium cumini (L.) Skeels Leaf on Oxidative Stress-Induced Diabetic Rats. Oxid Med Cell Longev. 2018 Jun;2018:5386079.

172. Srivastava Y, Venkatakrishna-Bhatt H, Gupta OP, Gupta PS. Hypoglycemia Induced by Syzygium cumini Linn. Seeds in Diabetes Mellitus. Asian Med J. 1983;26(7):489–91.

173. Kohli KR, Singh RH. A Clinical Trial of Jambu (Eugenia jambolana) in Non-Insulin Dependent Diabetes Mellitus. J Res Ayur Siddha. 1993;14(3/4):89–97.

174. Sahana DA, Shivaparakash G, Baliga A, Prabha A, Ganesh J, Pai MR. Effect of Eugenia jambolana on Plasma Glucose, Insulin Sensitivity and HDL-C Levels: Preliminary Results of a Randomized Clinical Trial. J Pharm Res. 2010;3(6):1268–70.

175. Silva SDn, Abreu IC, Silva GFC, Ribeiro RM, Lopes AdS, Cartágene MdSSds, et al. The Toxicity Evaluation of Syzygium cumini Leaves in Rodents. Rev Bras Farmacogn. 2012;22(1):102–8.

176. Bandiola TM, Ignacio1 GB, Yunson EGA, Bandiola PDB. Syzygium cumini (L.) Skeels: A Review of Its Phytochemical Constituents, Toxicity Studies, and Traditional and Pharmacological Uses. Int J App Pharm Bio Res. 2017;2(6):15–23.
Zulcafli et al.: Antidiabetic potential of Syzygium sp.

177. Widyawati T, Purnawan WW, Atangwho JJ, Yusoff NA, Ahmad M, Asmaiwi MZ. Anti-diabetic Activity of Syzygium polyanthum (Wight) Leaf Extract, the Most Commonly Used Herb Among Diabetic Patients in Medan, North Sumatera, Indonesia. Int J Pharm Sci Res. 2015;6(4):1698–704.

178. Kato E, Nakagomi R, Gunawan-Puteri MD, Kawabata J. Identification of hydroxychavicol and its dimers, the lipase inhibitors contained in the Indonesian spice, Eugenia polyantha. Food Chem. 2013 Feb;136(3-4):1239–42.

179. Lelono RA, Tachibana S, Itoh K. In vitro antioxidative activities and polyphenol content of Eugenia polyantha Wight grown in Indonesia. Pak J Biol Sci. 2009 Dec;12(24):1564–70.

180. Sumono A, Agustin Wulan SD. The Use of Bay Leaf (Eugenia polyantha Wight) in Dentistry. J Dent. 2008;41(3):147–50.

181. Sufi S, Premcharoen S, Thawatphan C, Sangthongprow S. Ethnobotany in Bung Khong Long Non-Hunting Area, Northeast Thailand. Kasetsart J. 2005;39:519–33.

182. Ismail A, Mohamed M, Sulaiman SA, Wan Ahmad WA. Autonomic Nervous System Mediates the Hypotensive Effects of Aqueous and Residual Methanolic Extracts of Syzygium polyanthum (Wight) Walp. var. polyanthum Leaves in Anaesthetized Rats. Evid Based Complement Altern Med. 2011;2011:716532.

183. Wong SP, Leong LP, Koh JH. Antioxidant Activities of Syzygium polyanthum (Wight) Leaf Extract Mixture of Eugenia polyantha and Zingiber purpurea. J Acupunct Zingiber Life. 2007 Oct;27(2):28–33.

184. Kandaker MM, Boyce AN. Growth, Distribution and Physiochemical Properties of Wax Apple (Syzygium samarangense) A Review. Aust J Crop Sci. 2016;10(12):1640–8.

185. Dykhuizen DE. The Quarterly Review of Biology. Chicago: University of Chicago Press; 1989. pp. 349–50.

186. Resurreccion-Magno MH, Villaseñor IM, Harada N, Monde K. Antihyperglycaemic flavonoids from Syzygium samarangense (Blume) Merr. and Perry. Phytother Res. 2005 Mar;19(3):246–51.
207. Najafian M, Jahromi MZ, Nowroznajehad MJ, Khajeaian P, Kargar MM, Sadeghi M, et al. Phloridzin reduces blood glucose levels and improves lipids metabolism in streptozotocin-induced diabetic rats. Mol Biol Rep. 2012 May;39(5):5299–306.

208. Hassan M, El Yazidi C, Landrier JF, Lairon D, Margotat A, Amiot MJ. Phloretin enhances adipocyte differentiation and adiponectin expression in 3T3-L1 cells. Biochem Biophys Res Commun. 2007 Sep;361(1):208–13.

209. Manahan T, Chakravarti S, Radhakrishnan AK, Palanisamy UD. In vivo toxicity evaluation of a standardized extract of Syzygium aqueum leaf. Toxicol Rep. 2014 Sep;1:718–25.

210. George A, Augustine R, Sebastian M. Diabetes Mellitus. 2016;22:325–36.

211. Syzygium aromaticum (L.) Merr. & L.M.Perry. [Internet]. cited 30 Nov 2019. Available from: http://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:6014421-1

212. Adefegha SA, Oboh G. In vitro inhibition activity of polyphenol-rich extracts from Syzygium aromaticum (L.) Merr. & Perry (Clove) buds against carbohydrate hydrolyzing enzymes linked to type 2 diabetes and Fe(II)-induced lipid peroxidation in rat pancreas. Asian Pac J Trop Biomed. 2012 Oct;2(10):774–81.

213. Unger RH. Lipotoxic diseases. Annu Rev Med. 2002;53(1):319–36.

214. Kuroda M, Mimaki Y, Ohtomo T, Yamada J, Nishiyama K. Unger RH. Lipotoxic diseases. Annu Rev Med. 2002;53(1):319–36.

215. Ngubane PS, Masola B, Musabayane CT. The effects of Syzygium aromaticum-derived oleanolic acid on glycogenic enzymes in streptozotocin-induced diabetic rats. Ren Fail. 2011;33(4):434–9.

216. Khathi A, Serumula MR, Myburg RB, Van Heerden FR, Musabayane CT. Effects of Syzygium aromaticum-derived triterpenes on postprandial blood glucose in streptozotocin-induced diabetic rats following carbohydrate challenge. PLoS One. 2013 Nov;8(11):e81632.

217. Tahir HU, Sarfraz RA, Ashraf A, Adil S. Chemical Composition and Antidiabetic Activity of Essential Oils Obtained from Two Spices (Syzygium aromaticum and Cuminum cyminum). Int J Food Prop. 2015;19(10):2156–64.

218. Prasad RC, Herzog B, Boone B, Sims L, Wultur-Law M. An extract of Syzygium aromaticum represses genes encoding hepatic gluconeogenic enzymes. J Ethnopharmacol. 2005 Jan;96(1-2):295–301.

219. Vijayasteltar L, Nair GG, Maliakel B, Kuttan R, et al. Safety assessment of a standardized polyphenolic extract of clove buds: subchronic toxicity and mutagenicity studies. Toxicol Rep. 2016 Apr;3:439–49.

220. Tajuddin AS, Ahmad S, Latif A, Qasmi IA. Aphrodisiac activity of 50% ethanolic extract of Myristica fragrans Houtt. (nutmeg) and Syzygium aromaticum (L) Merr. & Perry (clove) in male mice: a comparative study. BMC Complement Altern Med. 2003 Oct;3:6.

221. Agbaje EO, Adeneye AA, Daramola AO. Biochemical and toxicological studies of aqueous extract of Syzygium aromaticum (L.) Merr. & Perry (Myrtaceae) in rodents. Afr J Tradit Complement Altern Med. 2009 May;6(3):241–54.

222. Syzygium malaccense (Malay apple) [Internet]. cited 30 Nov 2019. Available from: https://www.cabi.org/isc/datasheet/52448/#tosummeryOfInvasive

223. Syzygium malaccense [Internet]. cited 30 Nov 2019. Available from: http://old.worldagroforestry.org/treebd/ AFTPDFS/Syzygium_malaccense.PDF

224. Arumugam B, Manaharan T, Heng CK, Kuppusamy UR, Palanisamy UD. Antioxidant and Antiglycemic Potentials of a Standardized Extract of Syzygium malaccense. Lebenswiss Technol. 2014;59(2):707–12.

225. Arumugam B, Palanisamy UD, Chua KH, Kuppusamy UR. Potential Antihyperglycaemic Effect of Myricetin Derivatives from Syzygium malaccense. J Funct Foods. 2016;22:325–36.

226. Bairy KL, Sharma A, Shalini A. Evaluation of the Hypoglycemic, Hypolipidemic and Hepatic Glycogen Raising Effects of Syzygium malaccense Upon Streptozotocin Induced Diabetic Rats. J Nat Rem. 2005;5(1):46–51.

227. Adebayo AH, Ogundare OC, Adegbite OS. Sub-acute Evaluation of Extract of Syzygium malaccense in Albino Rats. Res J Med Plant. 2015;9(2):60–71.

228. Rao BK, Rao CH. Hypoglycemic and antihyperglycemic activity of Syzygium alternifolium (Wt.) Walp. seed extracts in normal and diabetic rats. Phytomedicine. 2001 Mar;8(2):88–93.

229. Vedavathy S, Sudhakar A, Mrdula V. Tribal medicinal plants of chittoor. Anc Sci Life. 1997 Apr;16(4):307–31.

230. Vedavathy S. Studies on Medicinal Plant of Tirumala and Tirupathi, Chittoor District of Andhra Pradesh. S.V. University, Tirupati: Ph.D. Thesis; 1992.

231. Kasetti RB, Rajasekhar MD, Kondeti VK, Fatima SS, Kumar EG, Swapna S, et al. Antihyperglycemic and antihyperlipidemic activities of methanol:water (4:1) fraction isolated from aqueous extract of Syzygium alternifolium seeds in streptozotocin induced diabetic rats. Food Chem Toxicol. 2010 Apr;48(4):1078–84.

232. Kasetti RB, Nabi SA, Swapna S, Apparao C. Cinnamic acid as one of the antidiabetic active principle(s) from the seeds of Syzygium alternifolium. Food Chem Toxicol. 2012 May;50(5):1425–31.

233. Davies GJ, Bloxster TM, Henriass B. Recent structural insights into the expanding world of carbohydrate-active enzymes. Curr Opin Struct Biol. 2008 Dec;18(5):637–45.

234. Vucadlo DJ, Davies GJ. Mechanistic insights into glycosidase chemistry. Curr Opin Chem Biol. 2008 Oct;12(5):539–55.

235. Yang CY, Yen YY, Hung KC, Hsu SW, Lan SJ, Lin HC. Inhibitory effects of pu-erh tea on alpha glucosidase and alpha amylase: a systemic review. Nutr Diabetes. 2019 Aug;9(1):23.

236. Opie LH, Yellon DM, Gersh BJ. Controversies in the cardiovascular management of type 2 diabetes. Heart. 2011 Jan;97(1):6–14.
238. Sharma AK, Bharti S, Kumar R, Krishnamurthy B, Bhatia J, Kumari S, et al. Syzygium cumini ameliorates insulin resistance and β-cell dysfunction via modulation of PPAR, dyslipidemia, oxidative stress, and TNF-α in type 2 diabetic rats. J Pharmacol Sci. 2012;119(3):205–13.

239. Shen SC, Chang WC, Chang CL. Fraction from wax apple [Syzygium samarangense (Blume) Merrill and Perry] fruit extract ameliorates insulin resistance via modulating insulin signaling and inflammation pathway in tumor necrosis factor α-treated FL83B mouse hepatocytes. Int J Mol Sci. 2012;13(7):8562–77.

240. Huang DW, Chang WC, Wu JS, Shih RW, Shen SC. Vescalagin from Pink Wax Apple [Syzygium samarangense (Blume) Merrill and Perry] Alleviates Hepatic Insulin Resistance and Ameliorates Glycemic Metabolism Abnormality in Rats Fed a High-Fructose Diet. J Agric Food Chem. 2016 Feb;64(5):1122–9.

241. Widyawati T, Yusoff NA, Asmawi MZ, Ahmad M. Antihyperglycemic Effect of Methanol Extract of Syzygium polyanthum (Wight.) Leaf in Streptozotocin-Induced Diabetic Rats. Nutrients. 2015 Sep;7(9):7764–80.

242. Fatmawati, Panserga EG, Saleh MI. The Efficacy of Combination Extract Andrographis paniculata and Syzygium polyanthum on Glucose Uptake in Skeletal Muscle in Diabetic Rats. Bio Sci Med. 2018;2(4):39–46.

243. Anandharajan R, Jaiganesh S, Shankernarayanan NP, Viswakarma RA, Balakrishnan A. In vitro glucose uptake activity of Aegles marmelos and Syzygium cumini by activation of Glut-4, PI3 kinase and PPARγ in L6 myotubes. Phytotherapy. 2006 Jun;13(6):434–41.

244. Saravanan G, Pari L. Hypoglycaemic and Antihyperglycaemic Effect of Syzygium cumini Bark in Streptozotocin-induced Diabetic Rats. J Pharmacol Toxicol. 2008;3:1–10.

245. Khamchan A, Paseephol T, Hanchang W. Protective effect of wax apple (Syzygium samarangense (Blume) Merr. & L.M. Perry) against streptozotocin-induced pancreatic β-cell damage in diabetic rats. Biomed Pharmacother. 2018 Dec;108:634–45.

246. Krishnasamy G, Muthusamy K, Chellappan DR, Subbiah N. Antidiabetic, antihyperlipidaemic, and antioxidant activity of Syzygium densiflorum fruits in streptozotocin and nicotinamide-induced diabetic rats. Pharm Biol. 2016 Sep;54(9):1716–26.

247. Chandran R, George BP, Abrahamse H, Parimalazhagan T. Therapeutic effects of Syzygium munda gam bark methanol extract on type-2 diabetic complications in rats. Biomed Pharmacother. 2017 Nov;95:167–74.

248. Konda PY, Dasari S, Konanki S, Nagarajan P. In vivo antihyperglycemic, antihyperlipidemic, antioxidative stress and antioxidant potential activities of Syzygium paniculatum Gaertn. in Streptozotocin-induced diabetic rats. Heliyon. 2019 Mar;5(3):e01373.

249. Sathyanarayanan S, Chandran R, Thakkaraj S, Abrahamse H, Thangaraj P. Phytochemical composition, antioxidant and anti-bacterial activity of Syzygium calophyllifolium Walp. fruit. J Food Sci Technol. 2018 Jan;55(1):341–50.