Indonesian Journal of Pharmacy

VOL 34 (4) 2023: 519–540 | REVIEW ARTICLE

Revealing the Contribution of Phytochemicals in *Syzygium Cumini* As-Antidiabetics: A Systematic Review

Endra Pujiastuti[1,2], Agung Endro Nugroho[3], Khoirun Nisa[4] and Triana Hertiani[5*]

1. Doctoral Program of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281
2. Department of Pharmacy, Institut Teknologi Kesehatan Cendekia Utama Kudus, Jawa Tengah, Indonesia, 59381
3. Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Indonesia, 55281
4. Research Centre for Food Technology and Processing, The National Research and Innovation Agency, Yogyakarta, 55861
5. Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281

Article Info

Submitted: 27-01-2023
Revised: 12-07-2023
Accepted: 25-07-2023

*Corresponding author
Triana Hertiani

Email:
hertiani@ugm.ac.id

ABSTRACT

Diabetes mellitus (DM) is an endocrine system and metabolic disorder caused by defects in insulin secretion and action. *Syzygium cumini* (L.) Skeels (Myrtaceae) are often used in anti-diabetic medicine due to their high polyphenol contents. This study aims to provide a comprehensive review of the role of phytochemical compounds in *S cumini* as traditional antidiabetic medicinal plants. The review covers related articles on antidiabetic AND *S cumini* AND phytochemicals OR bioactive compounds. The examined articles were published from 2001 to January 2023. Pubmed, Science Direct, Scopus, and Google Scholar were utilized as the bibliographic databases in this systematic search. The inclusion criteria include articles written in English that describe experimental research, clinical trials, and randomized studies and articles containing phytochemical content profiling. The exclusion criteria were other types of reports such as literature reviews, conference articles, theses, dissertations, and cases that were irrelevant to the topic. The reporting item guidelines used for references in this review were the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Center for Systematic Reviews for Laboratory Animal Experiments (SYRCLE) risk of bias (RoB) tool. By the systematic compensation used, 15 articles that meet the requirements were obtained and were further reviewed thoroughly. Seeds, leaves, and bark of plant parts were reported to be non-toxic in acute experiments on mice or rats. *S. cumini* contains flavonol glycosides, especially myricetin, myricitrin, quercetin, and kaempferol; phenolics, such as ellagic acid, tannins, and gallic acid; alkaloids; and saponins. These compounds contributions to the overall anti-diabetic activity were discussed by covering an increase of insulin sensitivity, secretion, and usage of glucose in tissues; thereby reducing insulin resistance, oxidative stress, gluconeogenesis, and absorption of carbohydrates and sucrose. In conclusion, the review confirmed that the compounds of *S. cumini* have a potential for treating diabetes mellitus. Specifically, the seeds and leaves of *S. cumini* have a high potential as anti-diabetic herbal product, and thus making it crucial to find the research gap to support the development of this herbal compound by establishing preclinical and clinical trials and reliable analytical methods for phytochemical profiling.

Keywords: *Syzygium cumini,* Phytochemical, Diabetes Mellitus, Flavonoid, Phenolics

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic condition characterized by elevated blood sugar levels and impaired protein, lipid, and carbohydrate metabolism. Acute consequences from DM can include hyperosmolar hyperglycemia syndrome and diabetic ketoacidosis, while chronic cases may result in issues with the microvascular, macrovascular, and neuropathic systems (Wells *et al*., 2015). An increase in diabetes mellitus type 2 incidence generally occurs at the age of 60 years (IDF, 2021). Inappropriate control in DM may increase the risk of bacterial and fungal skin infections (Moini, *et al*., 2022), including diabetic retinopathy, nephropathy and neuropathy, which are complications of diabetes due to the microvascular lesion. High blood glucose levels increase the work on the kidneys, leading to nephropathy. Additionally, it harms the cardiovascular system, resulting in an increase in heart disease and stroke (Zheng *et al*., 2021). The level of blood glucose can be maintained with the help of oral anti-diabetic medications such sulfonylureas, biguanides, glitazones, meglitinides, glucosidase inhibitors, and thiazolidinediones. However, issues with the side effects like hypoglycemia, decreased appetite, tingling in the hands and feet, gastrointestinal issues, weariness, joint discomfort, and eye irritation have become increasingly worrisome (Tara *et al*., 2017). Considering that the medical treatment in most cases are for lifetime, anti-diabetic drugs not only should be effective but also should be safe fora long term use, easy to use, and available in rural areas. For this reason, it is necessary to develop a complementary medicine derived from natural ingredients for effective and safe medication (Yessoufou *et al*., 2013). Most of local people use *S. cumini* (L.) Skeels (Myrtaceae) to treat DM by utilizing its seeds or leaves to increase glucose uptake by L-6 cells *in vitro* (Narmatha & Maneemegalai, 2019).

*S. jambolan*a DC., *S. jambolanum* (Lam) DC., *Eugenia jambolana* Lam., *E. djouan*t Perr., and *E. cumi*ni (Linn) Druce are synonyms for *Syzygium cumini* (L). Lam's *E. caryophyllifo*lia. The Mytaceae family includes *Myrtus cumin*i Linn and *Calyptranthes jambolan*a Willd. According to (Stephen, 2012), *S. cumini* is also known as jambolana, black plum, jamun, Javanese plum, and Indian blackberry. The fruit, seeds, leaves, and bark of *S. cumini* are commonly used in Ayurvedic and Unani treatment. This plant contains numerous active phytochemicals, including phenolics, flavonoids, anthocyanins, carotenoids, essential oils, terpenes, and tannins, are present in this plant component (Mandal *et al*., 2023). *S. cumini* is an evergreen tree, which is easi to grow and is rich in polyphenols as compounds that contribute to the antidiabetic activity of most herbal products (Chagas *et al*., 2018). As a conclusion, the review confirmed that the compounds of *S. cumini* have a potential for serving as anti-diabetic mellitus, since the seeds and leaves of *S. cumini*, particularly have a high potential to serve as anti-diabetic herbal products. This review, thus has highlighted a research gap to support the development of this herbal compound by establishing preclinical and clinical trials and reliable analytical methods for phytochemical profiling.

MATERIALS AND METHODS

Study protocol

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria were used to perform this systematic review (Page *et al*., 2021).

Search strategy

This systematic review referred to all related articles published from 2001 to January 2023 by way of systematically searching from the Pubmed, Science Direct, Scopus, and Google Scholar databases. The Pubmed database search used Medical Subject Headings (MeSH) (Table I).

Inclusion criteria

The inclusion criteria used in the study were experimental research or clinical trials, and randomized studies. The articles used in this study are those written in English, and discuss the bioactive compounds from *S. cumini* for treating antidiabetic mellitus. The search was conducted by way of scanning in the title and abstract of the articles and then filtering it according to inclusion, exclusion, and eligibility criteria. The relevance of each article was determined by reading each article in full each article. All articles used were retrieved through the Mendeley Reference Manager.

Exclusion criteria

This systematic review met the following exclusion criteria: literature review, conference articles, theses, dissertations, and cases, and reports irrelevant to the topic.

Table I. Search strategy in the database

Database	Keyword
PubMed (MeSH)	(antidiabetes mellitus[Title/Abstract] OR antidiabetic[Title/Abstract] OR Hyperglycemic[Title/Abstract] AND (2012:2023[pdat])) AND (*Syzygium cumini*[Title/Abstract] OR *Syzygium jambolanum*[Title/Abstract] OR *Syzygium jambos*[Title/Abstract] OR *Eugenia cumini*[Title/Abstract] OR *Eugenia jambolana*[Title/Abstract] OR *Eugenia jambos*[Title/Abstract]
Science direct	(((antidiabetic OR Hyperglycemic) AND (*Syzygium cumini* OR *Syzygium jambos* OR *Eugenia cumini* OR *Eugenia jambolana* OR *Eugenia jambos*) AND (phytochemical constituents OR bioactive)))
Scopus	(((antidiabetic OR Hyperglycemic) AND (*Syzygium cumini* OR *Syzygium jambos* OR *Eugenia cumini* OR *Eugenia jambolana* OR *Eugenia jambos*) AND (phytochemical constituents OR bioactive)))
google scholar	antidiabetic AND Syzygium cumini AND phytochemical constituents OR bioactive

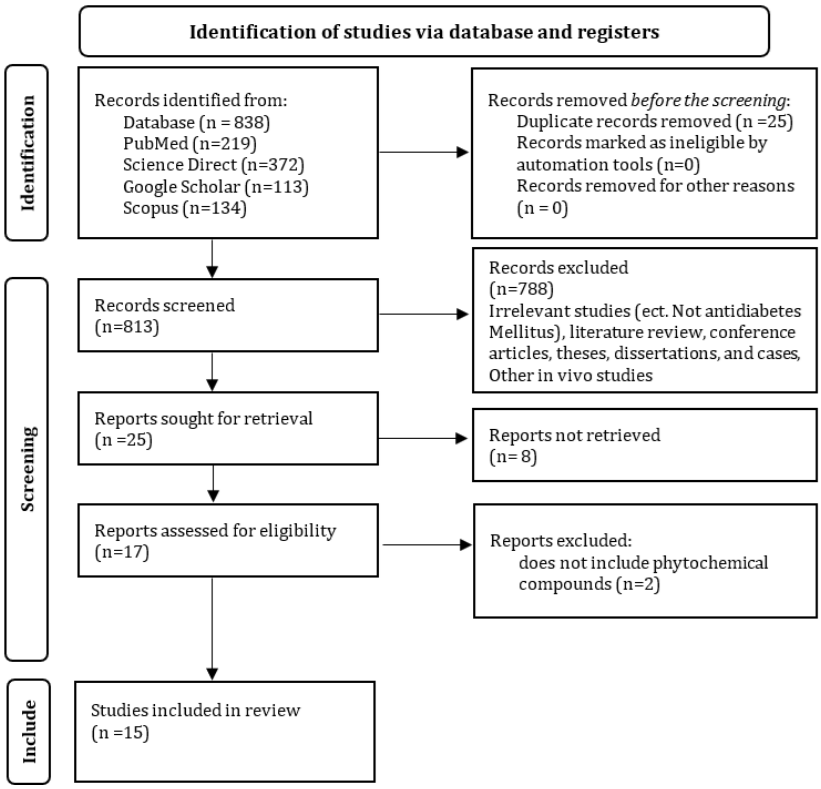

Figure 1. Flowchart of the Articles Selection Process Using the PRISMA Method

Eligibility criteria

This systematic review focuses on reports on *S.cumini* phytochemical compound profiles with the pharmacological activity as anti-diabetic conducted as in vivo assays. The selected articles must include phytochemical compound analytical method.

Selection of studies and data extraction

Each article referred to in this review have complied with the inclusion, exclusion and eligibility criteria. The systematic review process is presented in a flowchart using the PRISMA method (Figure 1). The writer conducted a checklist to obtain quality articles containing: the author's

name, year of research, type of research, type of sample, bioactive compounds, doses and induction ingredients, plant parts used, and duration of administration.

The articles used for this systematic review, in the form of preclinical study articles were assessed for the quality of specific tests on test animals using SYRCLE for the Risk of Bias (RoB) with the following types of bias checklists: selection bias with domain sequence generation, baseline characteristics and allocation concealment; performance bias with domain random housing and blinding; detection bias with domains random outcome assessment and blinding; attrition bias with domain incomplete data; reporting bias with domain selective outcome reporting; and other sources of bias (Hooijmans *et al*., 2014) (Table II).

RESULTS AND DISCUSSION

This systematic review explores the contribution of the bioactive contents in the anti-diabetic properties of *S. cumini*. At the beginning of the search, a total of 838 articles were obtained according to the keywords used in the PubMed, Science Direct, Scopus and Google Scholar databases. According to the articles' selection process using the PRISMA method, 15 articles were selected (Figure 1) based on the predetermined criteria, where the articles contained identification of phytochemical content and anti-diabetic activity *in vivo*. The results of the articles qualitative assessment for RoB through SYRCLE can be categorized as high bias (Table II) according to the type of performance bias, namely random housing, blinding and type detection bias, namely random outcome assessment.

Phytochemicals

Of the selected 13 articles, two articles compared the use of *S. cumini* as an antidiabetic agent with other plants, namely *Costus speciou*s, *T. ananassae,* and *S. cumini* with the result that *S. cumini* was more efficient in lowering levels of blood glucose *in vivo* (Gavillán-Suárez *et al*., 2015); The tannin fraction of *S. cumi*ni, the saponin fraction of *T. foenum graec*um, the flavonoid fraction of *T. chebula*, and the flavonoid fraction of *S. persica* all demonstrated that these plants' tannins, saponins, and flavonoids significantly decreased serum glucose levels and improved glucose tolerance. *S. persica* isolates' flavonoids demonstrated more potent anti-diabetic properties than those from of other plants (Bansode *et al*., 2017). One article comparing herbal medicine containing a mixture of *S. cumini* seeds, *Gymnema sylvestre* leaves, *A. indica* leaves, and *Z. officinale* (Ginger) demonstrated that herbal drugs and *S. cumini* had type 2 antidiabetic effects in rats (Proma *et al*., 2018). Ten other articles examined the potential of *S cumini* L. activity as anti-diabetic agent individually. Most of the plant parts used were the seeds of cumini, (8 articles); five studies used leaves; and only one report addressed the fruit and bark. Data on the activity of the phytochemical compound *S. cumini* for diabetes mellitus treatment (Table III).

An appropriate phytochemical analysis is urgently required in the search for bioactive compounds, identifying the constituents of plant extracts (Pant *et al*., 2017, Syukri *et al*., 2016; Nugroho *et al*., 2011). Five articles used phytochemical HPLC instrument one article used HPTLC, two articles used TLC, one article used HPLC-MS, one article used GCMS and three articles used color reaction (Table III). Several studies used various reagents or color reaction for phytochemical screening analysis, which considered unreliable because the resulting colour can be masked by impurities or other compounds. Therefore, it is necessary to conduct a more advanced analytical methods and instruments which provide higher sensitivity and selectivity.

Polyphenols themselves have been reported elsewhere as antidiabetic compounds in most herbal product (Constantin *et al*., 2014). Furthermore, Prabakaran & Shanmugave, (2018) reported that the methanol extract of *S. cumini* seeds contains alkaloids, steroids, cardiac glycosides, saponins, resins, terpenoids, beside flavonoids and phenolics (Prabakaran & Shanmugave, 2018). The leaves contain many phenolic compounds, the water extract also contains catechin, epicatechin, quercetin and myricetin 3-O-rhamnoside (Balyan *et al*., 2019).

Phytoconstituents reported in *S. cumini* seeds are gallic acid, chlorogenic, caffeic ellagic acids and catechins, epicatechin, quercetin, quercitrin, isoquercitrin, kaempferol, rutin, flavonoids, alkaloids, glycosides, saponins, tannins, triterpenoids, steroids. *S. cumini* leaves contain flavonoids, alkaloids, phenolics, glycosides, terpenes, tannins, flavonol glycosides, especially myricetin, myricitrin, quercetin, kaempferol, phenols, such as ellagic acid, ferulic acids, and gallic acids. The bark contains steroids, triterpenoid saponins, glycosides, carbohydrates, alkaloids, flavonoids, tannins, phenolics, and amino acids; while the fruit contains triterpenoids including

maslinic acid, ursolic acid, corosolic acid and oleanolic acid.

A more detailed report on the *S. cumini* seeds' phytoconsitutuents revealed the presence of flavonoid levels of 24.3 mg (Quercetin Equivalent) QE/g DW; phenolic content (methanol extract) 0.45 mg QE/mg extract; phenolic content (aqueous extract) of 0.18 mg QE/mg extract; tannin content of 3.361 mg tannic acid eq/g FW; saponin content of 0.6% mg quillaja/mg DW weight; and alkaloid content (aqueous fraction) of 1.80 % µg nicotine eq/mg (Gavillán-Suárez *et al*., 2015). The ethanol extract of *S.cumini* leaves contains 16.09% total phenolic content, 7.1% total tannin content and 1.217 ± 0.04% Myricetin (Baldissera *et al*., 2016). *S.cumini* fruit is rich in triterpenoids such as maslinic acid (9.71%, dry weight, DW), ursolic acid (6.8%, DW), corosolic acid (6.4%, DW) and oleanolic acid (4.1%). %, DW) (Xu *et al*., 2018). Report by Chagas *et al*., (2018) also stated that polyphenol-rich extract from *S.cumini* leaves contains gallic acid 11.15 ± 0.90 µg/mg; myricetin 192.70±16.50 µg/mg; quercetin 4.72 ± 0.06 µg/mg.

Flavonoids

Most studies reports that *Syzygium cumini* is rich in flavonoids. Bansode *et al*. (2017) revealed that flavonoids could increase liver glycogen levels and body weight in diabetic rats after administration of *S. cumini* extract. Mohamed *et al*., (2013) reported that flavonoid compounds play roles as antioxidants; and regenerate damaged pancreatic β cells (Sharma *et al*., 2013; Yasodamma & Alekhya, 2013). Upregulation of PPAR-α and PPAR-γ in 3T3-L1 preadipocytes can increase adipocyte homeostasis thereby causing a decrease in fat accumulation (Sharma *et al*., 2017). Flavonoids activate AMPK through the translocation and expression of GLUT4 in skeletal muscles (Eid *et al*., 2015). *In vivo* indicated that there was an increase in the expression of the PPARα gene in HepG2 cells in *S.cumini* extract, which is rich in flavonoids and can reduce serum of total cholesterol and total triglycerides levels (Sharma *et al*., 2012). Flavonoids in *cumini* seed extract are expected to play a role in enhancing absorption and storage of free fatty acids (FFA) in adipose tissue affecting insulin sensitivity reactions from PPARγ agonists, thus resulting in improvements in skeletal muscle, liver and pancreatic β cells from high FFA concentrations (Sharma *et al*., 2017).

Myricetin

Myricetin is a compound of the flavonoid class which has anti-diabetic, anti-inflammatory, antimicrobial and antibacterial activity (Choi *et al*., 2014; Grenier *et al*., 2015; Sanches *et al*., 2016). In rats fed with high sucrose and high-fat diet, myricetin prevented fatness and insulin resistance (Choi *et al*., 2014). The use of myricetin at a dose of 300 mg/Kg/day for 8 weeks could significantly reduce triglyceride levels in plasma and liver, increase expression of the enzyme PPARα in the liver, resulting in a decrease in intracellular fatty acids, which increased liver insulin resistance and improved regenerative pancreatic β cells, VLDL and serum triglycerides (Chagas *et al*., 2018; Sanches *et al*., 2016).

Myricetin increases PPARα expression in the liver, thus resulting in increased insulin sensitivity and hepatic lipid oxidations (Ding *et al*., 2012). Myricetin (MyR) reduces the expression of C/EBP α and PPAR γ by suppressing T3-L1 preadipocyte differentiation. MyR can significantly stimulate lipolysis in 3 T3-L1 adipocytes by decreasing the expression of perilipin A. The lipolytic regulation of MyR reduces obesity, thus regenerating the islets of Langerhans (Wang *et al*., 2015). The MyR effect can also protect pancreatic β cells from damage due to cytokine compounds and high glucose (HG) by weakening endoplasmic reticulum (ER) pressure, inactivating cyclin-dependent kinase 5 (CDK5), leading to upregulation of pancreatic duodenal homeobox 1 (PDX1) and sarcoendoplasmic reticulum calcium ATPase 2b (SERCA2b) to prevent from apoptosis (Ding *et al*., 2012; Karunakaran *et al*., 2019).

Quercetin

Quercetin is also a flavonoid that has an anti-diabetic effect by improving glucose absorption in sensitive tissues such as muscle, adipose, and liver (Gavillán-Suárez *et al*., 2015). Quercetin increases cell antioxidant activity by increasing insulin secretion and protecting pancreatic beta cells from ROS. Quercetin's mechanism of action is by reducing oxidative stress, protecting β cells, α-glucosidase inhibition, increasing glycogen synthesis, and stimulating glucose uptake in muscle cells through the AMPK pathway (Dhanya, 2022). Quercetin has anti-diabetic potential by increasing glucose uptake in the L6 myotube and GLUT4 expression in type 2 diabetes mellitus through the AMPK-P38 pathway (Dhanya *et al*., 2017).

Table II. Data on The Pharmacological Activity of *S. cumini* as anti-diabetes and the Phytochemical Content Profiling of the Material Used

Ref	Extract	Plant parts	Phytochemical contents (type of extract used)	Analytical Method	Dose	Induction	Test animals	Duration	Results
[Chatterjee *et al.*, 2012)	Ethyl acetate fraction	Seed	Gallic acid	HPTLC	20 mg/0.5 mL distilled water/100 g BW/Rat	Streptozotocin 3.5 mg/ 100 g BW	Rat	28 days	Blood Glucose Levels ↓, Glycated Hemoglobin Level ↓, Glycogen Content of The Liver and Skeleton ↑, Serum Insulin ↑, Hexokinase ↑, Glucose-6-Phosphatase ↓, Glucose-6-Phosphate Dehydrogenase ↑, Lactate Dehydrogenase ↓, Weight Gain ↑, SGPT ↓, SGOT ↓ No Toxicity Observed
[Gavillán-Suárez *et al.*, 2015)	Methanol and aqua extract	Leaf	Flavonoids, Alkaloids, Phenolics, Saponins Sterols, Cardiac Glycoside, Terpenoids, Tannins (Methanol Extract) Phenolic, Saponin (Water Extract)	TLC	2.3 mg/kg BW	Glucose 10% Insulin injection (8 unit/g BW)	Rat	10 weeks 120 min	Glucose Tolerance Test Db/Db↓, Ob/Ob↓ Insulin Tolerance Test Db / Db ↑, If / If ↑ Weight Gain ↑ No Toxicity Observed
[Bansode *et al.*, 2017)	Tannin fraction	Seed	Tannin	TLC	100 mg/kg BW	Alloxan 125 mg/kg BW	Rat	15 days	Serum Glucose Tolerance ↑, Weight Gain ↑, Liver Glycogen Levels ↑, Serum Glucose ↓, SOD ↑, CAT ↑,TBARS ↓, ROS ↓, No Toxicity Observed
[Baldissera *et al.*, 2016)	Hydroalcoholic extract	Leaf	Myricetin, Glycoside, Phenol, Tannin	HPLC	-	HFD 60% Streptozotocin 30 mg/kg BW	Rat	7 weeks	Serum Glucose Tolerance ↑, Weight Gain ↑, Liver Glycogen Level ↑, Serum Glucose ↓, Aspartate Aminotransferase (AST) ↑ and Alanine Aminotransferase (ALT) ↓, Cholesterol ↓, Triglycerides ↓ No Toxicity Observed
[Xu *et al.*, 2018)	Triterpenoid-enriched Jamun fruit extract	Fruit	Triterpenoid	HPLC	100mg/kg BW	Streptozotocin 40 mg/kg BW Glucose 10%	Mice	15, 30, 60, and 120 min GTT	Body Weight ↓, Glucose Content ↓, Liver Index ↑, Liver Glycogen Content ↑, Skeletal Muscle Glycogen Content ↑, Fasting Glucose Content ↓, Insulin Level ↑, B Index HOMA ↑, Glucose Homeostasis (GTT) ↓, AUC ↓, Normal Akt Phosphorylation, Foxo1expression ↑

Ref	Extract	Plant parts	Phytochemical contents (type of extract used)	Analytical Method	Dose	Induction	Test animals	Duration	Results
(Tripathi & Kohli, 2014)	Extracts of petroleum ether, chloroform, ethanol, aqua	Bark	Steroids, Triterpenoid Saponins, Glycosides, Carbohydrates, Alkaloids, Flavonoids, Tannins, Phenolics, Amino Acids	Color reaction	500 mg/Kg BW	glucose 2 g/kg BW Streptozotocin 50 mg/kg BW	Rat	48 h 21 days	Oral Glucose Tolerance Test (OGTT) ↓, Glucose Levels ↓, No Toxicity Observed
(Sanches *et al.*, 2016)	Hydroethanolic extract	Leaf	Flavonol Glycosides, Especially Myricetin, Myricitrin, Quercetin, Kaempferol, Phenols such as Ellagic Acid, Ferulic Acids, and Gallic Acids	HPLC-MS	500 mg/kg BW	glucose 10% Monosodium L-Glutamate (MSG)	Rat	60 days	Glucose ↓, Insulin Tolerance Test ↑, Insulin Resistance ↓, Body Weight ↓, Glycerol Release ↓, Total Cholesterol ↓, Triglycerides ↓, Fasting Slasma Insulinlevel ↓, Tyg Index ↓, HOMA IR ↓, HOMA B ↓
(Bitencourt *et al.*, 2015)	Aqueous extract	Seed	Gallic Acid; Chlorogenic Acid, Caffeic and Ellagic Acids; Catechins, Epicatechin, Quercetin, Quercitrin, Isoquercitrin, Kaempferol and Rutin.	HPLC	100 mg/kg BW	Streptozotocin 60 mg/kg BW	Rat	12 h(GTT)i) 21 days	Glucose ↓, Cholesterol ↑, Triglycerides ↓, Albumin↑, Creatinine↓, Urea↑ Fructosamine↓, Ceruloplasmin↑, Liver↑, Glycogen↓, HOMA-IR Index↓, HOMA-B B↑ Index
(Chagas, *et al.*, 2018)	70% Ethanol extract Etilasetat fraction	Leaf	Gallic acid, Myricetin and Quercetin	HPLC	50 mg/kg BW	alloxan 150 mg/kg BW	Rat	14 days	Triglycerides, Total Cholesterol, Tyg Index (Decreased Resistance) And Serum Glucose↓, Proliferation Assay (Increased Insulin Secretion By β Cells)
(Saifi *et al.*, 2016)	Hydrolcoholic extract	Seed	Flavonoids, Phenolic Group, Alkaloids, Glycosides, Saponins, Tannins, Steroids and Triterpenoids	Color reaction	500 mg/kg BW	alloxan 120 mg/kg, i.p	Rat	21 days	Blood Glucose Level ↓, Serum Ldl ↓, Hdl ↑, Serum Creatinine ↓, Serum Urea ↓, Serum Alkaline Phosphatase (Alp) ↓, Bilirubin ↑, Serum Glutamate Oxalate Transaminase (Sgot) ↓, Serum Glutamate Pyruvate Transaminase (Sgpt) ↓ No Toxicity Observed

Ref	Extract	Plant parts	Phytochemical contents (type of extract used)	Analytical Method	Dose	Induction	Test animals	Duration	Results
(Asanaliyar & Nadig, 2021)	Hydro-ethanolic extract	Seed	Polyphenols; Ellagic Acid	HPLC	100mg/kg or 200mg/kg or 400 mg/kg	High-Fat Diet (HFD) Streptozotocin 35mg/kg	Rat	21 days	Fasting Blood Glucose ↓, Serum Insulin ↑, Serum Triglycerides ↓ , Cholesterol ↓, HDL ↓ and LDL Level ↓, HOMA IR ↓ and HOMA B ↑ No Toxicity Observed
(Proma *et al.*, 2018)	Petroleum Ether Freeze Dried Extract	Seed	Steroids	Color Reaction	1,25 g/kg BW	streptozotocin 90 mg/kg BW	Rat	22 days	Body Weight ↓, HDL ↑, LDL ↓, Serum Glucose Level ↓, Serum Cholesterol ↓, Triglyceride Levels ↓,
(Sari *et al.*, 2020)	Ethanol extract	leaf	Flavonoids, Alkaloids, Phenolics, Glycosides, and Terpenes	GCMS	200 and 400 mg/kg	Alloxan 50 mg/kg BW	Mice	180 min 21 days	Oral Glucose Tolerance Level ↓, Blood Glucose Levels ↓, Glycosylated Hemoglobin (Hba1c) ↓, Creatinine Kinase (CK) ↓, Lactate Dehydrogenase (LDH) ↓, TBARS ↓, CAT ↑, SOD ↓, GSH ↓, No Toxicity Observed
(Yadav *et al.*, 2010)	Water extract, ethanol extract, methanol extract, hexane extract and chloroform extract	seed	Tannins, phenols, alkaloids, flavonoids, and saponin	Variation reagent Color Reaction	200, 100 and 50 mg/kg	Glucosa 2 mg/kg BW	Rat	1-6 h	Oral Glucose Tolerance Level ↓
(Sharma *et al.*, 2008)	Ethanol extract, Chloroform extract and ethyl acetate extract	seed	Rutin and Quercetin	HPLC	300 mg/kg BW	Streptozotocin 60 mg/kg BW Glucose 1 g/kg BW	mice	15 days 120 h	Fasting blood glucose levels ↓, very low density lipoprotein (VLDL) ↓, low density lipoprotein (LDL) ↓, high density lipoprotein (HDL) ↑, Total cholesterol (TC) ↓ and triglyceride (TG) ↓, Glycogen content of skeletal muscles, liver ↑ , and kidney ↓, hepatic glucose-6-phospahatase ↓, hepatic hexokinase ↑, Serum insulin level ↑, pancreatic histopathology showed a protective effect of the extract. Oral Glucose Tolerance Level ↓

Table III. Data on The Pharmacological Activity of *S. cumini* as anti-diabetes and the Phytochemical Content Profiling of the Material Used

Ref	Extract	Plant parts	Phytochemical contents (type of extract used)	Analytical Method	Dose	Induction	Test animals	Duration	Results
(Chatterjee *et al.*, 2012)	Ethyl acetate fraction	Seed	Gallic acid	HPTLC	20 mg/0.5 mL distilled water/100 g BW/Rat	Streptozotocin 3.5 mg/ 100 g BW	Rat	28 days	Blood Glucose Levels ↓, Glycated Hemoglobin Level ↓, Glycogen Content of The Liver and Skeleton ↑, Serum Insulin ↑, Hexokinase ↑, Glucose-6-Phosphatase ↓, Glucose-6-Phosphate Dehydrogenase ↑, Lactate Dehydrogenase ↓, Weight Gain ↑, SGPT ↓, SGOT ↓ No Toxicity Observed
(Gavillán-Suárez *et al.*, 2015)	Methanol and aqua extract	Leaf	Flavonoids, Alkaloids, Phenolics, Saponins Sterols, Cardiac Glycoside, Terpenoids, Tannins (Methanol Extract) Phenolic, Saponin (Water Extract)	TLC	2.3 mg/kg BW	Glucose 10% Insulin injection (8 unit/g BW)	Rat	10 weeks 120 min	Glucose Tolerance Test Db/Db↓, Ob/Ob↓ Insulin Tolerance Test Db / Db ↑, If / If ↑ Weight Gain ↑ No Toxicity Observed
(Bansode *et al.*, 2017)	Tannin fraction	Seed	Tannin	TLC	100 mg/kg BW	Alloxan 125 mg/kg BW	Rat	15 days	Serum Glucose Tolerance ↑, Weight Gain ↑, Liver Glycogen Levels ↑, Serum Glucose ↓, SOD ↑, CAT ↑,TBARS ↓, ROS ↓, No Toxicity Observed
(Baldissera *et al.*, 2016)	Hydroalcoholic extract	Leaf	Myricetin, Glycoside, Phenol, Tannin	HPLC	-	HFD 60% Streptozotocin 30 mg/kg BW	Rat	7 weeks	Serum Glucose Tolerance ↑, Weight Gain ↑, Liver Glycogen Level ↑, Serum Glucose ↓, Aspartate Aminotransferase (AST) ↑ and Alanine Aminotransferase (ALT) ↓, Cholesterol ↓, Triglycerides ↓ No Toxicity Observed

Ref	Extract	Plant parts	Phytochemical contents (type of extract used)	Analytical Method	Dose	Induction	Test animals	Duration	Results
(Xu *et al.*, 2018)	Triterpenoid-enriched Jamun fruit extract	Fruit	Triterpenoid	HPLC	100mg/kg BW	Streptozotocin 40 mg/kg BW Glucose 10%	Mice	15, 30, 60, and 120 min GTT	Body Weight ↓, Glucose Content ↓, Liver Index ↑, Liver Glycogen Content ↑, Skeletal Muscle Glycogen Content ↑, Fasting Glucose Content ↓, Insulin Level ↑, B Index HOMA ↑, Glucose Homeostasis (GTT) ↓, AUC ↓, Normal Akt Phosphorylation, Foxo1expression ↑
(Tripathi & Kohli, 2014)	Extracts of petroleum ether, chloroform, ethanol, aqua	Bark	Steroids, Triterpenoid Saponins, Glycosides, Carbohydrates, Alkaloids, Flavonoids, Tannins, Phenolics, Amino Acids	Color reaction	500 mg/Kg BW	glucose 2 g/kg BW Streptozotocin 50 mg/kg BW glucose 10%	Rat	48 h 21 days	Oral Glucose Tolerance Test (OGTT) ↓, Glucose Levels ↓, No Toxicity Observed
(Sanches *et al.*, 2016)	Hydroethanolic extract	Leaf	Flavonol Glycosides, Especially Myricetin, Myricitrin, Quercetin, Kaempferol, Phenols such as Ellagic Acid, Ferulic Acids, and Gallic Acids	HPLC-MS	500 mg/kg BW	Monosodium L-Glutamate (MSG)	Rat	60 days	Glucose ↓, Insulin Tolerance Test ↑, Insulin Resistance ↓, Body Weight ↓, Glycerol Release ↓, Total Cholesterol ↓, Triglycerides ↓, Fasting Slasma Insulinlevel ↓, Tyg Index ↓, HOMA IR ↓, HOMA B ↓
(Bitencourt *et al.*, 2015)	Aqueous extract	Seed	Gallic Acid; Chlorogenic Acid, Caffeic and Ellagic Acids; Catechins, Epicatechin, Quercetin, Quercitrin, Isoquercitrin, Kaempferol and Rutin.	HPLC	100 mg/kg BW	Streptozotocin 60 mg/kg BW	Rat	12 h (GTT)i) 21 days	Glucose ↓, Cholesterol ↑, Triglycerides ↓, Albumin↑, Creatinine↓, Urea↑ Fructosamine↓, Ceruloplasmin↑, Liver↑, Glycogen↓, HOMA-IR Index↓, HOMA-B B↑ Index

Ref	Extract	Plant parts	Phytochemical contents (type of extract used)	Analytical Method	Dose	Induction	Test animals	Duration	Results
(Chagas, *et al.*, 2018)	70% Ethanol extract Etilasetat fraction	Leaf	Gallic acid, Myricetin and Quercetin	HPLC	50 mg/kg BW	alloxan 150 mg/kg BW	Rat	14 days	Triglycerides, Total Cholesterol, Tyg Index (Decreased Resistance) And Serum Glucose↓, Proliferation Assay (Increased Insulin Secretion By β Cells)
(Saifi *et al.*, 2016)	Hydrolcoholic extract	Seed	Flavonoids, Phenolic Group, Alkaloids, Glycosides, Saponins, Tannins, Steroids and Triterpenoids	Color reaction	500 mg/kg BW	alloxan 120 mg/kg, i.p	Rat	21 days	Blood Glucose Level ↓, Serum Ldl ↓, Hdl ↑, Serum Creatinine ↓, Serum Urea ↓, Serum Alkaline Phosphatase (Alp) ↓, Bilirubin ↑, Serum Glutamate Oxalate Transaminase (Sgot) ↓, Serum Glutamate Pyruvate Transaminase (Sgpt) ↓ No Toxicity Observed
(Asanaliyar & Nadig, 2021)	Hydro-ethanolic extract	Seed	Polyphenols; Ellagic Acid	HPLC	100mg/kg or 200mg/kg or 400 mg/kg	High-Fat Diet (HFD) Streptozotocin 35mg/kg	Rat	21 days	Fasting Blood Glucose ↓, Serum Insulin ↑, Serum Triglycerides ↓, Cholesterol ↓, HDL ↓ and LDL Level ↓, HOMA IR ↓ and HOMA B ↑ No Toxicity Observed
(Proma *et al.*, 2018)	Petroleum Ether Freeze Dried Extract	Seed	Steroids	Color Reaction	1.25 g/kg BW	streptozotocin 90 mg/kg BW	Rat	22 days	Body Weight ↓, HDL ↑, LDL ↓, Serum Glucose Level ↓, Serum Cholesterol ↓, Triglyceride Levels ↓,
(Sari *et al.*, 2020)	Ethanol extract	leaf	Flavonoids, Alkaloids, Phenolics, Glycosides, and Terpenes	GCMS	200 and 400 mg/kg	Alloxan 50 mg/kg BW	Mice	180 min 21 days	Oral Glucose Tolerance Level ↓, Blood Glucose Levels ↓, Glycosylated Hemoglobin (Hba1c) ↓, Creatinine Kinase (CK) ↓, Lactate Dehydrogenase (LDH) ↓, TBARS ↓, CAT ↑, SOD ↓, GSH ↓, No Toxicity Observed

Ref	Extract	Plant parts	Phytochemical contents (type of extract used)	Analytical Method	Dose	Induction	Test animals	Duration	Results
(Yadav *et al*., 2010)	Water extract, ethanol extract, methanol extract, hexane extract and chloroform extract	seed	Tannins, phenols, alkaloids, flavonoids, and saponin	Variation reagent Color Reaction	200, 100 and 50 mg/kg	Glucosa 2 mg/kg BW	Rat	1-6 h	Oral Glucose Tolerance Level ↓
(Sharma *et al*., 2008)	Ethanol extract, Chloroform extract and ethyl acetate extract	seed	Rutin and Quercetin	HPLC	300 mg/kg BW	Streptozotocin 60 mg/kg BW	mice	15 days	Fasting blood glucose levels ↓, very low density lipoprotein (VLDL) ↓, low density lipoprotein (LDL) ↓, high density lipoprotein (HDL) ↑, Total cholesterol (TC) ↓ and triglyceride (TG) ↓, Glycogen content of skeletal muscles, liver ↑ , and kidney ↓, hepatic glucose-6-phospahatase ↓, hepatic hexokinase ↑, Serum insulin level ↑, pancreatic histopathology showed a protective effect of the extract.
						Glucose 1 g/kg BW		120 h	Oral Glucose Tolerance Level ↓

Activation of the AMPK pathway by quercetin is associated with G6Pase inhibition. Quercetin can affect glucose homeostasis in skeletal and liver muscles (Eid *et al*., 2015).

Alkaloids

Certain alkaloids exhibit show effects in treating hypercholesterolemia, hypertriglyceridemia, hyperlipidemia and/or dyslipidemia and complications associated with metabolic diseases such as fatness and diabetes mellitus (Gavillán-Suárez *et al*., 2015). High glucose levels cause disruption of insulin secretion, and damage to pancreatic beta cells and mitochondria, alkaloids can prevent this from happening (Pereira *et al*., 2021). Alkaloids, such as Hernandezine (HER), which prevents from pAMPK dephosphorylation, are able to generate activate AMPK signalling in cells and tissues.

Alkaloids also have anti-diabetic and anti-obesity effects of type 2 DM rats (Bai *et al*., 2022). One of the effects of indole alkaloids is as a DPP-IV inhibitor, increasing the proliferation of endocrine cells and pancreatic β cells (Shukla & Srinivasan, 2012). Alkaloids such as Eurocristatine (ECT) can increase insulin resistance, improve lipid metabolism, lower blood glucose levels, accelerate glycogen synthesis in mice db/db and increase the PI3K/AKT signalling pathway as a target for diabetes mellitus treatment (Zhang *et al*., 2020).

Phenolik

The fruit variety of Syzygium cumini (pulp, seed coat, and kernel) contains phenolics, which have antioxidant and anti-diabetic abilities. Among the phenolic substances are Ellagic acid, Galic acid, tannins, and saponins (Shila *et al*., 2017).

Ellagic acid

Ellagic acid and its derivatives are mostly found as the compounds of phenolic in the lyophilized *Syzygium cumini* fruit extracts (Gavillán-Suárez *et al*., 2015). *S. cumini* has high quantities of ellagic acid, a polyphenolic antioxidant that normalizes blood glucose, insulin serum levels, and carbohydrate-metabolizing enzyme levels, leading to a marked rise in serum and fasting blood glucose levels (Sampath *et al*., 2013).

One of the characteristics of diabetes mellitus is high glucose levels which cause neurotropic inflammation in the hippocampus and cerebral cortex. Ellagic Acid (EA) is one of the phenolic compounds in *S. cumini* which can prevent neuron loss caused by decreased blood glucose levels, anti-inflammatory and increased tissue neurotrophic factors levels (NGF, BDNF, IGF-1) in diabetic rats (Farbood *et al*., 2019). EA has an antioxidant effect by downregulating P47phox and upregulating NRF2 in the liver, thereby reducing glucose levels and improving insulin resistance which can be seen by increasing Akt phosphorylation. In addition, steatosis and oxidative stress decreased, while insulin sensitivity increased (Polce *et al*., 2018).

Gallic acid

Gallic acid can be found in *S cumini* seeds. This compound has strong antioxidant activity with oxidation-reduction, absorption and neutralization properties. The antioxidant activity occurs by liberating radicals, quenching singlet and triplet oxygen, and removing peroxides (Chatterjee *et al*., 2012). Gallic acid, ellagic acid, triterpenoids, tannins and saponins can restore lipid profiles to normal and increase GLUT4 mRNA resulting in increased GLUT4 levels in type 2 diabetes mellitus rats (Sampath *et al*., 2013).

Metabolic processes involving gallic acid occur by altering adipose tissue interscapular genes via thermogenesis via activation of the AMP-activated protein kinase (AMPK)/Knockdown Sirtuin 1(Sirt1)/peroxisome proliferator-activated receptor-coactivator1 (PGC1) pathway. This activation has the potential for insulin resistance in metabolic diseases as a therapeutic intervention (Doan *et al*., 2015). Galic acid can reduce the levels of blood glucose and slow down non-alcoholic fatty liver disease (NAFLD) in rats. Gallic acid will reduce lipid levels and upregulate β-oxidation and ketogenesis (Chao *et al*., 2021).

Tannins

Tannins can lower blood glucose levels by inhibiting the enzymes α-glucosidase (α-amylase and sucrase) (Tripathi & Kohli, 2014; Yasodamma & Alekhya, 2013). In diabetic rats, oxidative stress, plasma cholesterol levels, and LDL levels decreased due to the influence of tannin (Velayutham *et al*., 2012). Tannins can lower levels of glutamate oxaloacetate transaminase (GOT), total cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) while raising levels of high-density lipoprotein (HDL) and liver glycogen. Blood glucose levels, glutamate pyruvate transaminase (GPT), play a role in preventing hyperlipidemia in streptozotocin-nicotinamide-induced rats (Kumar *et al*., 2018).

Saponins

Saponins can lower blood glucose levels through the inhibition of α-glucosidation enzymes

in the intestines (Tripathi & Kohli, 2014; Yasodamma & Alekhya, 2013). Saponins are able to increase insulin secretion in INS-1 pancreatic β-cells through the PI3K/Akt/FoxO1 signalling pathway in vivo (Liu *et al*., 2021). Furostanol saponins have the effect of reducing postprandial hyperglycemia by inhibiting α-glucosidase enzymes, aldose reductase inhibitors in secondary complications of diabetes mellitus and inducing insulin biosynthesis and anti-hypercholesterolemia (Ezzat *et al*., 2017).

In db/db diabetes mellitus rats, saponins can modify excessive lipid levels, lower blood glucose and plasma insulin levels, increase insulin sensitivity and glycogen synthesis, and increase insulin sensitivity. The mechanism of hypoglycemia in saponins is done by regulation of the IRS-1/PI3K/AKT signalling pathway and GLUT-4 expression (Xu *et al*., 2018). Saponins can improve glucose homeostasis so that insulin sensitivity in the liver and cell tissues increases through increasing glycogen levels in the liver, reducing triacylglycerol in the liver insulin signalling pathway and activating PPAR-c (Kwon *et al*., 2012).

Unlike the polyphenolics, the alkaloids and saponins contents reported in *S. cumini* have yet to be appropriately identified. Considering that those group of compounds may also contribute to the overall anti-diabetic activity, an isolation and identification of the phytochemical contents of the *S. cumini* especially for the seeds and the leaves are worth taking. An appropriate phytochemical profiling with a sensitive, selective, yet efficient is necessary in providing a quality assurance in herbal medicine production.

Preclinical trial

The study model for anti-diabetes mellitus activity *in vivo* depends on the inducer or diabetogenic agents used in the experiment. We found different diabetagonic agents used in the reports of which two studies used streptozotocin with doses between 50-90 mg/kg BW; 3 studies used a combination of streptozotocin and glucose; three studies used alloxan 50-150 mg/kg BW; and 1 study used monosodium L-glutamate (MSG). The duration of the research was around 14-70 days including acclimation, induction, and treatment with the tested samples. The glucose tolerance test was carried out in a duration of 20-180 minute.

Streptozotocin can cause damage to pancreatic β cells resulting in insulin destruction. This results in hyperglycemia, glycosuria, hypoinsulinemia and induced weight loss in experimental animals (Bisht *et al*., 2013). Obesity, hyperglycemia, hyperinsulinemia, β-cell dysfunction, hyperlipidemia, and increased TNF-α serum levels are characteristic of increased insulin resistance (IR). In experimental animals induced by HFD-STZ, the expression of PPARγ, PPARα and insulin resistance (IR) proteins increase (Barrière *et al*., 2018). HFD-STZ results in type 2 diabetes, increases insulin resistance and decrease GLUT4 expression in muscles, and trus causing abnormal cytokine production (TNF-α) resulting in chronic inflammation, increased adipocyte lipocytes and increased free fatty acids (FFA) (Nadig *et al*., 2021).

Alloxan (2, 4, 5, 6-tetraoxypyrimidine; 5, 6-dioxyuracil) is a diabetogenic agent that works by causing damage to some pancreatic β cells that affects pancreatic β cell function, insulin concentration and pancreatic antioxidant system, causing fasting blood glucose levels to increase (Ighodaro *et al*., 2018). Alloxan is relatively toxic to pancreatic β cells through the accumulation of reactive oxygen species (ROS), which causes necrosis and death of pancreatic cells that reduce insulin secretion (Takemoto *et al*., 2016).

In general, *Syzygium cumini* plants are rich in polyphenols. Polyphenols are phytochemical compounds and one of their benefits is as strong antioxidants by counteracting free radicals (Denisov & Afanas'ev, 2005). The formation of reactive free radicals is mostly by hyperglycemia. This causes oxidative stress on pancreatic β cells, causing complications of diabetes mellitus (Oguntibeju *et al*., 2020). Polyphenolic compounds act as antioxidants by suppressing DNA obstruction (Tripathi & Kohli, 2014), and serve as antidiabetic agent by reducing blood glucose levels, glycated haemoglobin, glucose-6 phosphatase activity and increasing liver glycogen levels, insulin sensitivity, pancreatic β-cell and β-cell function, antioxidant enzyme activity and hexokinase, as well as Glucose Transporter 2 (Ajiboye *et al*., 2018). The mechanism of the phytochemical compounds of *Syzygium cumini* L contributing to the overall anti-diabetic mellitus (Figure 2).

Toxicity

Toxicity tests include acute, sub-acute and chronic toxicity in the development of new drug products. The administration of a single dose of each animal was carried out in the acute toxicity test to determine animal behaviour and the LD_{50} or median lethal dose.

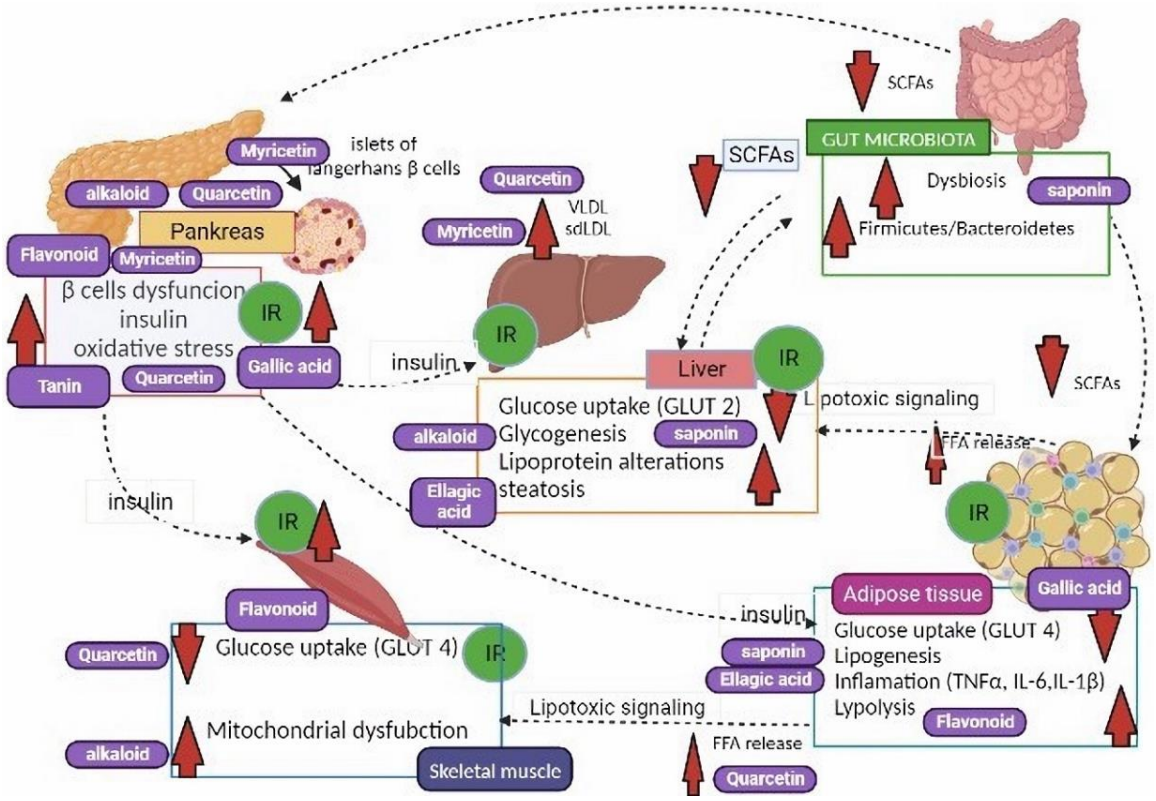

Figure 2. The mechanism of the phytochemical compound *Syzygium cumini* as an anti-diabetic mellitus

Test animals were observed for any of these abnormal behaviours respiratory distress, hyperexcitability, diarrhoea, drooling, motor disturbances and death. Sub-acute toxicity tests werw perfomed by giving daily doses to animals, starting from a therapeutic dose and gradually increased every two to three days, entained by observing signs of toxicity. Chronic toxicity assays were carried out on two species, namely rodents and non-rodents, with doses of the drug given every day for six months (Bansode *et al*., 2017; Bhardwaj & Gupta, 2012)

This review article contains nine studies on toxicity assays. Research by Chatterjee *et al*., (2012) revealsed that the *S. cumini* ethyl acetate fraction is non-toxic, indicated by a normal increased in body weight, no autonomic, behavioural or neurological changes as well as no increased of GOT and GPT serum activity observed. These parameters showed that no increasing glucose utilization and reduced hepatorenal dysfunction observed which serve as the general indicator of metabolic toxicity.

Based on the Organization for Economic Cooperation and Development (OECD) Guidelines (OECD, 2001), observations were made of changes in the skin and fur, eyes and mucous membranes and behaviour patterns, tremors and seizures when the stem bark extract and tannin fraction of *S. cumini* were administered orally at a dose of 5000 mg/kg body weight. The results of the toxicity test showed that administration of stem bark extract and tannin fraction of *S. cumini* did not cause acute toxicity (Gavillán-Suárez *et al*., 2015; Tripathi & Kohli, 2014). Another acute oral toxicity study used a single dose of 2000 mg/kg BW of the leaves and seeds ethanol extracts of *S. cumini* of which the observations were made after dosing every first 30 minutes, periodically for the first 24 hours. Afterwards, it was observed every day for 14 days. The results showed no change in behaviour and no death observed in all groups (Asanaliyar & Nadig, 2021; Saifi *et al*., 2016; Sari *et al*., 2020). Other toxicity studies on the ethanol extract of *S.cumini* leaves were conducted at a dose of 0.05 g/kg; 0.1g/kg; 0.25 g/kg orally daily for 30, 90, and

180 days. The test results showed no changes in body weight, behavioural effects, and death. Histological examination of the liver, kidneys, lungs, heart, stomach, intestines and pancreas did not show any morphological disturbances and that the extract did not cause chronic and acute toxicity (Silva *et al*., 2011).

The locals population are familiar with and frequently utilize *Syzygium cumini* as a traditional remedy. The entire plant, including the seeds, leaves, fruit, flowers, and bark, can be utilized as a traditional diabetic treatment. The fruit is usually consumed fresh. Other ways of consumption are in form of tea or jam (Garg *et al*., 2019), juice (Kapoor & Ranote, 2016), ready to serve (RTS) beverage (Barman & Saikia Barooah, 2016), and wine (Patil *et al*., 2012). The high content of phenolic compounds in this plant can serve as an anti-diabetic agent (Chagas *et al*., 2018). Besides, it phenolic content, ellagic acid has reported to be potential as chem oprevetion of lung cancer (Chamnansilpa *et al*., 2020), while its gallic acid may serve as cardioprotective (Atale *et al*., 2013). Antioxidant potential is associated with a high level of flavonoids (Eshwarappa *et al*., 2014), which can further play a role in the proliferative agent for hyperlipidemia and obesity due to anthocyanin (Chamnansilpa *et al*., 2020)

CONCLUSION

This study provides a systematic review on the contribution of the phytochemicals reported in *Syzygium cumini* extract as anti-diabetes mellitus *in vivo*. This literature review revealed that those phytochemical compounds in *S. cumini* namaly phenolics: ellagic acid, gallic acid, and tannins; flavonoids: myricetin and quercetin; alkaloids, and saponins may contribute to the overall anti-diabetic properties. These bioactive compounds stimulate insulin secretion, increase insulin sensitivity and use of glucose in tissues, reduce insulin resistance, oxidative stress and gluconeogenesis, and slow down the absorption of carbohydrates and sucrose. As a conclusion, the review confirms that *S. cumini* has the potential to be developed as an anti-diabetes mellitus agent. In particular, seeds and leaves of S. cumini have high potential to be developed as herbal products for anti-diabetic agent. This review has highlighted a research gap to support the development of this compound through, established preclinical and clinical trials and reliable analytical methods for phytochemical profiling, which is urgently required for the aforementioned purpose.

ACKNOWLEDGMENTS

The authors would like to express gratitude to Universitas Gadjah Mada for its assistance in providing research facilities, and to the Center for Education Financial Services and Indonesia Endowment Funds for Education for financial support as Doctoral Scholarship through Indonesian Education Scholarships 2021.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Ajiboye, B. O., Ojo, O. A., Akuboh, O. S., Okesola, M. A., Idowu, O. T., Oyinloye, B. E., & Talabi, J. Y. (2018). The protective effect of polyphenol-rich extract of Syzygium cumini leaves on cholinesterase and brain antioxidant status in alloxan-induced diabetic rats. *Jordan J. Biol Sci*. *11*(2), 163–169.

Asanaliyar, M., & Nadig, P. (2021). In - Vivo anti-diabetic activity of hydro-ethanolic seed extract of Syzygium cumini (L.). *Biomedical and Pharmacology Journal*, *14*(1), 241–247. https://doi.org/10.13005/bpj/2119

Atale, N., Chakraborty, M., Mohanty, S., Bhattacharya, S., Nigam, D., Sharma, M., & Rani, V. (2013). Cardioprotective role of Syzygium cumini against glucose-induced oxidative stress in H9C2 cardiac myocytes. *Cardiovascular Toxicology*, *13*(3), 278–289. https://doi.org/10.1007/s12012-013-9207-1

Bai, J., Zhang, S., Cao, J., Sun, H., Mang, Z., Shen, W. L., & Li, H. (2022). Hernandezine, a natural herbal alkaloid, ameliorates type 2 diabetes by activating AMPK in two mouse models. *Phytomedicine*, *105*(July), 154366. https://doi.org/10.1016/j.phymed.2022.154366

Baldissera, G., Sperotto, N. D. M., Rosa, H. T., Henn, J. G., Peres, V. F., Moura, D. J., Roehrs, R., Denardin, E. L. G., Dal Lago, P., Nunes, R. B., & Saffi, J. (2016). Effects of crude hydroalcoholic extract of Syzygium cumini (L.) Skeels leaves and continuous aerobic training in rats with diabetes induced by a high-fat diet and low doses of streptozotocin. *Journal of Ethnopharmacology*, *194*, 1012–1021. https://doi.org/10.1016/j.jep.2016.10.056

Balyan, U., Verma, S. P., & Sarkar, B. (2019). Phenolic compounds from Syzygium cumini (L.) Skeels leaves: Extraction and membrane

purification. *Journal of Applied Research on Medicinal and Aromatic Plants*, *12*(January), 43–58. https://doi.org/10.1016/j.jarmap.2018.12.002

Bansode, T. S., Salalkar, B. K., Dighe, P., Nirmal, S., & Dighe, S. (2017). Comparative evaluation of antidiabetic potential of partially purified bioactive fractions from four medicinal plants in alloxan-induced diabetic rats. *Ayu*, *38*(3–4), 165–170. https://doi.org/10.4103/ayu.AYU_18_17

Barman, N., & Saikia Barooah, M. (2016). Development of functional RTS beverage from Jamun (Syzygium cumini L.) and Melastoma malabathricum. *Journal of Agricultural Engineering and Food Technology*, *3*(4), 293–298.

Barrière, D. A., Noll, C., Roussy, G., Lizotte, F., Kessai, A., Kirby, K., Belleville, K., Beaudet, N., Longpré, J. M., Carpentier, A. C., Geraldes, P., & Sarret, P. (2018). Combination of high-fat/high-fructose diet and low-dose streptozotocin to model long-term type-2 diabetes complications. *Scientific Reports*, *8*(1), 1–17. https://doi.org/10.1038/s41598-017-18896-5

Bhardwaj, S., & Gupta, D. (2012). Study of acute, sub acute and chronic toxicity test. *International Journal of Advanced Research in Pharmaceutical & Bio Sciences*, *1*, 103+.

Bisht, R., Bhattacharya, S., Plant, A. J., & Res, S. (2013). *Effect of various extracts of Desmodium gangeticum on Streptozotocin-nicotinamide induced type-2 diabetes*. *3*(3), 28–34.

Bitencourt, P. E. R., Bona, K. S. De, Cargnelutti, L. O., Bonfanti, G., Pigatto, A., Boligon, A., Athayde, M. L., Pierezan, F., Zanette, R. A., & Moretto, M. B. (2015). Syzygium cumini seed extract ameliorates adenosine deaminase activity and biochemical parameters but does not alter insulin sensitivity and pancreas architecture in a short-term model of diabetes. *Journal of Complementary & Integrative Medicine*, *12*(3), 187–193. https://doi.org/10.1515/jcim-2015-0008

Chagas, V. T., Coelho, R. M. R. de S., Gaspar, R. S., da Silva, S. A., Mastrogiovanni, M., Mendonça, C. de J., Ribeiro, M. N. de S., Paes, A. M. de A., & Trostchansky, A. (2018). Protective effects of a polyphenol-rich extract from Syzygium cumini (L.) Skeels leaf on oxidative stress-induced diabetic rats. *Oxidative Medicine and Cellular Longevity*, *2018*, 5386079. https://doi.org/10.1155/2018/5386079

Chamnansilpa, N., Aksornchu, P., Adisakwattana, S., Thilavech, T., Mäkynen, K., Dahlan, W., & Ngamukote, S. (2020). Anthocyanin-rich fraction from Thai berries interferes with the key steps of lipid digestion and cholesterol absorption. *Heliyon*, *6*(11), e05408. https://doi.org/https://doi.org/10.1016/j.heliyon.2020.e05408

Chao, J., Cheng, H. Y., Chang, M. L., Huang, S. S., Liao, J. W., Cheng, Y. C., Peng, W. H., & Pao, L. H. (2021). Gallic acid ameliorated impaired lipid homeostasis in a mouse model of high-fat diet—and streptozotocin-induced NAFLD and Diabetes through improvement of β-oxidation and ketogenesis. *Frontiers in Pharmacology*, *11*(February), 1–14. https://doi.org/10.3389/fphar.2020.606759

Chatterjee, K., Ali, K. M., De, D., Panda, D. K., & Ghosh, D. (2012). Antidiabetic and antioxidative activity of ethyl acetate fraction of hydromethanolic extract of seed of Eugenia jambolana Linn through in-vivo and in-vitro study and its chromatographic purification. *Free Radicals and Antioxidants*, *2*(1), 21–30. https://doi.org/https://doi.org/10.5530/ax.2012.2.6

Choi, H. N., Kang, M. J., Lee, S. J., & Kim, J. I. (2014). Ameliorative effect of myricetin on insulin resistance in mice fed a high-fat, high-Sucrose diet. *Nutrition Research and Practice*, *8*(5), 544–549. https://doi.org/10.4162/nrp.2014.8.5.544

Constantin, R. P., Constantin, R. P., Bracht, A., Yamamoto, N. S., Ishii-Iwamoto, E. L., & Constantin, J. (2014). Molecular mechanisms of citrus flavanones on hepatic gluconeogenesis. *Fitoterapia*, *92*, 148–162. https://doi.org/10.1016/J.FITOTE.2013.11.003

Denisov, E.T., & Afanas'ev, I. . (2005). *Oxidation and Antioxidants in Organic Chemistry and Biology* (1 St). CRC Press. https://doi.org/. https://doi.org/10.1201/9781420030853

Dhanya, R. (2022). Quercetin for managing type 2 diabetes and its complications, an insight into multitarget therapy. *Biomedicine and Pharmacotherapy*, *146*(November 2021), 112560. https://doi.org/10.1016/j.biopha.2021.112

560

Dhanya, R., Arya, A. D., Nisha, P., & Jayamurthy, P. (2017). Quercetin, a lead compound against type 2 diabetes ameliorates glucose uptake via AMPK pathway in skeletal muscle cell line. *Frontiers in Pharmacology*, *8*(JUN), 1–9. https://doi.org/10.3389/fphar.2017.00336

Ding, Y., Zhang, Z. F., Dai, X. Q., & Li, Y. (2012). Myricetin protects against cytokine-induced cell death in RIN-m5f β cells. In *Journal of Medicinal Food* (Vol. 15, Issue 8, pp. 733–740). https://doi.org/10.1089/jmf.2011.2033

Doan, K. V., Ko, C. M., Kinyua, A. W., Yang, D. J., Choi, Y. H., Oh, I. Y., Nguyen, N. M., Ko, A., Choi, J. W., Jeong, Y., Jung, M. H., Cho, W. G., Xu, S., Park, K. S., Park, W. J., Choi, S. Y., Kim, H. S., Moh, S. H., & Kim, K. W. (2015). Gallic acid regulates body weight and glucose homeostasis through AMPK activation. *Endocrinology*, *156*(1), 157–168. https://doi.org/10.1210/en.2014-1354

Eid, H. M., Nachar, A., Thong, F., Sweeney, G., & Haddad, P. S. (2015). The molecular basis of the antidiabetic action of quercetin in cultured skeletal muscle cells and hepatocytes. *Pharmacognosy Magazine*, *11*(41), 74–81. https://doi.org/10.4103/0973-1296.149708

Eshwarappa, R. S. B., Iyer, R. S., Subbaramaiah, S. R., Richard, S. A., & Dhananjaya, B. L. (2014). Antioxidant activity of Syzygium cumini leaf gall extracts. *BioImpacts*, *4*(2), 101–107. https://doi.org/10.5681/bi.2014.018

Ezzat, S. M., Motaal, A. A., & El Awdan, S. A. W. (2017). In vitro and in vivo antidiabetic potential of extracts and a furostanol saponin from Balanites aegyptiaca. *Pharmaceutical Biology*, *55*(1), 1931–1936. https://doi.org/10.1080/13880209.2017.1343358

Farbood, Y., Rashno, M., Ghaderi, S., Khoshnam, S. E., Sarkaki, A., Rashidi, K., Rashno, M., & Badavi, M. (2019). Ellagic acid protects against diabetes-associated behavioral deficits in rats: Possible involved mechanisms. *Life Sciences*, *225*, 8–19. https://doi.org/10.1016/j.lfs.2019.03.078

Garg, S., Ghosh, P., Rana, S. S., & Pradhan, R. C. (2019). Preparation and quality evaluation of nutritionally enriched jam made from blends of Indian blackberry and other fruits. *International Journal of Fruit Science*, *19*(1), 29–44. https://doi.org/10.1080/15538362.2018.1536872

Gavillán-Suárez, J., Aguilar-Perez, A., Rivera-Ortiz, N., Rodríguez-Tirado, K., Figueroa-Cuilan, W., Morales-Santiago, L., Maldonado-Martínez, G., Cubano, L. A., & Martínez-Montemayor, M. M. (2015). Chemical profile and in vivo hypoglycemic effects of Syzygium jambos, Costus speciosus and Tapeinochilos ananassae plant extracts used as diabetes adjuvants in Puerto Rico. *BMC Complementary and Alternative Medicine*, *15*, 244. https://doi.org/10.1186/s12906-015-0772-7

Grenier, D., Chen, H., Lagha, A. Ben, Fournier-Larente, J., & Morin, M. P. (2015). Dual action of myricetin on Porphyromonas gingivalis and the inflammatory response of host cells: A promising therapeutic molecule for periodontal diseases. *PLoS ONE*, *10*(6), 1–14. https://doi.org/10.1371/journal.pone.0131758

Hooijmans, C. R., Rovers, M. M., De Vries, R. B. M., Leenaars, M., Ritskes-Hoitinga, M., & Langendam, M. W. (2014). SYRCLE's risk of bias tool for animal studies. *BMC Medical Research Methodology*, *14*(1), 1–9. https://doi.org/10.1186/1471-2288-14-43

IDF. (2021). IDF Diabetes Atlas. In *International Diabetes Federation* (10th ed.). https://doi.org/10.1016/j.diabres.2013.10.013

Ighodaro, O. M., Adeosun, A. M., Asejeje, F. O., Soetan, G. O., & Kassim, O. O. (2018). Time course effects of 5,5-dihydroxyl pyrimidine-2,4,6-trione (alloxan) as a diabetogenic agent in animal model. *Alexandria Journal of Medicine*, *54*(4), 705–710. https://doi.org/10.1016/j.ajme.2018.05.005

Kapoor, S., & Ranote, P. S. (2016). Antioxidant components and physico-chemical characteristics of jamun powder supplemented pear juice. *Journal of Food Science and Technology*, *53*(5), 2307–2316. https://doi.org/10.1007/s13197-016-2196-x

Karunakaran, U., Elumalai, S., Moon, J. S., Jeon, J. H., Kim, N. D., Park, K. G., Won, K. C., Leem, J., & Lee, I. K. (2019). Myricetin protects against high glucose-induced β-cell apoptosis by attenuating endoplasmic reticulum stress via inactivation of cyclin-dependent kinase

5. *Diabetes & Metabolism Journal*, *43*(2), 192–205. https://doi.org/10.4093/DMJ.2018.0052

Kumar Issac, P., Jayaseelan, A., Chandrakumar, S., Jaiganesh, S., Snehaa Chandrakumar, S., & Sundaresan, S. (2018). Tannins of Jatropha Gossypifolia exert anti-hyperlipidemic effect in streptozotocin-nicotinamide induced diabetic rats. *European Journal of Biomedical AND Pharmaceutical Sciences*, *5*(2), 607–614.

Kwon, D. Y., Kim, Y. S., Ryu, S. Y., Choi, Y. H., Cha, M. R., Yang, H. J., & Park, S. (2012). Platyconic acid, a saponin from Platycodi radix, improves glucose homeostasis by enhancing insulin sensitivity in vitro and in vivo. *European Journal of Nutrition*, *51*(5), 529–540. https://doi.org/10.1007/s00394-011-0236-x

Liu, Y., Mu, S., Chen, W., Liu, S., Cong, Y., Liu, J., & Jia, N. (2021). Saponins of Momordica charantia increase insulin secretion in INS-1 pancreatic β-cells via the PI3K/Akt/FoxO1 signaling pathway. *Endocrinología, Diabetes y Nutrición*, *68*(5), 329–337. https://doi.org/10.1016/J.ENDINU.2020.05.005

Mandal, S. K., Das, A., Devkota, H. P., & Das, N. (2023). *Chapter 38 - Syzygium cumini (L.) Skeels.* (T. Belwal, I. Bhatt, & H. B. T.-H. F. and B. Devkota (eds.); pp. 403–418). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-323-85591-4.00001-5

Mohamed, A. A., Ali, S. I., & El-Baz, F. K. (2013). Antioxidant and antibacterial activities of crude extracts and essential oils of Syzygium cumini leaves. *PLoS ONE*, *8*(4). https://doi.org/10.1371/journal.pone.0060269

Moini, J., Adams, M., & LoGalbo, A. (2022). *Complications of Diabetes Mellitus: A Global Perspective* (1st Editio). CRC Press. https://doi.org/https://doi.org/10.1201/9781003226727

Nadig, P., Asanaliyar, M., & Salis, K. M. (2021). Establishment of long-term high-fat diet and low dose streptozotocin-induced experimental type-2 diabetes mellitus model of insulin resistance and evaluation of seed extracts of Syzygium cumini. *Journal of HerbMed Pharmacology*, *10*(3), 331–338. https://doi.org/10.34172/jhp.2021.38

Narmatha, M., & Maneemegalai, S. (2019). An In-Vitro Study of Syzygium cumini Seed Extract on Glucose Uptake Activity in L-6 Cell Lines. *Journal of Drug Delivery and Therapeutics*, *9*, 256–259.

Nugroho AE, Anas Y, Arsito PN, Wibowo JT, Riyanto S, Sukari MA. 2011, Effects of marmin, a compound isolated from Aegle marmelos Correa, on contraction of the guinea pig-isolated trachea. *Pak J Pharm Sci*., 24(4):427-433.

Oecd. (2001). *OECD/OCDE 423 OECD Guideline for Testing of Chemicals Acute Oral Toxicity-Acute Toxic Class Method*.

Oguntibeju, O. O., Aboua, Y., & Kachepe, P. (2020). Possible therapeutic effects of vindoline on testicular and epididymal function in diabetes-induced oxidative stress male Wistar rats. *Heliyon*, *6*(4), e03817. https://doi.org/10.1016/j.heliyon.2020.e03817

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *The BMJ*, *372*. https://doi.org/10.1136/bmj.n71

Pant, D. R., Pant, N. D., Saru, D. B., Yadav, U. N., & Khanal, D. P. (2017). Phytochemical screening and study of antioxidant, antimicrobial, antidiabetic, anti-inflammatory and analgesic activities of extracts from stem wood of pterocarpus marsupium roxburgh. *Journal of Intercultural Ethnopharmacology*, *6*(2), 170–176. https://doi.org/10.5455/jice.20170403094055

Patil, S. S., Thorat, R. M., & Rajasekaran, P. (2012). Utilization of Jamun Fruit (Syzygium cumini) for production of red wine. *Journal of Advanced Laboratory Research in Biology*, *2*(2), 200–203.

Pereira, A. P. A., Fernando Figueiredo Angolini, C., de Souza-Sporkens, J. C., da Silva, T. A., Coutinho Franco de Oliveira, H., & Pastore, G. M. (2021). Brazilian sunberry (Solanum oocarpum Sendtn): Alkaloid composition and improvement of mitochondrial functionality and insulin secretion of INS-1E cells. *Food Research International*, *148*(May),

110589. https://doi.org/10.1016/j.foodres.2021.110589

Polce, S. A., Burke, C., França, L. M., Kramer, B., Paes, A. M. de A., & Carrillo-Sepulveda, M. A. (2018). Ellagic acid alleviates hepatic oxidative stress and insulin resistance in diabetic female rats. *Nutrients*, *10*(5), 1–15. https://doi.org/10.3390/nu10050531

Prabakaran, K., & Shanmugave, G. (2018). Antidiabetic activity and phytochemical constituents of Syzygium cumini seeds in Puducherry region, South India. *International Journal of Pharmacognosy and Phytochemical Research*, *9*(07). https://doi.org/10.25258/phyto.v9i07.11168

Proma, N. M., Naima, J., Islam, M. R., Alam Papel, J., Rahman, M. M., & Hossain, M. K. (2018). Phytochemical constituents and antidiabetic properties of Syzygium Cumini Linn. Seed. *International Journal of Pharmaceutical Sciences and Research*, *9*(5), 1806. https://doi.org/10.13040/IJPSR.0975-8232.9(5).1806-14

Saifi, A., Chauhan, R., & Dwivedi, J. (2016). Assessment of the antidiabetic activity of Syzygium cumini (Linn.) Skeels in alloxan induced diabetic rats . *Research Journal of Pharmacology and Pharmacodynamics*, *8*(3), 91. https://doi.org/10.5958/2321-5836.2016.00017.3

Sampath, S., Narasimhan, A., Chinta, R., Nair, K. R. J., Khurana, A., Nayak, D., Kumar, A., & Karundevi, B. (2013). Effect of homeopathic preparations of Syzygium jambolanum and Cephalandra indica on gastrocnemius muscle of high fat and high fructose-induced type-2 diabetic rats. *Homeopathy*, *102*(3), 160–171. https://doi.org/10.1016/j.homp.2013.05.002

Sanches, J. R., França, L. M., Chagas, V. T., Gaspar, R. S., Dos Santos, K. A., Gonçalves, L. M., Sloboda, D. M., Holloway, A. C., Dutra, R. P., Carneiro, E. M., Cappelli, A. P. G., & Paes, A. M. de A. (2016). Polyphenol-rich extract of Syzygium cumini leaf dually improves peripheral insulin sensitivity and pancreatic islet function in monosodium L-glutamate-Induced Obese Rats. *Frontiers in Pharmacology*, *7*, 48. https://doi.org/10.3389/fphar.2016.00048

Sari, A. N., Januardi, J., & Diningrat, D. S. (2020). Effect of ethanol extract of Jamblang Aceh (Syzygium cumini) in diabetic mice (Mus musculus) and its potential as anti-diabetic agent. *Elkawnie*, *6*(1), 37. https://doi.org/10.22373/ekw.v6i1.5496

Sharma, B., Siddiqui, M. S., Kumar, S. S., Ram, G., & Chaudhary, M. (2013). Liver protective effects of aqueous extract of Syzygium cumini in Swiss albino mice on alloxan induced diabetes mellitus. *Journal of Pharmacy Research*, *6*(8), 853–858. https://doi.org/https://doi.org/10.1016/j.jopr.2013.07.020

Sharma, B., Siddiqui, M. S., Kumar, S. S., Ram, G., & Chaudhary, M. (2017). Pharmacological evaluation of aqueous extract of syzigium cumini for its antihyperglycemic and antidyslipidemic properties in diabetic rats fed a high cholesterol diet-Role of PPARγ and PPARα. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, *89*, 447–453. https://doi.org/10.1016/j.biopha.2017.02.048

Sharma, B., Viswanath, G., Salunke, R., & Roy, P. (2008). Effects of flavonoid-rich extract from seeds of Eugenia jambolana (L.) on carbohydrate and lipid metabolism in diabetic mice. *Food Chemistry*, *110*(3), 697–705. https://doi.org/10.1016/j.foodchem.2008.02.068

Sharma, K. A., Bharti, S., Kumar, R., Krishnamurthy, B., Bhatia, J., Kumari, S., & Arya, D. S. (2012). Syzygium cumini ameliorates insulin resistance and β-cell dysfunction via modulation of PPAR, dyslipidemia, oxidative stress, and TNF-α in type 2 diabetic rats. *Journal of Pharmacological Sciences*, *119*(3), 205–213. https://doi.org/10.1254/jphs.11184fp

Shila, H. P. G., Darshna, N. G., & Patel, G. H. S. V. (2017). Antidiabetic and antioxidant functionality associated with phenolic constituents from fruit parts of indigenous black jamun (Syzygium cumini L .) landraces. *Journal of Food Science and Technology*, *54*(10), 3180–3191. https://doi.org/10.1007/s13197-017-2756-8

Shukla, A., & Srinivasan, B. P. (2012). 16,17-Dihydro-17b-hydroxy isomitraphylline alkaloid as an inhibitor of DPP-IV, and its effect on incretin hormone and β-cell

proliferation in diabetic rat. In *European Journal of Pharmaceutical Sciences* (Vol. 47, Issue 2, pp. 512–519). https://doi.org/10.1016/j.ejps.2012.07.012

Silva, S. do N., Abreu, I. C., Silva, G. F. C., Ribeiro, R. M., Lopes, A. de S., Cartágenes, M. do S. de S., Freire, S. M. de F., Borges, A. C. R., & Borges, M. O. da R. (2011). The toxicity evaluation of Syzygium cumini leaves in rodents. *Revista Brasileira de Farmacognosia*, *22*(1), 102–108. https://doi.org/10.1590/S0102-695X2011005000181

Stephen, A. (2012). *Syzygium cumini (L.) Skeels: A multipurpose tree, its phytotherapic and pharmacological uses*. 22–32. https://doi.org/6.2012/R-739-JPCOL

Syukri, Y., Martien, R., Lukitaningsih, E., Nugroho, A.E., 2016, Quantification of andrographolide isolated from Andrographis paniculata Nees obtained from traditional market in Yogyakarta using validated HPLC, Indones. J. Chem., 16(2):190-197.

Takemoto, K., Doi, W., & Masuoka, N. (2016). Protective effect of vitamin E against alloxan-induced mouse hyperglycemia. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1862*(4), 647–650. https://doi.org/10.1016/j.bbadis.2015.12.022

Tara, J., Shrestha, M., Shrestha, H., Prajapati, M., Karkee, A., & Maharjan, A. (2017). Adverse Effects of oral hypoglycemic agents and adherence to them among patients with Type 2 diabetes mellitus in Nepal. *Journal of Lumbini Medical College*, *5*(1), 34–40. https://doi.org/10.22502/JLMC.V5I1.126

Tripathi, A. K., & Kohli, S. (2014). Pharmacognostical standardization and antidiabetic activity of Syzygium cumini (Linn.) barks (Myrtaceae) on streptozotocin-induced diabetic rats. *Journal of Complementary and Integrative Medicine*, *11*(2), 71–81. https://doi.org/10.1515/jcim-2014-0011

Velayutham, R., Sankaradoss, N., & Ahamed, K. N. (2012). Protective effect of tannins from Ficus racemosa in hypercholesterolemia and diabetes induced vascular tissue damage in rats. *Asian Pacific Journal of Tropical Medicine*, *5*(5), 367–373. https://doi.org/10.1016/S1995-7645(12)60061-3

Wang, Q., Wang, S. ting, Yang, X., You, P. pan, & Zhang, W. (2015). Myricetin suppresses differentiation of 3 T3-L1 preadipocytes and enhances lipolysis in adipocytes. *Nutrition Research*, *35*(4), 317–327. https://doi.org/10.1016/j.nutres.2014.12.009

Wells, B. G., DiPiro, J. T., Schwinghammer, T. L., & DiPiro, C. V. (2015). *Pharmacotherapy Handbook: Ninth Edition*. *ninth*.

Xu, J., Liu, T., Li, Y., Yuan, C., Ma, H., Seeram, N. P., Liu, F., Mu, Y., Huang, X., & Li, L. (2018). Hypoglycemic and hypolipidemic effects of triterpenoid-enriched Jamun (: Eugenia jambolana Lam.) fruit extract in streptozotocin-induced type 1 diabetic mice. *Food and Function*, *9*(6), 3330–3337. https://doi.org/10.1039/c8fo00095f

Xu, J., Wang, S., Feng, T., Chen, Y., & Yang, G. (2018). Hypoglycemic and hypolipidemic effects of total saponins from Stauntonia chinensis in diabetic db/db mice. *Journal of Cellular and Molecular Medicine*, *22*(12), 6026–6038. https://doi.org/10.1111/jcmm.13876

Yadav, M., Lavania, A., Tomar, R., Prasad, G. B. K. S., Jain, S., & Yadav, H. (2010). Complementary and comparative study on hypoglycemic and antihyperglycemic activity of various extracts of Eugenia jambolana seed, Momordica charantia fruits, Gymnema sylvestre, and Trigonella foenum graecum seeds in rats. *Applied Biochemistry and Biotechnology*, *160*(8), 2388–2400. https://doi.org/10.1007/s12010-009-8799-1

Yasodamma, N., & Alekhya, C. (2013). Antidiabetic Activity of Sebastiania chamaelea Muell. Arg. leaf extracts in alloxan induced diabetic albino rats. *International Journal of Pharmacy and Pharmaceutical Sciences*, *5*(3), 577–583.

Yessoufou, A., Gbenou, J., Grissa, O., Hichami, A., Simonin, A. M., Tabka, Z., Moudachirou, M., Moutairou, K., & Khan, N. A. (2013). Anti-hyperglycemic effects of three medicinal plants in diabetic pregnancy: Modulation of T cell proliferation. *BMC Complementary and Alternative Medicine*, *13*. https://doi.org/10.1186/1472-6882-13-77

Zhang, H., Hui, J., Yang, J., Deng, J., & Fan, D. (2020). Eurocristatine, a plant alkaloid from Eurotium cristatum, alleviates insulin resistance in db/db diabetic mice via activation of PI3K/AKT signaling pathway. *European Journal of Pharmacology*,

887(September), 173557. https://doi.org/10.1016/j.ejphar.2020.173557

Zheng, B., Su, B., Price, G., Tzoulaki, I., Ahmadi-Abhari, S., & Middleton, L. (2021). Glycemic control, diabetic complications, and risk of dementia in patients with diabetes: Results from a large U.K. cohort study. *Diabetes Care*, *44*(7), 1556–1563. https://doi.org/10.2337/dc20-2850