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REVIEW ARTICLE

Antidiabetic Property of *Muntingia calabura*: A Review.

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Abstract

Muntingia calabura (*M. calabura*) plant is known to possess various medicinal values, and numerous scientific studies have supported its pharmacological properties. It has been extensively documented that *M. calabura* has antidiabetic properties. Therefore, this review aims to gather all information related to the antidiabetic activity of *M. calabura* and present it as a comprehensive review article. Literature has been retrieved from several databases, such as Google Scholar, Research Gate, Wiley, Science Direct, National Center for Biotechnology Information (NCBI), Pubmed, and Springer Link. In this review, several papers will be referred to, including *in vitro* studies (α-glucosidase, α-amylase and dipeptidyl peptidase-IV (DPP-IV)), *in vivo* studies (animal induced with streptozotocin (STZ) and alloxan), and studies on bioactive compounds of the *M. calabura* plant. From the review, *M. calabura* extracts were reported to have a significant effect on antidiabetic activity due to the presence of compounds with high antioxidant activity, such as flavonoids and phenolic acids. Furthermore, the bioactive compounds that possess significant antidiabetic activity were identified. Hence, this plant was concluded to have an important role in future drug development for antidiabetic purposes, and future studies by other researchers can be more accessible by referring to this presented review paper.

Keywords: *alloxan, alpha-amylase, alpha-glucosidase, streptozotocin, Muntingia calabura.*

Introduction

Diabetes mellitus (DM) is a complex metabolic disorder of glucose metabolism [1]. The ability to maintain the blood glucose level (BGL) is the ey factor in managing this disorder. DM can disrupt the fat, protein, and carbohydrate metabolism, leading to micro-and macrovascular complications. Furthermore, DM can be either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). T1DM is characterized by insulin insufficiency, and is a chronic illness resulting from the loss of pancreatic β-cells, and leading to hyperglycemia as a secondary consequence [2].

Meanwhile, T2DM is characterized by a reduction of insulin production caused by β-cell dysfunction. [3]. Despite being the primary energy source for the human body, an excess of glucose in the bloodstream can be extremely damaging and lead to well-known consequences of DM. Globally, DM affects 5% of the population, and World Health Organization (WHO) predicts that around 380 million people will be diagnosed with diabetes in the future [4]. Prevalence of diabetes in Malaysia has increased drastically from 13.4% in 2015 to 18.3% in 2019 [5]. This increase is attributed to factors such as lifestyle, geographical locations and lack of dietary habits.

Currently, the treatment for T1DM involves lifelong insulin administration, while lifestyle modifications with additional medications such as metformin serve as the first-line treatment for T2DM [6,7]. However, if glycaemic control cannot be achieved, oral medicines, such as sulfonylureas, thiazolidinediones (TZDs, also known as glitazones), dipeptidyl peptidase-IV (DPP-IV) inhibitors, sodium-glucose cotransporter 2 (SGLT-2) inhibitor, α-glucosidase inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are used. The final therapeutic options include amylin antioxidants, growth factors, bile acid sequestrants, dopamine agonists, and analogues.

The current antidiabetic drug therapies are mostly reported to have side effects. The side effects include diarrhoea, lactic acidosis and abdominal cramps, as reported by Barella et al. [8], after consuming metformin. In addition, diabetic patients often reported problems such as hypertension and hyperuricemia [9]. These limitations have initiated the attempt to explore management strategies that involve the exploration of medicinal plants because they are cost-effective and reported to have fewer side effects. Globally, plants that possess medicinal properties have been widely discovered and explored for therapeutic use. Tafesse et al. [10], have reported that about 80–85% of populations rely on medicinal usage of the plants to ensure their primary health care is in excellent condition. *M. calabura*, known as "Jamaican cherry," is a medicinal plant of significant interests to researchers. It is a species of the American continent, widely cultivated in warm areas in Asia. Researchers have taken an interest in its antidiabetic activity to regulate hyperglycemia in diabetic patients. Traditionally, the plant has been reported for its pharmacological properties such as antioxidant [11], anti-bacterial [12], cardioprotective effects [13], antiproliferative [14], antinociceptive [15, 16, 17], anti-inflammatory [18, 19], and antidiabetic [15].

This paper aims to review the antidiabetic properties of *M. calabura,* with the goal of encouraging further research on its potential benefits for diabetes and other pharmacological properties. Therefore, this review will provide comprehensive information on the plant's antidiabetic activity, offering insights for future research focused on discovering novel antidiabetic compounds from the plant.

Muntingia calabura

Botanical aspect

M. calabura (Figure 1) is a plant that grows rapidly, and the flowers are continuously blooming on fan-like branches. The height is

almost 7.5 to 12 m, with the branches evenly spreading, making it appear unique. The *M. calabura* leaves are evergreen and ranging from 5 to 12.5 cm in length. They are oblong or alternately lanceolate, pointed at the apex, with dark green colouring at the base and on the upper surface, with slight hairiness, and the undersides are light green. The flowers have five petals with white and yellow stamens in the centre. The fruits are numerous, round in shape, with a diameter of 1 to 1.25 cm, their colour varies by variety, appearing as red or yellow, and containing thousands of tiny seeds in the soft pulp [15].

Traditional uses

Based on previous research by Mahmood et al. [15], *M. calabura* is abundant and can be easily found along the roadside. The traditional uses of *M. calabura* in Malaysia are not widely known, and technically, this plant is categorized as a neglected plant. Although the traditional claims of this plant are lacking in Malaysia, there are several reports of this plant from other countries. Sarojini and Mounika [20] reported that in Peruvian folklore, there was significant interest in the traditional use of this plant. The plant alleviated lower extremities swelling, while barks and flowers were used as antiseptic agents. Additionally, the leaves were boiled or steeped in hot water to be consumed orally, to treat headaches and colds and reduce swelling of the prostate gland.

In Colombia, it was used as a tranquilizer and tonic from infusing the flowers. In the Philippines, the flowers were reported to be employed in the treatment of headaches, incipient colds, and as tranquilizers, antispasmodics and antidyspeptics [21]. Beyond medicinal use, the fruits can also be used as a condiment for making jam and as filling in pastry items [22].

Antidiabetic activity of *M. calabura*

In vitro studies

There are few enzymes involved in glucose regulation which inhibit or decrease carbohydrate metabolism. In 2015, α-glucosidase inhibitory activity in rats' intestines was reported by Adam et al. [23], by using methanolic extract of *M. calabura* leaves (MEMCL) and aqueous extract of *M. calabura* leaves (AEMCL) extracts. The results showed extracts of *M. calabura* inhibited α-glucosidase activity in the rats' intestines with IC_{50} values of 0.88±0.60 mg/mL and 1.45±0.19 mg/mL, respectively. The results indicate the plant's ability to slow down glucose absorption from the small intestine, thereby reducing hyperglycaemia.

In 2018, Nor Azman et al. [24], discovered potential α-glucosidase inhibitors from 16 extracts of *M. calabura* as a therapeutic approach to reducing postprandial hyperglycemia. This study used the leaves, fruits, stems and roots of M. *calabura,* collected from Bangi, Selangor, Malaysia. The extracts were prepared in hexane, ethyl acetate, 75% ethanol, and aqueous for all parts of the plant. The inhibition of α-glucosidase activity was screened at 50.00, 25.00, 12.50, 6.25, 3.13, 1.56, and 0.56 ppm. These concentrations were prepared by two-fold serial dilution. Acarbose served as positive control in this study. The results revealed that the aqueous leaf and aqueous root extracts of *M. calabura* exhibited the most potent inhibition of α-glucosidase as the IC_{50} values recorded were 0.15 and 0.41 μg/mL, respectively, compared to acarbose, which had IC_{50} value of 4.3 μg/mL.

On the other hand, Setyaningsih et al. [25] reported a study demonstrating an appreciable inhibitory activity in 10 plant samples, including *M. calabura* collected from Kebun Raya Bogor, Indonesia. Different plant parts were extracted and analyzed for their dipeptidyl peptidase-IV (DPP-IV) inhibitory activity. The results indicated that the ethanolic extract of *M. calabura* leaves has the potencial in inhibiting the DPP-IV enzyme with an inhibitory percentage of 74.12%. In comparison, the inhibition of DPP-IV for the positive control (sitagliptin) was 85.18%.

Panneerselvam et al. [26] claimed that *M. calabura* may have more significant potential in antidiabetic activity by studying the inhibition of α-glucosidase and α-amylase enzymes. The

leaves of *M. calabura* were obtained from Park, Chennai, and the extraction was carried out using petroleum ether, chloroform, methanol and water as the solvent. From the results obtained, the minimum α-amylase inhibitory activity of *M. calabura* leaves extract was 93.75% (at 20µg/mL), while the maximum was 61.93±0.21 (at 100g/mL). The result for acarbose (the standard drug) was 273.5% (at 20µg/mL) for minimum and 71.29% (at 100µg/mL) for maximum. The results also showed that MEMCL reported the second-highest inhibition of α-amylase compared to acarbose, which exhibited the highest inhibition. Consequently, MEMCL was estimated to exhibit 80% α-amylase activity. The numerical results for inhibition of α-glucosidase in *M. calabura* leaves extracts were not provided, but based on the figures provided, MEMCL showed the second-highest inhibition of α-glucosidase, followed by the chloroform and aqueous extracts, which were considered to exhibit moderate inhibition of α-glucosidase. The petroleum ether extracts showed the lowest inhibition compared to acarbose. Thus, MEMCL was concluded to exhibit 60% of α-glucosidase activity based on the results.

In vivo studies

The leaves of *M. calabura* were collected from the Roman Catholic Church, Station Ghanpur, Warangal, Andhra Pradesh, India, and methanol was used to extract the leaves using the maceration technique [27]. The study observed the effect of 500 mg/kg body weight (BW) of MEMCL on the oral glucose tolerance test (OGTT) in rats. The results obtained showed that 500 mg/kg BW of MEMCL reduced the blood glucose levels (BGL) to the normal level within 90 min (from 128.54 mg/dL at 30 min to 79.82 mg/dL at 120 min) compared to the standard group, which reduced the BGL to the normal level within 30 min (from 93.23 mg/dL at 30 min to 72.09 mg/dL at 60 min) [27]. Following the extract administration, BGL was measured at 2, 4, 6, and 8 hours to investigate the hypoglycaemic action in euglycemic rats. At 6 h, the MEMCL dose of 500 mg/kg BW reduced BGL significantly from 83.19 mg/dL at 0 hr to 62.62 mg/dL at 6 hr. As for the standard group, the results also showed a significant reduction in BGL from 79.56 mg/dL at 0 hr to 62.15 mg/dL at 2 hr.

In another study, the fruit of *M. calabura* was evaluated for its antidiabetic potential. The *M. calabura* fruits were procured in Indonesia's Kabupaten, Klaten, and the fruit extract was produced by extracting the fruits using 70% ethanol. The rats were given 100, 200, and 400 mg/kg BW of ethanol extract of *M. calabura* fruits (EEMCF) for four consecutive weeks. At the end of the treatment in week 4, the control diabetic rats showed increased BGL. In comparison, the extract-treated groups showed a significant reduction in their BGL. Furthermore, EEMCF with the dose of 100 mg/kg was reported to be the most potent dose for antidiabetic activity as it can reduce the glucose level from 513 mg/dL (week 2) to 109 mg/dL (week 4) [28].

Busman et al. [29] reported the leaves of *M. calabura* have the potential to increase cecum microbiota by influencing the total coliforms and lactic acid bacteria in the gut and can improve pancreatic cell damage by increasing the number of normal pancreatic cells. The study was conducted on alloxan-induced hyperglycaemic rats with the alloxan administration dose of 160 mg/kg BW. The ethanol extract of *M. calabura* leaves (EEMCL) with doses of 300, 400, or 500 mg/kg BW was given for 14 days. The results revealed that the groups administered with the *M. calabura* extract were able to mitigate the pancreatic cell damage. The group treatment of 500 mg/kg BW of *M. calabura* leaves extract showed the most significant results, with an abundant number of normal pancreatic cells. Thus, the study concluded that *M. calabura* can be a natural treatment option for recovering from pancreatic cell damage.

The effectiveness of AEMCL in treating diabetes was examined by Aligita et al. [30] using two animal models: insulin deficiency and insulin-resistant models. *M. calabura* leaves were sourced from Bumi Herbal, Bandung, Indonesia,

and subjected to aqueous extraction. The parameters observed were fasting blood glucose (FBG) levels for insulin deficiency models and values of constant insulin tolerance (KITT) for insulin-resistant models. The insulin deficiency model, diabetes was induced by administering alloxan at a dose of 50 mg/kg intravenously. For the insulin resistance model, lipid emulsion was administered orally at a dose of 0.42 mL/2g. The animals were divided into six groups (I, II, III, IV, V, and VI). Group I served as the negative control (not induced by alloxan or lipid emulsion), group II as the diabetic control (induced but received no treatment), and group III served as the positive control, treated with 0.65 mg/kg glibenclamide (insulin deficiency model) and 135 mg/kg metformin (insulin resistance model). Group IV, V and VI received extract doses of 100, 200, and 400 mg/kg, respectively. The treatment spanned for 14 consecutive days. The insulin deficiency model measured the FBG on days 3, 7, 11 and 14. Then, two mice from each group were randomly selected to be sacrificed, and the pancreatic organ was isolated for histologic observation. Meanwhile, for insulin resistance models, the values of KITT of insulin sensitivity before, after, and after treatment were measured and analyzed. Consequently, insulin deficiency models showed that the higher the dose, the more significant the decrease in FBG. From the results, the FBG changes for groups IV, V and VI on day 14 were 13%, 22% and 29%, respectively, as compared to group III (glibenclamide group). The FBG changes on day 14 was 43%. However, in this study, they reported that all the treatment groups had reduced the FBG, but all groups had not reached normal levels yet. Thus, only group VI claimed to have the same activity as group III. Lastly, for insulin resistance models, the results revealed that administering lipid emulsion at a dose of 0.42 mL/20g affected the value of KITT in all groups. Before induction, the KITT value was between 1.48 - 2.00, but after induction, the KITT value was reduced to the range between 0.14 - 0.21. Then, after 14 days, the KITT value of the metformin group was increased (from 0.21 - 2.91), similar to the extract group with a dose of 200 (from 0.09 - 1.57) and 400 (from 0.14 - 2.31) mg/kg BW. It was postulated that only the extract group receiving a 400 mg/kg dose had the same efficacy as metformin. Hence, the study concluded that *M. calabura* leaves extract could enhance insulin sensitivity in the insulin resistance model.

The antidiabetic activity of EEMCL also agreed with the study conducted by Herlina et al. [31]. *M. calabura* leaves were extracted using 20 % ethanol and maceration as an extraction method. In this study, the rats were divided into six groups, and they were diabetic-induced using alloxan (130 mg/kg). Group 1 acts as a control group and was given a normal diet. Group 2 served as the negative control and received 0.5% CMC Na solution; meanwhile, group 3 served as the positive control, receiving 0.43 mg/200g of glibenclamide. Lastly, groups 4, 5, and 6 were given EEMCL at doses of 65, 130 and 260 mg/kg BW. The parameters used in this study were the value of area under the curve (AUC), the percentage of decrease in BGL (% DBGL), and effective dose 50 (ED_{50}). The value of AUC_{0-15} was used to calculate the changes in BGL from day 0 to day 15. Theoretically, decreasing the AUC value of the treatment group, the better the activity in lowering BGL. The ED_{50} can also be calculated by using linear regression between dose and % DBGL. From the results, all the groups except the control group showed adaptation of DM as the BGL increased dramatically after administration of alloxan. Other than that, the results showed the average AUC_{0-15} of the negative control is the highest (4367.5) due to no treatment given to this group as compared to the positive control, the average AUC0-15 is 2732.5 while the average AUC_{0-15} of groups 4, 5, and 6 were 3105.0, 2962.5, and 2810.00 respectively. The % DBGL for groups 4, 5, and 6 were 28.9%, 32.16% and 35.66%, respectively, while the % DBGL for positive control was 37.43%. Lastly, the results revealed that the effective dose of EEMCL was 692.42 mg/kg. This showed that EEMCL has potency in

the antidiabetic study due to the results giving a significant effect, same as a positive control group.

Yemineni et al. [32], performed a study on STZ-induced diabetes mice to evaluate the hypoglycaemic activity of methanol extract of *M. calabura* stem bark (MEMCSB). The rats were split into four groups, where group I and group II were normoglycemic and negative control rats, respectively. Groups III and IV served as the treatment groups, receiving doses of the extract of 250 and 500 mg/kg BW, respectively. It was revealed that MEMCSB reduced BGL significantly in a dose-dependent manner in groups III and IV compared to the control. Before therapy, the BGL for groups III and IV were 102.83 and 103.33 mg/dL, respectively. The BGL levels in rats after 120 minutes of administration with the extract were 85.66 mg/dL and 77.16 mg/dL, respectively.

Phytochemical compounds in *M. calabura*

Table 1 provides a summary of the phytochemical components reported from different parts of *M. calabura*, sourced from 2003 to 2023. The leaves extract of *M. calabura* was analyzed, and the phytoconstituents were identified using nuclear magnetic resonance (NMR). From this study, methanol extract was partitioned into ethyl acetate and twenty-five bioactive compounds were identified, including one new flavanone, which was (2R,3R)-7-methoxy-3,5,8trihydroxyflavanone [33]. Chen et al. [34] further investigated the chemical constituents of *M. calabura* leaves extracted using methanol and identified twenty flavonoids using NMR [34].

Apart from the leaves, the fruits of *M. calabura* were also extracted and isolated for their potential metabolites. The fruit was collected from Indonesia and extracted with aqueous water. The four bioactive compounds isolated were previously reported to possess antidiabetic effects [35]. Gomathi et al. [36] conducted a study on *M. calabura* fruits collected from India. Powdered fruits of *M. calabura* were extracted by a mixture of solvents consisting of acetone, methanol, and water, which were then analyzed using GCMS. The most abundant compounds found in the extract were terpenes (phytol), followed by carboxylic acids, isoprenoids, phenolic acids and flavonoids.

In another study by Yusuf et al. [37], the extract of *M. calabura* leaves collected from Selangor, Malaysia, was subjected to LCMS and NMR analysis. About four compounds were isolated from the petroleum ether fraction partitioned from the crude methanol extract. The compounds were identified as flavonoids. Similarly, Sufian et al. [38], carried out isolation works using the leaves of *M. calabura* obtained from the same location [37]. The powdered leaves were extracted by methanol, which was then partitioned into ethyl acetate and further purification was done using vacuum liquid chromatography and radial chromatography. Then, the leaves extracts were successfully identified using ^{1}H and ^{13}C-NMR. The compounds were confirmed as flavonoids.

An investigation by Zakaria et al. [39], identified four compounds from the leaves' methanol extract using high-performance liquid chromatography (HPLC), which corresponds to the phytochemical screening carried out consisting of triterpenes, flavonoids, tannins, and saponins were present in the leaves extract of *M. calabura*.

In addition, Kuo et al. [40] have evaluated the stem woods of *M. calabura,* which were obtained from Taiwan. The stem wood was crushed and extracted with methanol, which then parted into dichloromethane. The identified compounds from the NMR analysis with the most abundant phytochemical constituents were confirmed to be flavonoids.

Ragasa et al. [41] have evaluated the chemical constituents from the fruits of *M. calabura*. The fruits were collected from San Pedro, Laguna and extracted using dichloromethane. Based on the results, four compounds were identified using NMR. The study reported that the predominantly phytochemical constituents present in the fruits of *M. calabura* extracts were terpenoids and fatty acids. The GCMS analysis revealed that

flavonoids were among the major compound classes identified via the instrument observed in this study [42]. Next, a study in 2017 was conducted by Lin et al. [43] using *M. calabura* fruits collected from Kaohsiung, Taiwan. The fruits were extracted with ethanol and identified using HPLC.

Pereira et al. [44] evaluated the bioactive compounds present in the fruits of *M. calabura* and its antioxidant activity. The fruit was collected from various trees of *M. calabura* in Campinas, Brazil. The extract was analysed to detect carbohydrates in the *M. calabura* fruits, and the results showed the presence of carbohydrates. The volatile constituents were detected using GCMS, with terpenes found to be most abundant. Apart from that, analysis by UHPLC-MS revealed the presence of main phenolic acids. The study's outcome suggests that *M. calabura* possesses significant antioxidant potential reflected by high phenolic compounds.

The UHPLC-MS analysis by Zakaria et al. [45] displayed compounds prominently consisting of phenolic acids. Apart from that, when extracts were analyzed using GCMS, eight flavonoids were identified [45]. The phytochemical profile of dried leaves using three different drying methods, namely freeze-drying, drying and air-drying, were investigated. Each of the respective dried leaves was extracted using an ultrasonic bath sonicator followed by chromatographic analysis using ultrahigh performance liquid chromatography–electrospray ionization tandem mass spectrometry (UHPLC-ESI-MS/MS) [46]. The ethyl acetate fractions of *M. calabura* leaves were further partitioned to afford n-hexane, chloroform, and ethyl acetate fractions and analysed for its phytochemical constituents using GCMS [47].

A recent investigation was conducted in 2023 by Nur et al. [48] to standardize *M. calabura* fruits collected from various locations in South Sulawesi Province, Indonesia. The fruits were extracted using the ultrasonic method. The results of the GCMS analysis obtained 36 compounds belonging to the benzoate, phenolic, alkaloid, terpenoid, steroid, and fatty acid ester groups.

Most of the reported studies have shown that the extract of *M. calabura* possesses antidiabetic activity via enzyme inhibition in the mechanism of DM and lowering the BGL in the diabetes-induced animal models. In the *in vitro* studies, *M. calabura* exerted inhibition of α-glucosidase, α-amylase, and DPP-IV enzymes. On the other hand, in the *in vivo* studies, *M. calabura* showed antidiabetic activity by lowering the BGL in rats induced by STZ or alloxan.

The significant antidiabetic potential exerted by *M. calabura* could be due to its high antioxidant activity. Plants containing flavonoids have potent antioxidant activity and can be the ideal method for treating DM [49]. The function of antioxidant agents is to protect from the deleterious effects of hyperglycemia and also benefit glucose metabolism [50].

M. calabura is a plant rich in antioxidants. This is proven by many studies carried out by the researchers. For example, an investigation by Vijayanand and Thomas [51], using *M. calabura* fruit extracts, determined the antioxidant capacity by measuring the Cupric Ion Reducing Antioxidant Capacity (CUPRAC), Ferric Ion Reducing Antioxidant Power (FRAP) and total phenolic content (TPC) values. The extracts were prepared using various solvents, including water, chloroform, methanol and ethanol. The results of TPC were only available for CEMCF, which was 3.8 μg. As for the CUPRAC assay, EEMCF showed the highest (55.6%), followed by MEMCF (44.4%). Meanwhile, in the FRAP assay, CEMCF showed the highest percentage (70%), followed by MEMCF, which was the second highest (50%). Hence, *M. calabura* extract was indicated to have potency in antioxidant activity. Not only that, the recent study by Pereira et al. [44], reported flavonoid compounds present in the fruits of *M. calabura*, such as quercetin, naringenin, epigallocatechin, gallocatechin, and catechin, were reported to have the highest antioxidant activity. High antioxidant activity was also believed related to the synergistic effect

between the phenolic acids and flavonoids. A study by Unuofin and Lebelo, [52], reported that compounds derived from such as phenolic compounds (flavonoids and phenolic acids) were involved in the development of T2DM by activation of AMP-activated protein kinase (AMPK) pathways and restrain the activation of nuclear transcription factor-kappa B (NF-kB) pathways which caused improved intolerance towards glucose and the sensitivity of insulin.

In addition, *M. calabura* extracts were reported to contain many phytochemicals, including flavonoids, saponins, triterpenes and tannins [39].. Flavonoids were believed to reduce BGL by improving the secretion of insulin, and they also can promote the proliferation of pancreatic β-cells [53]. Furthermore, diabetic pathways involve different kinds of enzymes having their specific role or function in the progression of the disease. They are involved in the pathogenesis of the disease, control and modulate auto-phosphorylation of insulin receptors, and uptake of glucose-by-glucose transporter type 4 (GLUT4), as stated by Kitada et al. [54]. Apart from that, flavonoids also can promote GLUT4. Hence, the extract of *M. calabura* was proven to have antidiabetic activity. Additionally, flavonoids contribute to antioxidative effects by acting as biological targets in T2DM, such as α-glycosidase and DPP-IV enzymes [55]. Therefore, as the plant contains flavonoids, it can be a radical scavenger to prevent and manage T2DM.

Several compounds from the list in Table 1 were reported to have antidiabetic activity. Among them are quercetin, kaempferol, catechin, thiamine, ascorbic acid, riboflavin, rutin, naringenin, chrysin, and βsitosterol [56–58].

Quercetin is classified as flavonol. It is stated that quercetin plays an important role in the regulation of hepatic gene expression and lipid metabolism. Additionally, quercetin stimulates glucose uptake through a MAPK (mitogen-activated protein kinase) insulin-dependent [58,59].

Kaempferol is also classified as flavonol. The mechanism of action of kaempferol is the activation of AMPK and a decrease in serum levels of both tumour necrosis factor-α (TNF-a) and C-reactive protein (CRP) [56]. This showed that kaempferol has a mechanism similar to metformin, where AMPK is a major cellular regulator of lipid and glucose mechanisms [60].

Catechin is under the class of flavanol. It is usually present in green tea, chocolate, beans and cherry [56]. According to Fu et al. [61], due to the presence of catechin and other antidiabetic compounds in green tea, the study reported that tea and its extract possess an antidiabetic activity by reducing oxidative stress, inhibiting α-glucosidase and α-amylase activities.

Ascorbic acid, also known as vitamin C, is a water-soluble antioxidant. As an antioxidant, this compound acts as a biomarker of oxidative stress. Oxidative stress occurs in T2DM due to redox imbalance, glucose autoxidation and reduced activity of antioxidant enzymes. Additionally, ascorbic acid helps in the pathway glucose ascorbate antagonism, in which glucose and ascorbate need support from insulin before penetrating the cell membrane. Glucose and ascorbate also will compete with each other. Therefore, intake of ascorbic acid or vitamin C is important for better control of diabetes [62].

Thiamine, also called vitamin B1, is found in many foods such as meat, nuts, beans, and yeast. It also acts as a coenzyme for the pyruvate dehydrogenase, transketolase (Tk) and α-ketoglutarate dehydrogenase complex enzymes. These enzymes play important roles in glucose metabolism and are reported to improve DM conditions [63].

Riboflavin is vitamin B_2, a soluble water vitamin easily found in plants, grains, and dairy products. Riboflavin is important for the intermediary metabolism of carbohydrates, lipids, and amino acids, and it can support antioxidant cellular activity. It is also reported that riboflavin in the diabetic condition of mice, riboflavin can alter lipid peroxidation, antioxidant levels, protein carbonylation and tissue damage by reducing reactive oxygen species (ROS). Therefore, it also causes a reduction in hyperglycemia by

improving the absorption of sugar from the intestine [64].

Rutin is classified as flavonol, and the scientific name is 3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucoside [65]. Rutin was reported to have potency in reducing BGL of STZ-induced diabetes animal models. The study also observed a significant improvement in pancreatic islets cells in treated animals [66]. It is also reported to regulate the glucose uptake in the muscle, hence maintaining the glucose concentration in the blood [67].

Naringenin was reported to have antidiabetic properties by reducing BGL in animal models. It is stated that naringenin enhances the GLUT1, which causes the BGL to decrease. In addition, the treated animals also show significant improvement in the stimulation of AMPK and cause an increment in insulin sensitivity [68].

Chrysin, also known as 5, 7-dihydroxyflavone, is a flavonoid that naturally synthesized in vegetables and fruits. According to Ahad et al. [69], chrysin was administered to the animal models which STZ has induced. It is reported to diminish the TNF-α expression in the renal, and the activation of NF-kB was suppressed [69].

The β-sitosterol is classified as steroids under a subgroup of phytosterols and can be produced from stigmasterol [70]. β-sitosterol was reported to reduce BGL in STZ-induced diabetes. In animal models, β-sitosterol can also lower nitric oxide (NO) and HbA1c, and it also improves insulin levels.[71].

In a nutshell, it could be deduced that the antidiabetic activity possessed by *M. calabura* could be due to the presence of various phytochemicals, with the major one being the flavonoids. On the other hand, *M. calabura* is also rich in antioxidants and radical scavenging properties, which could also contribute to the antidiabetic activity of the plant. In addition, several bioactive compounds have been identified in the plant. Thus, the synergistic effect of the bioactive compounds could also be another reason for the significant antidiabetic activity exerted by *M. calabura*.

Discussion

Previous studies have successfully demonstrated the antidiabetic activity of *M. calabura* by evaluating the *in vitro* and *in vivo* studies. To ensure long-term safety in its use, toxicology tests on the plant extract could be further investigated. Additionally, the metabolic studies of the plant extract should be conducted to uncover the underlying metabolic processes involved.

Conclusion

In conclusion, the antidiabetic activity of *M. calabura* extract has been explored in this review. I*n vitro* studies have shown a significant effect, exerting potent α-glucosidase, α-amylase, and DPP-IV inhibitory activity. As for the *in vivo* studies, the results also demonstrated that the extract of *M. calabura* significantly reduces BGL in animal models with induced diabetes. Furthermore, bioactive compounds with significant antidiabetic activity were successfully identified. Therefore, it is clear that *M. calabura* plants have the potential for antidiabetic activity.

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Table 1. Summary of phytochemical constituents and bioactive compounds isolated from various parts of *M. calabura*

Location of plant collection	Part of plant	Phyto-chemical constituents	Name of compound	Types of extract	References
Along a river bank, in Colombiana, River Curanja, Purus, Peru.	Leaves	Flavonoids	(2R,3R)-7-Methoxy 3,5,8-trihydroxy Flavanone, Pinocembrin, Pinobanksin, Pinostrobin Isoliquiritigenin, Gnaphaliin, Cabreuvin, Chrysin, Isokaemferide, Ermanin, Lupenone, 8-Methoxy-3,5,7-trihydroxyflavone, 5,4'-Dihydroxy-3,7,8-trimethoxyflavone, 5-Hydroxy-3,7,8,4'-tetramethoxyflavone, 2',4'-Dihydroxychalcone, (2S)-7-Hydroxyflavanone, 7-Hydroxyisoflavone2', 4'-Dihydroxydihydrochalcone, 7-Hydroxyflavone, 3,3'-Dimethoxyflavone, 3,8-Dimethoxy-5,7,4'-trihydroxyflavone, 5-Hydroxy-3,7,8-tetrimethoxyflavone, (2S)-5'-Hydroxy 7,8,3',4'-tetramethoxyflavan,2α,3β-Dihydroxy olean-12-en-28-oic acid	Ethyl acetate-soluble partition of methanol extract	Su et al., 2003 [33]
Kaohsiung City, Taiwan.	Leaves	Flavonoids	2',4'-Dihydroxy-3'-methoxydihydrochalcone (-)-3'-Methoxy- 2',4',β-trihydroxydihydrochal cone, (2S)-(-)-5'-Hydroxy-7,3'4'-trimethoxy-flavanone, Muntingone, 5-Hydroxy-7methoxyflavone, 3,7-Dimethoxy-5-hydroxyflavone, 5-Hydroxy-7-3,6,7-trimethoxyflavone, 6,7-Dimethoxy-5-ydroxyflavone, 3,5-Dihydroxy-7- methoxyflavone, 3,5-Dihydroxy-6,7- dimethoxyflavone, 8-Methoxy-3,5,7- trihydroxyflavone, 5,7-Dihydroxy-3,4-dimethoxyflavone, Galangin, Chrysin, 7-Hydroxyflavanone, 7-Hydroxy-8-methoxyflavanone, 4'-Hydroxy-7-methoxyflavanone, 2'4'-Dihydroxychalcone, 19. 2',4'-Dihydroxy-3'-methoxychalcone, 20. 2',4'-Dihydroxydihydrochal cone	Methanol extract	Chen et al., 2005 [34]
Indonesia	Fruits	Carotenoids, minerals	Ascorbic acid, Fiber, β-Carotene, Niacin	Aqueous extract	Verdayanti, 2009 [35]
Salem, Tamil Nadu, India.	Fruits	Flavonoids and terpenoids	γ -sitosterol, Stigmasterol, Campesterol, β-Cholest-5-en-3-ol, α-tocopherol, γ -tocopherol, 3-Cyclopentyl, propionic acid, Octanoic acid, 2-dimethylamino ethyl, ester, Ethyl stearate, Ethyl linolenate, Ethyl linoleate, Cyclopropaneoctanoic acid, 2-ethylcyclopropyl methyl ester, Phytol, Ethyl hexadecanoate, n-Hexadecanoic acid, (2E)-3,7,11,15-Tetramethyl-2- hexadecen-1-ol, Neophytadiene, 1-Desoxy-d-mannitol n-Nonanoic acid, 1,2,3-Propanetriol, monoacetate .2,3-Dihydro- benzofuran, Octanoic acid, 2,3-Dihydro-3,5-dihydroxy-6-methyl-4H-pyran, Isoamyl acetate, 1,3,5,-Triazine-2,4,6, Triimine	Polyphenol extract	Gomathi et al., 2013 [36]

Natural habitat in Shah Alam, Selangor, Malaysia.	Leaves	Flavonoids	5,7-Dihydroxy-3,8- dimethoxyflavone, 2.3,7-Dimethoxy-5- hydroxyflavone, 3.2',3'-Dihydroxy-4'- methoxychalcone, Calaburone	Petroleum ether partition of methanol extract	Yusuf et al., 2013 [37]
	Leaves	Flavonoids	1.5,7-Dihydroxy-3,8- dimethoxyflavone, 2',4'-Dihydroxychalcone, 5-Hydroxy-3,8-dimethoxyflavone, 3,5,7-Trihydroxy-8-methoxyflavone	Ethyl acetate partition of methanol extract	Sufian et al., 2013 [38]
	Leaves	Flavonoids, triterpenes, saponins, and tannins.	Rutin, Quercitrin, Fisetin, Dihydroquercetin	Methanol extract	Zakaria et al., 2014 [39]
Changzhi Township, Pingtung County, Taiwan.	Stem, wood	Flavonoids	β-Sitostenone, β-Sitosterol, 5-Hydroxy-7-methoxyflavone, 2S)-5'-Hydroxy-7,8,3',4'- tetramethoxyflavan, (2S)-8,5'-Dihydroxy-7,3',4'- trimethoxyflavan, (2S)-5'-Hydroxy-7,8,3',4'- tetramethoxyflavan, (M),(2S),(2"S)-,(P),(2S),(2"S)- 7,8,3',4',5',7",8",3"',4"' ,5"'-Decamethoxy- 5,5"-biflavan, (M),(2S),(2"S)-,(P),(2S),(2"S)-8,5',8"-Trihydoxy-7,3',4',7",3"',4"',5"'-heptamethoxy-5,5"- biflavan 7,8,3',4',5'-Pentamethoxyflavone, 4'-Hydroxy-7,8,3',5'-tetramethoxyflavone, (E)-Ferulic acid (R)-2',β-Dihydroxy-3',4'- dimethoxydihydrochal cone, (2S)-7-Hydroxy- flavanone, Gallic acid, Quercetin	CH_2Cl_2-soluble fraction of methanol extract	Kuo et al., 2014 [40]
San Pedro, Laguna, Philippine.	Fruit	Terpenoids, and fatty acids.	Squalene, Linoleic acid, Palmitic acid, β-Sitosterol β-Sitosterol	Dichloromethane and ethane extract	Ragasa et al., 2015 [41]
National Agricultural Training Center (NATC), Malang, Indonesia.	Leaves	Flavonoids, Terpenoids and tannins	β -Carotene, α -Tocopherol, Lupeol, α-Amyrin β-Sitosterol, α-Lonone, Eugenol, Eugenol, Nerol, Geraniol, Linalool, α-Terpineol, Thymol, Myrcene	Aqueous extract	Triswaningsih et al., 2017 [42]
National Agricultural Training Center (NATC), Malang, Indonesia.	Leaves	Phenolic acids, and flavonoids	Riboflavin, Maltose, Quercetin, Ellagic acid, Catechin, Kaempferol, Thiamine, Biotin, Pantothenic acid, Fructose, Glucose, Ascorbic acid, Dehydroascorbic acid, Gallic acid, Pyridoxine, Cinnamic acid, Malic acid, Niacin, Succinic acid, Fumaric acid	Aqueous extract	Triswaningsih et al., 2017 [42]
Kaohsiung, Taiwan.	Fruits	Flavonoids and phenolic acids.	Luteolin, Diosmin, Rosmarinic acid, Rutin ρ-Anisic acid, Syringic acid, Sinapic acid, Ferulic acid, ρ-Coumaric acid, Epicatechin, Caffeic acid, Vanillic acid, ρ-Hydroxybezoic acid, Gentistic acid, Gallic acid	Ethanol extract	Lin et al., 2017 [43]

Campinas-SP, Brazil.	Fruits	Hydroxycinnamic acids, hydroxybenzoic acids, and flavonoids	Cyanidin-3-O- glucoside, Delphinidin-3-O-glucosideFerulic acids, Sinapic acid, ρ-Coumaric acid, Caffeic acid, Gentisic acid, Vanillic acid, 4-Hydroxybenzoic acid, Protocatechuic acid, Gallic acid, Rutin, Quercetin, Epicatechin, Catechin, Epigallocatechin, Gallocatechi, Naringenin	Polyphenol extract	Pereira et al., 2018 [44]
		Terpenoids (terpenes)	α-Cedrene, α-Zingiberene, α-Bergamotene, cis-3-Nonen-1-ol, Methyl salicylate, 3-Hexen-1-ol Limonene, α-Curcumene, β-Himachalene, Dendrolasin, β-Farnesene		
		Carbohydrates	Maltoheptaose, Maltohexaose, Maltopentaose, 1-Kestose, Sucrose, Fructose, Glucose		
Natural habitat in Serdang, Selangor, Malaysia.	Leaves	Phenolic acids	Gallic acid, Protocatechuic acid, Ferulic acid, Quercetin-3-O-glucuronide, Quercitrin-2″-O-gallate,P entagalloyl-hexoside II, Kaempferol-3-O-galactoside, Myricetin, Quercetin-3-O- galactoside, Isoferulic acid, Afzelin-O-gallate, Quercetin, Quercetin dimer, Pinocembrin (isomer 1), Kaempferol-3-O- glucoside, Rhamnetin, Pinobaksin, Kaempferol, Pinocembrin (isomer 2), Chrysin, Kaempferide I, Genistein, Kaempferide II, Ermanin I, Ermanin II, Pinostrobin	Methanol extract	Zakaria et al., 2019 [45]
		Flavonoids	Methanone, 6-Phenanthridinephenyl-, oxime, (E)-13-Docosenamide, (Z) 1,1′:3′,1″-Terphenyl, 4′,6′-dimethoxy- 2,2″,3,3″,5,5″,6,6″-octamethyl- Cholest-4-en-3-one, 2- hydroxy-, (2.alpha.)-Alpha-tocopherol, 2-(Acetoxymethyl)-3-(methoxycarbonyl)bip henylene, 6Methyl-2 phenylindole, 5-Methyl-2-phenylindolizine	Methanol extract	Zakaria et al., 2019 [45]
Serdang, Selangor, Malaysia.	Leaves	Flavonoids and phenolic acids	Geniposide, Daidzein, Quercitrin, 6-hydroxyflavanone, Kaempferol, Formononetin	Ethanol extract	Zolkeflee et al., 2022 [46]
North Sumatera Province, Indonesia.	Leaves	Diterpene	Phytol	Ethyl acetate extract	Situmorang et al., 2022 [47]
South Sulawesi Province, Indonesia.	Fruits	Terpenoid	3-Isopropyl-6a,10b-Dimethyl8-(2-Oxo-2-Phenyl-Ethyl)-DodecahydroBenzo[F]Chromen-7, (2R,3R,4ar,5S,8as)-2-Hydroxy-4a,5-Dimethyl-3-(Prop-1-En-2-Yl)Octahydronaphthalen-1	Ethanol extract	Nur et al., 2023 [48]
		Alkaloid	1-Methyl-Cyclohexanacarboxylic Acid-(2H-[1,2,4]Triazol-3-YL)-Amide, 1,4-Diazabicyclo[4.3.0]Nonan-2,5-Dione, 3-Methyl, N,N'-Bis-3-Oxapentamethyleneformamidinum, Dithiocarboxylate, Propanoic Acid, 2,2-Dimethyl-, (2,3,3a,9a-Tetrahydro-3-Hydroxy-6-Oxo-6H-Furo[2',3':4,5]	Ethanol extract	Nur et al., 2023 [48]
		Phenolic	2,6-Di-Tert-Butyl-4-Methylphenol	Ethanol extract	Nur et al., 2023 [48]

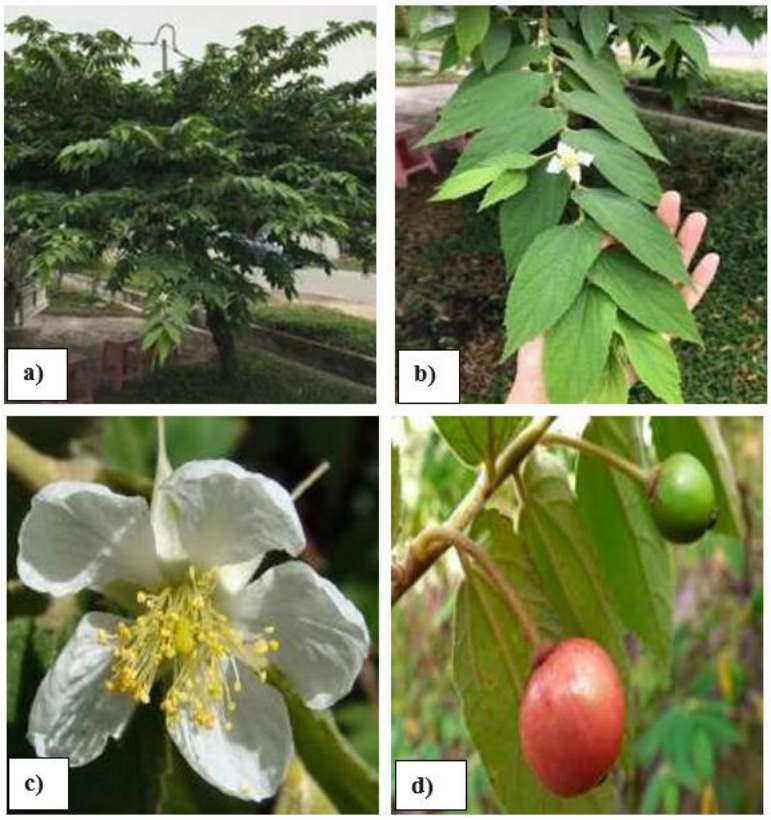

Figure 1. The various parts of *M. calabura*. a) The tree of *M. calabura*. b) The leaves of *M. calabura.* c) The flower of *M. calabura.* d) The fruits of *M. calabura.*

References

[1]. Kazeem MI, Adamson JO, Ogunwande IA. Modes of inhibition of α-amylase and α-glucosidase by aqueous extract of morinda lucida benth leaf. Biomed Res Int 2013;2013. https://doi.org/10.1155/2013/527570.

[2]. Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. Nat Rev Dis Prim 2017;3:1–18. https://doi.org/10.1038/nrdp.2017.16.

[3]. Tan SY, Mei Wong JL, Sim YJ, Wong SS, Mohamed Elhassan SA, Tan SH, et al. Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention. Diabetes Metab Syndr Clin Res Rev 2019;13:364–72. https://doi.org/10.1016/j.dsx.2018.10.008.

[4]. Zarei A, Vaezi G, Malekirad AA, Abdollahi M. Effects of ethanol extract of *Salvia hydrangea* on hepatic and renal functions of streptozotocin-induced diabetic rats. Avicenna

J Phytomed 2015;5:138–47.

[5]. Ismail, Rosnah, Noor Hassim Ismail, Azmi Mohd Tamil, Mohd Hasni Ja'afar, Zaleha Md Isa, Nafiza Mat Nasir, Farnaza Ariffin et al. Prevalence and factors associated with prediabetes and diabetes mellitus among adults: Baseline findings of PURE Malaysia cohort study.CEGH 21 2023;21:101279. https://doi.org/10.1016/j.cegh.2023.101279.

[6]. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14:88–98. https://doi.org/10.1038/nrendo.2017.151.

[7]. Wong CY, Martinez J, Dass CR. Oral delivery of insulin for treatment of diabetes: status quo, challenges and opportunities. J Pharm Pharmacol 2016;68:1093–108. https://doi.org/10.1111/jphp.12607.

[8]. Barrella N, Eisenberg B, Simpson SN. Hypoglycemia and severe lactic acidosis in a dog following metformin exposure. Clin Case Reports 2017;5:2097–104. https://doi.org/10.1002/ccr3.1255.

[9]. Ito H, Abe M, Mifune M, Oshikiri K, Antoku S, Takeuchi Y, et al. Hyperuricemia Is Independently Associated with Coronary Heart Disease and Renal Dysfunction in Patients with Type 2 Diabetes Mellitus. PLoS One 2011;6:1–7. https://doi.org/10.1371/journal.pone.0027817.

[10]. Tafesse TB, Hymete A, Mekonnen Y, Tadesse M. Antidiabetic activity and phytochemical screening of extracts of the leaves of Ajuga remota Benth on alloxan-induced diabetic mice. BMC Complement Altern Med 2017;17:1–9. https://doi.org/10.1186/s12906-017-1757-5.

[11]. Zakaria ZA, Mohamed AM, Jamil NSM, Rofiee MS, Hussain MK, Sulaiman MR, et al. In vitro antiproliferative and antioxidant activities of the extracts of Muntingia calabura leaves. Am J Chin Med 2011;39:183–200. https://doi.org/10.1142/S0192415X11008749.

[12]. Ramasamy R, Nanjundan J, Kp S. Screening of antibacterial activity of Muntingia calabura leaves extracts against bacterial pathogens 2017;5:313–6.

[13]. Nivethetha M, Jayasri J, Brindha P. Effects of Muntingia calabura L. on isoproterenol-induced myocardial infarction. Singapore Med J 2009;50:300–2.

[14]. Zakaria ZA, Sulaiman MR, Jais AMM, Somchit MN, Jayaraman KV, Balakhrisnan G, et al. The antinociceptive activity of Muntingia calabura aqueous extract and the involvement of L-arginine/nitric oxide/cyclic guanosine monophosphate pathway in its observed activity in mice. Fundam Clin Pharmacol 2006;20:365–72. https://doi.org/10.1111/j.1472-

8206.2006.00412.x.

[15]. Mahmood ND, Nasir NLM, Rofiee MS, Tohid SFM, Ching SM, Teh LK, et al. Muntingia calabura: A review of its traditional uses, chemical properties, and pharmacological observations. Pharm Biol 2014;52:1598–623. https://doi.org/10.3109/13880209.2014.908397.

[16]. Zakaria, Z. A., Hassan, M. H., Nurul Aqmar, M. N., Abd Ghani, M., Mohd Zaid, S. N., Sulaiman, M. R., Hanan Kumar, G., & Fatimah CA. Effects of various nonopioid receptor antagonists on the antinociceptive activity of *Muntingia calabura* extracts in mice. Methods rified petroleum ether partition of *Muntingia calabura* leaves. Rev Bras Farmacogn 2016;26:408–19. https://doi.org/10.1016/j.bjp.2015.12.007.

[17]. Zakaria ZA, Mohd Sani MH, Kadir AA, Kek TL, Salleh MZ. Antinociceptive effect of semi-purified petroleum ether partition of *Muntingia calabura* leaves. Rev Bras Farmacogn 2016;26:408–19. https://doi.org/10.1016/j.bjp.2015.12.007.

[18]. Zakaria ZA, Nor Hazalin NAM, Zaid SNHM, Ghani MA, Hassan MH, Gopalan HK, et al. Antinociceptive, anti-inflammatory and antipyretic effects of *Muntingia calabura* aqueous extract in animal models. J Nat Med 2007;61:443–8. https://doi.org/10.1007/s11418-007-0167-2.

[19]. Preethi K, Premasudha P, Keerthana K. Anti-inflammatory activity of *Muntingia calabura* fruits. Pharmacogn J 2012;4:51–6. https://doi.org/10.5530/pj.2012.30.10.

[20]. Sarojini S, Mounika B. Muntingia calabura (Jamaica Cherry): An Overview. PharmaTutor 2018;6:1. https://doi.org/10.29161/pt.v6.i11.2018.1.

[21]. Vadivel, K., Kumar, G. S., Babu, S. M. Ex vivo Antispasmodic Activity of Aqueous Extract of Flowers of Muntingia calabura Linn. on Excised Rabbit's Jejunum. Pharmacognosy research. 2017;9:3:301–303. https://doi.org/10.4103/pr.pr_99_16

[22]. Miranda JR-, Barrientos JMJ-, Canseco JH-, Rivera MR-, Santos BH-. Physicochemical properties of Muntingia calabura fruit and its effect on the quality characteristics of cookies. Emir J Food Agric [Internet]. 2021 Aug. 18 [cited 2023 Oct. 11];33(7):555-64. Available from: https://www.ejfa.me/index.php/journal/article/view/2724

[23]. Adam Z, Hassali HA, Khamis S. *In vitro* antidiabetic, anti-glycation, and antioxidant activities of *Muntingia calabura* L. leaves extracts. Int Conference of Natural product, 2015.

[24]. I.I. Nor Azman N, Hashim N, Ahmad R. *In-vitro* α-Glucosidase Inhibitory Activities of *Muntingia calabura* Linn. Int J Eng Technol 2019;7:183.

https://doi.org/10.14419/ijet.v7i4.14.27525.

[25]. Setyaningsih EP, Saputri FC, Mun'im A. The Antidiabetic Effectivity of Indonesian Plants Extracts via DPP-IV Inhibitory Mechanism. J Young Pharm 2019;11:161–4. https://doi.org/10.5530/jyp.2019.11.34.

[26]. Panneerselvam G, Jothi Narendiran N, Vasanth S, Bupesh G, Prabhu K, Krishnamurthy R. Phytochemical screening, *in vitro* antidiabetic activity of *Muntingia calabura* leaves extract on alpha-amylase and alpha-glucosidase enzymes. Int J Res Pharm Sci 2020;11:1210–3. https://doi.org/10.26452/ijrps.v11i1.1960.

[27]. Chaitanya G, Kumar BR, Mohan GK, Pradesh A. Antidiabetic effect of leaves of M*utingia calabura* l., in normal and alloxan-induced diabetic rats. pharmacologyonline 2011;2:626–32.

[28]. Pramono VJ, Santoso R. Pengaruh Ekstrak Buah Kersen (*Muntingia calabura*) terhadap Kadar Gula Darah Tikus Putih (Rattus novergicus) yang Diinduksi Streptozotocin (STZ). J Sain Vet 2014;32:218–23.

[29]. Busman, Hendri, Reza Pina Lestari, Emantis Rosa, and Achmad Arifiyanto. "Kersen (*Muntingia calabura* L.) ethanol extract repairs pancreatic cell damage, total coliforms, and lactic acid bacteria in hyperglycemic mice. Journal of Pure & Applied Microbiology 2022 16:3.

[30]. Aligita W, Susilawati E, Sukmawati IK, Holidayanti L, Riswanti J. Antidiabetic activities of Muntingia calabura L. leaves water extract in type 2 diabetes mellitus animal models. Indones Biomed J 2018;10:165–70. https://doi.org/10.18585/inabj.v10i2.405.

[31]. Herlina H, Amriani A, Solihah I SR. Antidiabetic Activity Test Of Ethanolic Seri Leave's (Muntingia Calabura L.) Extract In Male Rats Induced by alloxan. Sci Technol Indones 2018;3:7–13.

[32]. Yemineni M, Kancharlapalli VR, Pn S. Preliminary Phytochemical Investigation and Evaluation of Hypoglycemic Activity of Methanolic Extract of *Muntingia calabura* L Stem Bark Against Normal and Streptozotocin-Induced Diabetes. Asian J Pharm Clin Res 2019;12:1–6.

[33]. Su BN, Parka EJ, Vigo JS, Graham JG, Cabieses F, Fong HHS, et al. Activity-guided isolation of the chemical constituents of *Muntingia calabura* using a quinone reductase induction assay. Phytochemistry 2003;63:335–41. https://doi.org/10.1016/S0031-9422(03)00112-2.

[34]. Chen JJ, Lee HH, Duh CY, Chen IS. Cytotoxic chalcones and flavonoids from the leaves of *Muntingia calabura*. Planta Med 2005;71:970–3. https://doi.org/10.1055/s-2005-871223.

[35]. Verdayanti T. E. Uji efektifitas jus buah kersen (*Muntingia calabura* L.) terhadap penurunan kadar glukosa darah pada tikus putih (Rattus norvegicus). Malang: Universitas Muhammadiyah Malang. From: Undergraduate Theses from JIPTUMMPP 2009.

[36]. Gomathi R, Anusuya N MS. A dietary antioxidant supplementation of Jamaican cherries (*Muntingia calabura* L.) attenuates inflammatory-related disorders. Food Sci Biotechnol 2013;3:787–794.

[37]. Mohamad Yusof MI, Salleh MZ, Lay Kek T, Ahmat N, Nik Azmin NF, Zakaria ZA. Activity-guided isolation of bioactive constituents with antinociceptive activity from *Muntingia calabura* L. Leaves using the formalin test. Evidence-Based Complement Altern Med 2013;2013. https://doi.org/10.1155/2013/715074.

[38]. Sufian AS, Ramasamy K, Ahmat N, Zakaria ZA, Yusof MIM. Isolation and identification of antibacterial and cytotoxic compounds from the leaves of *Muntingia calabura* L. J Ethnopharmacol 2013;146:198–204. https://doi.org/10.1016/j.jep.2012.12.032.

[39]. Zakaria ZA, Sani MHM, Cheema MS, Kader AA, Kek TL, Salleh MZ. Antinociceptive activity of methanolic extract of *Muntingia calabura* leaves: Further elucidation of the possible mechanisms. BMC Complement Altern Med 2014;14:1–12. https://doi.org/10.1186/1472-6882-14-63.

[40]. Kuo WL, Liao HR, Chen JJ. Biflavans, flavonoids, and a dihydrochalcone from the stem wood of *Muntingia calabura* and their inhibitory activities on neutrophil pro-inflammatory responses. Molecules 2014;19:20521–35. https://doi.org/10.3390/molecules191220521.

[41]. Ragasa CY, Tan MCS, Chiong ID, Shen CC. Chemical constituents of *Muntingia calabura* L. Der Pharma Chem 2015;7:136–41.

[42]. Triswaningsih D, Kumalaningsih S, Wignyanto, Pratikto. Identification of chemical compounds cherry leaves (*Muntingia calabura*) powder as a natural antioxidant. Int J Agron Agric Res 2017;10:84–91.

[43]. Lin JT, Chang YY, Chen YC, Shen BY, Yang DJ. Molecular mechanisms of the effects of the ethanolic extract of *Muntingia calabura* Linn. fruit on lipopolysaccharide-induced pro-inflammatory mediators in macrophages. Food Funct 2017;8:1245–53. https://doi.org/10.1039/c6fo01735e.

[44]. Pereira GA, Arruda HS, de Morais DR, Eberlin MN, Pastore GM. Carbohydrates, volatile

and phenolic compounds composition, and antioxidant activity of calabura (*Muntingia calabura* L.) fruit. Food Res Int 2018;108:264–73. https://doi.org/10.1016/j.foodres.2018.03.046.

[45]. Zakaria ZA, Mahmood ND, Omar MH, Taher M, Basir R. Methanol extract of *Muntingia calabura* leaves attenuates CCl4-induced liver injury: possible synergistic action of flavonoids and volatile bioactive compounds on endogenous defence system. Pharm Biol 2019;57:335–44. https://doi.org/10.1080/13880209.2019.1606836.

[46]. Zolkeflee NKZ, Ramli NS, Azlan A, Abas F. *In vitro* Antidiabetic Activities and UHPLC-ESI-MS/MS Profile of *Muntingia calabura* Leaves Extract. Molecules 2022;27. https://doi.org/10.3390/molecules27010287.

[47]. Situmorang RFR, Gurning K, Kaban VE, Butar-Butar MJ, Perangin-Angin SAB. Determination of Total Phenolic Content, Analysis of Bioactive Compound Components, and Antioxidant Activity of Ethyl Acetate Seri (*Muntingia calabura* L.) Leaves from North Sumatera Province, Indonesia. Open Access Maced J Med Sci 2022;10:240–4. https://doi.org/10.3889/oamjms.2022.8362.

[48]. S. Nur ANA, Nursamsiar, Sami FJ, Fadri A, Khairi N, Sapra and A. Standardization And Gc-Ms Analysis Of Kersen 2023;46:173–87.

[49]. Siddiqua A, Premakumari KB, Sultana R, Vithya, Savitha. Antioxidant activity and estimation of total phenolic content of *Muntingia calabura* by colorimetry. Int J ChemTech Res 2010;2:205–8.

[50]. Meng Bo LJ and CH. Antioxidant and Antiinflammatory Activities of Curcumin on Diabetes Mellitus and its Complications. Curr Pharm Des 2013;19:2101–2113.

[51]. Vijayanand S, Thomas AS. Screening of Michelia Champacca and *Muntingia calabura* Extracts For Potential Bioactives. Int J Pharma Sci Res 2016;7:266–73.

[52]. Unuofin JO, Lebelo 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;2020. https://doi.org/10.1155/2020/1356893.

[53]. Rhamdani S.R. Pengaruh ekstrak etanol daun *Muntingia calabura* L. terhadap kadar glukosa darah mencit (Mus musculus L.) swiss webster jantan dewasa yang dikondisikan. Institut Teknologi Bandung, 2008.

[54]. Kitada M, Zhang Z, Mima A, King GL. Molecular mechanisms of diabetic vascular complications. J Diabetes Investig 2010;1:77–89. https://doi.org/10.1111/j.2040-

1124.2010.00018.x.

[55]. Sarian MN, Ahmed QU, Mat So'Ad SZ, Alhassan AM, Murugesu S, Perumal V, et al. Antioxidant and antidiabetic effects of flavonoids: A structure-activity relationship based study. Biomed Res Int 2017;2017. https://doi.org/10.1155/2017/8386065.

[56]. Gothai S, Ganesan P, Park SY, Fakurazi S, Choi DK, Arulselvan P. Natural phyto-bioactive compounds for the treatment of type 2 diabetes: Inflammation as a target. Nutrients 2016;8. https://doi.org/10.3390/nu8080461.

[57]. Sachithanandam V, Lalitha P, Parthiban A, Mageswaran T, Manmadhan K, Sridhar R. A Review on Antidiabetic Properties of Indian Mangrove Plants with Reference to Island Ecosystem. Evidence-Based Complement Altern Med 2019;2019. https://doi.org/10.1155/2019/4305148.

[58]. Fatiha M, Fatma B, Awatif B, Nesrine A, Djebli, Noureddine, et al. Antidiabetic bioactive compounds from plants. Med Technol J 2018;2:215–9. https://doi.org/10.26415/2572-004x-vol2iss2p215-219.

[59]. Valensi P, Le Devehat C, Richard JL, Farez C, Khodabandehlou T, Rosenbloom RA, et al. A multicenter, double-blind, safety study of QR-333 for the treatment of symptomatic diabetic peripheral neuropathy: A preliminary report. J Diabetes Complications 2005;19:247–53. https://doi.org/10.1016/j.jdiacomp.2005.05.011.

[60]. Coughlan KA, Valentine RJ, Ruderman NB, Saha AK, Inzucchi SE, Dennis T, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Biol Chem 2005;13:1–10. https://doi.org/10.1172/JCI13505.Role.

[61]. Fu QY, Li QS, Lin XM, Qiao RY, Yang R, Li XM, et al. Antidiabetic effects of tea. Molecules 2017;22:1–19. https://doi.org/10.3390/molecules22050849.

[62]. Santosh HN, David CM. Role of ascorbic acid in diabetes mellitus: A comprehensive review. J Med Radiol Pathol Surg 2017;4:1–3. https://doi.org/10.15713/ins.jmrps.79.

[63]. Luong. The Impact of Thiamine Treatment in the Diabetes Mellitus. J Clin Med Res 2012;4:153–60. https://doi.org/10.4021/jocmr890w.

[64]. Alam MM, Iqbal S, Naseem I. Ameliorative effect of riboflavin on hyperglycemia, oxidative stress and DNA damage in type-2 diabetic mice: Mechanistic and therapeutic strategies. Arch Biochem Biophys 2015;584:10–9. https://doi.org/10.1016/j.abb.2015.08.013.

[65]. Ganeshpurkar A, Saluja AK. The Pharmacological Potential of Rutin. Saudi Pharm J 2017;25:149–64. https://doi.org/10.1016/j.jsps.2016.04.025.

[66]. Kamalakkannan N, Prince PSM. Antihyperglycaemic and antioxidant effect of rutin, a polyphenolic flavonoid, in streptozotocin-induced diabetic wistar rats. Basic Clin Pharmacol Toxicol 2006;98:97–103. https://doi.org/10.1111/j.1742-7843.2006.pto_241.x.

[67]. Kappel VD, Zanatta L, Postal BG, Silva FRMB. Rutin potentiates calcium uptake via voltage-dependent calcium channel associated with stimulation of glucose uptake in skeletal muscle. Arch Biochem Biophys 2013;532:55–60. https://doi.org/10.1016/j.abb.2013.01.008.

[68]. Pu P, Gao DM, Mohamed S, Chen J, Zhang J, Zhou XY, et al. Naringin ameliorates metabolic syndrome by activating AMP-activated protein kinase in mice fed a high-fat diet. Arch Biochem Biophys 2012;518:61–70. https://doi.org/10.1016/j.abb.2011.11.026.

[69]. Ahad A, Ganai AA, Mujeeb M, Siddiqui WA. Chrysin, an anti-inflammatory molecule, abrogates renal dysfunction in type 2 diabetic rats. Toxicol Appl Pharmacol 2014;279:1–7. https://doi.org/10.1016/j.taap.2014.05.007.

[70]. Saeidnia S. The Story of Beta-sitosterol- A Review. European J Med Plants 2014;4:590–609. https://doi.org/10.9734/ejmp/2014/7764.

[71]. Gupta R, Sharma AK, Dobhal MP, Sharma MC, Gupta RS. Antidiabetic and antioxidant potential of β-sitosterol in streptozotocin-induced experimental hyperglycemia. J Diabetes 2011;3:29–37. https://doi.org/10.1111/j.1753-0407.2010.00107.x.