REVIEW ARTICLE

A Review of *Cosmos caudatus* as A Promising Antidiabetic Plant

Suganya Murugesu, Vikneswari Perumal, Tavamani Balan, Sharon Fatinathan, Puvana Devi Selvarajoo, Maryam Anis Binti Rozali, Noor Izati Abd Aziz

Faculty of Pharmacy and Health Sciences, Universiti Kuala Lumpur Royal College of Medicine Perak, 30450 Ipoh, Perak, Malaysia

ABSTRACT

Cosmos caudatus Kunth is an edible plant commonly known for its beneficial medicinal effects on human health and traditionally used to treat various health conditions, including diabetes. This review summarizes the current state of knowledge about this plant, to provide some basic information about this herb that reflects its antidiabetic potential through multiple mechanisms. Currently, available evidence suggests that *C. caudatus* possess some pharmacological effects, including anti-inflammatory, antimicrobial, the formation of healthy bone and regulation of blood pressure and glucose levels. The review summarized the antidiabetic activity and its significant phytoconstituents in *C. caudatus*

Keywords: *Cosmos caudatus*, Diabetes mellitus, α-glucosidase, Antidiabetic, Medicinal plant

Corresponding Author:
Vikneswari Perumal, PhD
Email: vikneswari@unikl.edu.my
Tel: +605- 243 2635 ext. 856

INTRODUCTION

The dependence of human beings to nature in all aspects of life is undeniable, especially as the main source when it comes to food and medicine. Humans have found remedy from nature to ease the medical conditions that occurred throughout their revolutions. During critical times various plants with medicinal values were identified through their use and experience. Some are applied as a remedy in various forms to heal the sick. The recognition and development of these medicinal plants have become a significant part of human civilization. In current times, research on medicinal plants are evolving to even more astounding findings that bring beneficial health effects in human beings. Various plants are utilized and prepared traditionally as the panacea for multiple conditions. Plants are a diverse source of phytoconstituents that exhibit effects of a different kind towards the human body system. Some of the components obtained from the plant's matrix carry important and valuable pharmacological effects in healing. Thus, its use and application have been growing with time (1-3).

In the practice of modern medicine, synthetic drugs used with regimens or combining drugs have undeniable adverse and side effects. Medicinal plants are being investigated for their pharmacological potential as an alternative solution to overcome this. One such plant, edible yet comes with therapeutic potential is *Cosmos caudatus* Kunth (Fig. 1) which belongs to the Asteraceae family, known to be native to Central America and can be found in Asian countries, including Malaysia. Locally, it is famous as 'Ulam Raja' which means King's Salad. The term 'ulam' refers to the salad and ready to eat right away with meals in Malaysia (4-6).

This remedial plant can grow up to 3 m in height and has purple or pink and white ray petals with yellow florets in the centre. The unique leaves are pinnate and bloomed into five leaflets. People are eating the shoots and leaves raw due to its inimitable taste that makes it flavourful (7). This perennial aromatic herb has its

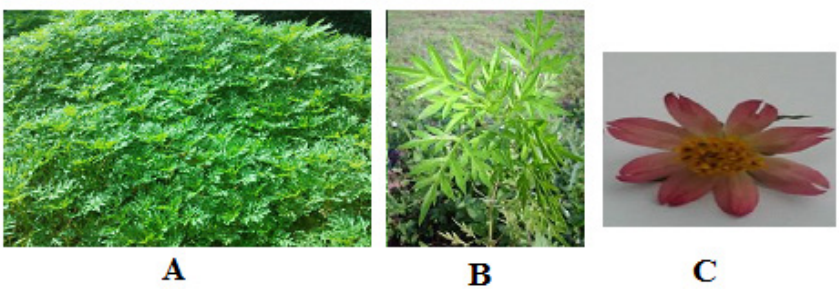

Fig. 1: *Cosmos caudatus* Kunth;
A-Whole plant, B- Leaves, C- Flower

medicinal values such as treatment for several ailments including hypertension, diabetes mellitus and arthritis (8). A previous study reported that this plant possesses multiple therapeutic effects, including its capacity to improve blood circulation, cleanse blood plasma, improve bone absorption, and treat respiratory issues (7). Typically, this herb can be eaten raw because of the taste and its exclusive aroma. It can act as a flavouring agent and as a preservative in the traditional mixture (7). Apart from that, *C. caudatus* is also applied as effective pest control of especially caterpillars, namely Aphid, Dysdercus, and Plutella xylostella (9). This herb has been reported to comprise various types of metabolites such as flavonoids, flavonoid glycosides, amino acids, phenolics, anthocyanins, β-carotene, ascorbic acid, carbohydrates, and minerals (calcium, phosphorus, iron, magnesium, and potassium) (10-11).

Diabetes mellitus (DM) is a chronic illness that occurs either hereditary or an assimilated deficiency in insulin secretion and failure of organs to secrete insulin (12). The previous studies (13) reported that elevated blood glucose could lead to microvascular and macrovascular complications. The regulation of multiple mechanisms of action that contribute to this disorder can manage diabetes mellitus. The prescription of oral antidiabetic drugs includes sulfonylureas, biguanides, thiazolidinediones, meglitinides and α-glucosidase inhibitors. The long-term use of these drugs could cause many side effects such as bloating, diarrhoea, skin itching, and weight gain. Therefore, the search for novel phytoconstituents from medicinal plants as an alternative to current medication with better efficacy and lesser side effects are on-going since the last few decades (14-15). The antidiabetic efficacy of medicinal plants has been reported using different techniques via in vitro, in vivo, and preclinical analysis. This short review aims to summarize on the findings that reflect the antidiabetic potential of *C. caudatus*.

IN VITRO STUDY OF *COSMOS CAUDATUS*

Enzyme inhibition

One of the therapeutic managements of hyperglycaemia in type 2 diabetes mellitus (T2DM) patients is through the inhibition of α-glucosidase, and α-amylase enzymes involved in the catalysing of carbohydrate (16-17). A good inhibitory profile against those enzymes by *C. caudatus* leaves has been reported previously.

The α-glucosidase enzyme is an intestinal enzyme found at the brush border of the small intestine. Inhibitors of this enzyme may postpone carbohydrate digestion which diminishes the glucose absorption rate, thus lessening the postprandial rise of plasma glucose (18-19). The α-glucosidase inhibitors (miglitol and acarbose), lower the blood glucose level subsequently after a starch load. The inhibition of carbohydrate catalysis causes alteration of glucose from disaccharide to monosaccharide. This inhibition will eventually reduce the absorption rate of glucose into the systemic circulation (20-21).

A previous study applying in vitro assay (22) which investigated the hexane extract of this plant leaves showed more than 70% inhibition of the α-glucosidase enzyme. Similar research was done (23) in which the 80% ethanolic leaves extract of *C. caudatus* showed a lower IC_{50} value of 58.4 µg/mL compared to the positive control, acarbose 117.06 µg/mL. Technically, the lower IC_{50} value reflects high inhibitory activity. Meanwhile, the 100% ethanolic extract of *C. caudatus* leaves showed the highest inhibitory activity compared to the natural inhibitor, quercetin, and the control drug, acarbose with the IC_{50} value of 13.7, 29.8 and 96.0 µg/mL, respectively (24). Apart from that, the α-glucosidase inhibitory activity analysis using alcoholic crude and solvent fractions have shown that the leaves and its phytoconstituents of different natures may have contributed to its inhibiting potential. The 80% ethanolic extract crude and its fractions (DCM, EA, BuOH) showed better inhibitory values compared to quercetin, the positive control with the IC_{50} values of 27.56, 85.73, 40.90, 74.84 and 109.30 µg/mL, respectively (25). Many studies consistently reported on α-glucosidase inhibitory activity from this plant, where the 80% extract showed greater potency than the standard used in the analysis; quercetin, with the IC50 value of 39.18 and 110.50 µg/mL respectively (8), which is agreeable with a previously reported study (23). Several studies included within the review indicated that the *C. caudatus* leaves have displayed great activity against α-glucosidase that subsequently controls glucose absorption.

The α-amylase enzyme is calcium metalloenzymes that function in the presence of calcium. The pancreatic α-amylase is the most crucial, which catalyses the hydrolysis of internal α-1, 4-glycosidic linkages in starch into shorter oligosaccharides (17). Therefore, the inhibition of α-amylase helps to lower the high glucose levels, which usually occurs after a meal by reducing the speed in which it can convert starch to simple sugars in animals (26). However, previous research (17) reported that excessive inhibition of α-amylase could lead to excessive floating of undigested carbohydrates in the intestine. Subsequently, this can be potentially vulnerable to fermentation of colon bacteria that may cause some unwanted side effects like flatulence, bloating, and diarrhoea. Additionally, a study (22) reported that the hexane extract of *C. caudatus* leaves exhibited high α-glucosidase inhibition but low inhibition of the α-amylase enzyme.

IN VIVO STUDY OF *COSMOS CAUDATUS*

The next level of preliminary studies will be the in vivo techniques which applies animal models or living cells for further investigation of the pharmacological effects of plant and its components. Multiple animal studies

have been carried out using *C. caudatus* leaves extracts with different animal models such as the streptozotocin (STZ)-induced rats and alloxan-induced diabetes with or without high-fat diet (HFD) model. The different animal models were used to investigate the antiobesity, antihyperlipidemic or antihypercholesterolemic properties.

This section has included obesity and hyperlipidaemia studies and the relevant findings to DM. Obesity is a predisposing factor for most non-communicable diseases (NCD), including T2DM, since it can alter the fat and sugar metabolism in diabetic patients. Adipose tissue is the primary fat storage site composed of adipocytes that also function as an endocrine organ that regulates metabolic homeostasis through synthesis of various biological compounds, including both glucose and lipid (27-29). Insulin resistance is a common onset in T2DM, which leads to reduced sensitivity of body cells, including fat and muscle cells. Subsequently, it will disrupt the glucose uptake by these cells, resulting in hyperglycaemia and hyperlipidaemia. Hyperlipidaemia is another metabolic disorder typically associated with a sedentary lifestyle and eating habits, with rising prevalence worldwide. The improvement of glucose and fat metabolisms may help to regulate hyperglycaemia and hyperlipidaemia in prediabetic individuals and T2DM patients (29-30). Regulation of metabolic dysfunction using daily salad ('ulam') intake as a cost-effective remedy may ease the lives of the affected individuals. However, to our knowledge, no cellular studies were reported for the *C. caudatus* plant extracts.

Apart from that, the liver is a vital organ having a crucial role in fat and glucose regulation in the human body. Liver cell or hepatocytes play a pivotal role as hepatic insulin resistance, which is one of the underlying causes of metabolic syndrome due to the direct distortion of the glucose metabolism which will subsequently lose control over glucose output into the blood circulation (29). Therefore, a sustained hepatic function is essential in glucose metabolism to avoid the occurrence of metabolic disorders.

A research carried out (31) using the powder of *C. caudatus* leaves at the dosage of 700 and 1400 mg for every 200 g of body weight (BW) for the treatment of STZ-induced diabetic rats for 21 consecutive days, displayed lowered blood glucose levels of about 38.4% and 49.09%, respectively for both the dosages applied. Besides that, the treated rats group have shown noticeable healing of the pancreatic beta cells with recovering insulin levels.

The effects of *C. caudatus* ethanolic extract on the STZ-induced hypercholesterolemic-diabetic Wistar rats were investigated at the dosage of 400 mg/kg (32), revealing that the extract had effectively lowered the cholesterol and the blood glucose levels. A continual study (33) on the histopathological part of the treated rats' pancreas measured the damage in scoring using Kruskal-Wallis test with 0–30% cytoplasmic degeneration observed in both the metformin and extract-treated groups, apparently better than the diabetic control group. A similar study (34) using 600 mg/kg ethanol extract of *C. caudatus* leaves significantly reduced serum glucose level by 42.5% (from 152.2 to 87.25 mg/dL) comparable to the glibenclamide treated control group showing 43.4% (from 190–105.7 mg/dL) reduction in alloxan-induced diabetic rats. Another study conducted in the same year, (35) reported on the effects of 96% ethanolic extract of *C. caudatus* in HFD-STZ-induced diabetic (cholesterolemic-diabetic) rat model. The blood glucose profile showed significant normalization (~300 mg/dL to ~100 mg/dL) at the dosage of 400 mg/kg for 49 days. Meanwhile, the elevated total cholesterol level had tremendously reduced from 3663.4 mg/dL to 209.4 mg/dL. The histopathological examination revealed the regenerative effects of *C. caudatus* extract on pancreatic tissues with the average scoring of 0.25 like the positive control used.

Another finding involving HFD rats treated with an ethanolic extract from *C. caudatus* leaves showed a significant reduction in the weight and improved fat and glucose metabolism observed through the improvement of the obesity biomarker including the insulin levels, plasma lipid profiles, leptin, ghrelin and adinopectin. The extract reduced lipid absorption via the intestine and adipocyte marker regulation (36). A similar study (37) on HFD rats treated with 200 mg/kg of ethanolic extract of *C. caudatus* showed a significant reduction in plasma triglycerides (TG), total cholesterol, low-density lipoprotein-cholesterol (LDL) and glucose along with improvements in high-density lipoprotein-cholesterol (HDL) and the atherogenic index value. The plant leaves have exhibited potential antiobesity effects with the regulation of the relevant parameters.

Apart from the animal models, a registered preclinical study (38) of *C. caudatus* leaves supplementation to diabetic patients were carried out. Their randomized controlled trial analysis of eight weeks comprised 77 subjects consisting of 38 diabetic-ulam groups and 39 diabetic controls. With both the groups receiving the standard lifestyle advice, the diabetic-ulam group subjects were fed 15 g of ulam extract while the control group was not given anything. After eight weeks of supplementation, various biometrics were measured, and significant changes were observed with reduced serum insulin and homeostatic model assessment-insulin resistance (HOMA-IR) levels, which represents insulin resistance. Besides that, the quantitative insulin sensitivity check index (QUICKI) was found to be increased, indicating improved insulin sensitivity and the glycosylated haemoglobin (HbA1c) level was improved in the diabetic-ulam group. Besides the biometric improvements, none of the patients had complained

about adverse signs such as gastrointestinal disturbances upon consumption along with the absence of hypo- and hyperglycaemic conditions. Furthermore, no significant changes occurred in the kidney and liver functions in the supplemented group. The clinical trial had shown that supplementation of the extract is considered safe and has the potential to improve insulin resistance and insulin sensitivity in T2DM patients.

ANTIDIABETIC PHYTOCONSTITUENTS IN *COSMOS CAUDATUS* AND THEIR MECHANISM OF ACTION

The presence of a wide range of phytoconstituents has made plants the most reliable source of food and medicine to human. Various plant phytoconstituents have been isolated, identified, and applied for various medicinal purposes. Antioxidants are also a major component in plant matrix that possess multiple pharmacological effects and can be used to combat a wide range of diseases. Some of the major classes of plant phytoconstituents include flavonoids, phenols, terpenoids, glycosides, sterols, tannins, and alkaloids. These components could exhibit various pharmacological effects, and some are yet to be identified. Likewise, *C. caudatus* consists of multiple compounds that contribute to its antidiabetic and antiobesity activities. The chemical structure of the compounds reported from *C. caudatus* is illustrated in Fig. 2 and listed in Table I.

Plant constituents' function in various mechanisms depending on their properties which is majorly contributed by the functional groups present in it. Generally, the inhibition activity of plant phytoconstituents involves the molecular interaction between the potential functional groups present in the main structure or the ring(s) with the observed enzyme(s). The number of specific functional groups and its position in the structure chemically influence the desired effects in the mechanism involved (39). Technically, the bioactivity of plant constituents is determined by the presence of functional groups such as the hydroxyl, methoxy, methyl, nitro, chloro, fluoro, bromo and others attached to the main structure (40). Mainly, the compounds with hydroxyl groups are known to be effective in inhibiting both the enzymes (α-glucosidase and α-amylase). The inhibition activities are affected by the presence of methoxy groups in a specific position in the ring structure (41).

Similarly, the presence of other substituents such as the methyl, nitro, chloro, fluoro, and bromo at a specific position in the constituents does not display the intended effects (40). This scenario was reported in the experiment using flavanones such as pinocembrin, pinostrobin, and alpinetin against α-glucosidase inhibition (42). Besides that, both hydroxy and methoxy groups are known to be the electron-donating groups and function by enhancing the electronic density to the aromatic ring they are attached. However, the methoxy group is more likely to cause retardation to the aromatic ring it bounds to due to its steric hindrance leading to its inability to function as a hydrogen bond donor (40, 43).

A previous study suggested that addition of non-polar, rotatable, methyl and methoxy substituents to the compounds may increase the lipophilicity and molecular weight of the compounds that subsequently reduce its capability to inhibit the enzyme and contributes to higher IC50 value. Apart from that, the increasing number

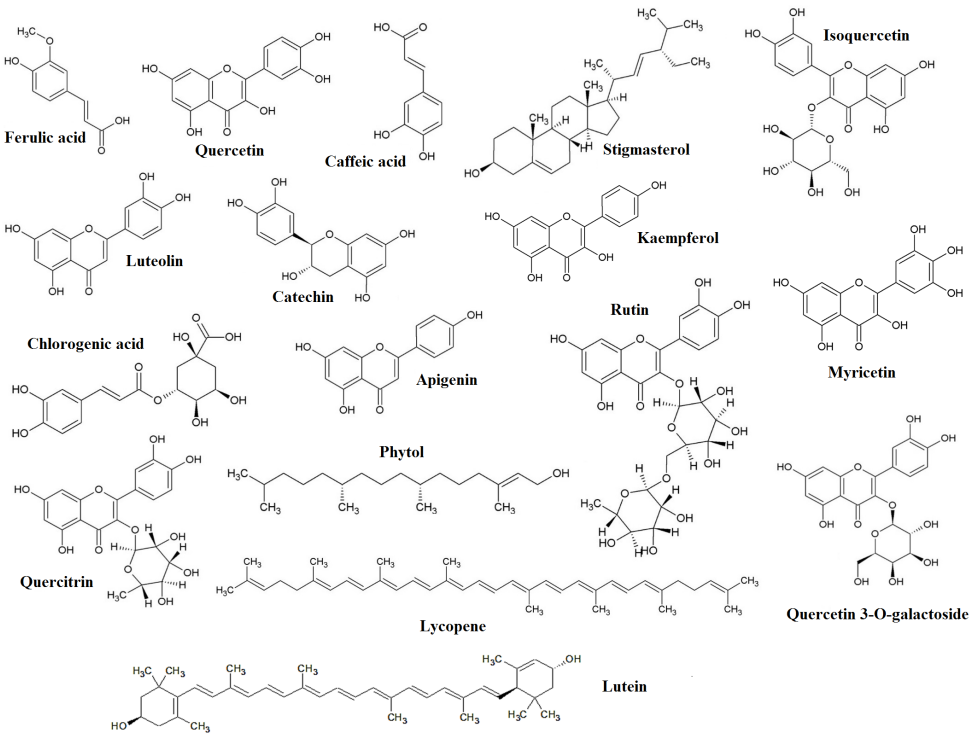

Fig. 2: Antidiabetic compounds reported from *Cosmos caudatus* plant

Table I: Antidiabetic phytoconstituents in *Cosmos caudatus*

Class	Subclass	Constituents	References
Flavonoids	Flavonol	Quercetin Myricetin Kaempferol Rutin Proanthocyanidins	40, 43, 45, 46
	Flavonoid glycoside	Quercetin-3-O-glucoside Quercetin-3-O-arabinofuranoside Quercetin-3-O-rhamnoside Quercetin 3-O-xyloside Quercetin 3-O-galactoside Quercetin deoxyl-hexose	4, 25, 46
	Flavan-3-ol	Catechin	43
	Flavone	Luteolin Apigenin	40
Phenolics	Hydroxycinnamic acid	Chlorogenic acid Caffeic acid Ferulic acid Cryptochlorogenic acid Neochlorogenic acid	40, 46
Terpenes/Terpenoids	Sesquiterpene	Caryophyllene α-farnesene β-elemene α-copaene γ-muurolene γ-cadinene α-farnesene	41
	Diterpene alcohol	Phytol	41
	Carotenoid	β-carotene Lycopene Lutein	40, 43 82
	Sesquiterpenoid alcohol	α-cadinol	41
Miscellaneous	Sterol	Stigmasterol	43
	Fatty acid	α-linolenic acid	43
	Organic acid	Benzoic acid Cyclohexen-1-carboxylic	43
	Sugar	Myo-inositol	43
	Vitamin	α-tocopherol	43

of hydrogen donor through the addition of hydroxyl substituent could contribute to a much lower IC50 value indicating significant inhibition. The presence of both hydroxyl and methoxy in a compound may display inhibition through hydrogen bonding interaction with the enzyme protein. However, it may not be a significant activity. The same study mentioned that adding more hydroxyl substituents alone will not enhance the activity. Still, the position of the substituent in the ring is essential, especially for flavonoids that are composed of a 15-carbon basic skeleton containing two phenyl rings of A and B with a heterocyclic ring C (43-44). Similarly, in a molecular study, the position of dihydroxyl groups at C3 and C4 of flavonoids' B ring-like catechol was reported to conjugate effectively with the active site residues of α-glucosidase enzyme. This is because the substituents will be highly potent in the electron cloud distribution that increases the accessibility to donate hydrogen atoms to form a hydrogen bond with the active site residues which directly contributes to its bioactivity (45).

In an investigation of selected plant constituents' inhibition of α-glucosidase and α-amylase enzymes, presence of hydroxyl group at the steric position were reported to exhibit higher inhibition potential. The study reported that the number of hydroxyl groups present in the flavonols investigated influences the activity where compounds containing more than three hydroxyl groups showed better activity compared to the ones with a lesser hydroxyl group (16). The substitution of the hydroxyl groups in the aromatic ring of the constituents (e.g. bromophenol and its derivatives) displayed significantly higher inhibition activity. In comparison, lower activity was observed upon replacement of the hydroxy group with a methoxy group (41). However, in a broader sense, hydrophobic compounds with the presence of much lesser or absence of hydroxyl group seemed to exhibit allosteric binding interaction that causes inhibition (46-47). Overall, the activity of compounds is influenced by the presence of hydroxyl group at a specific position in the ring. These changes may occur due to the conformational changes occurring upon the interactions (16, 47).

C. caudatus was reported to be rich in flavonoids and phenolics that contribute to most of its pharmacological activities (48). The presence of flavonoids (quercetin, kaempferol, luteolin and apigenin), phenolics (myricetin, chlorogenic, caffeic, and ferulic acids) and β-carotene were identified using high-performance liquid chromatography (HPLC) analysis (48). Similarly, quercitrin and rutin were detected as major compounds in the methanolic extract of the *C. caudatus* leaves using HPLC (4). Apart from that, the gas chromatography-mass spectroscopy (GCMS) analysis of the essential oil contents from the whole plant of *C. caudatus* revealed a wide range of terpenes including caryophyllene, α-farnesene, β-elemene, α-copaene, γ-muurolene, γ-cadinene, and α-farnesene along with sesquiterpenoid alcohol (α-cadinol) and diterpene alcohol (phytol) (50). Besides that, the identification of potential α-glucosidase inhibitors present in the ethanolic extract of *C. caudatus* leaves were carried out using HPLC. The analysis reported the presence of chlorogenic acid, rutin, quercetin rhamnoside and glycoside (51). Similarly, the investigation for the novel α-glucosidase inhibitors of the same solvent extract using discriminant analysis was carried out. The identified inhibitors were α-tocopherol, myo-inositol, stigmasterol, catechin, lycopene, cyclohexene-1-carboxylic, benzoic, and α-linolenic acid. They were found to be active against the observed enzyme activity (52).

Study on metabolomic characterization has exhibited stigmasterol as a potential α-glucosidase inhibitor with the IC50 of 65.31 µg/mL. Stigmasterol displayed a higher affinity with lower binding energy (–8.66 kcal/mol) towards the active site of the α-glucosidase crystal structure of Saccharomyces cerevisiae isomaltase that was analysed using the molecular docking tool (53). Quantification of phytoconstituents is commonly done before isolation of novel compounds. Likewise,

three major compounds from *C. caudatus*, viz., rutin, quercitrin and quercetin were successfully quantified where the recovery reported was more than 90% for all compounds, with quercitrin to be the most abundant component (54). The results are comparable to another research work (55) that signified the presence of proanthocyanidins, quercetin derivatives (quercetin-3-O-glucoside, quercetin-3-O-arabinofuranoside, quercetin-3-O-rhamnoside, and quercetin deoxy-hexose), catechin, chlorogenic, neochlorogenic, cryptochlorogenic, caffeic, and ferulic acids.

A recent study applying LCMS/MS for the separation of ethyl acetate and butanol extracts of *C. caudatus* leaves have revealed similar compounds composed of flavonoids; majorly rutin and some derivatives of quercetin (quercetin 3-O-xyloside and quercetin 3-O-galactoside). Meanwhile, the NMR analysis of ethanolic extract showed a similar profile. In addition, flavonoids such as quercitrin, catechin, and rutin are claimed as the prominent components of the plant that exerts its antidiabetic activity (8, 25). A previous study has reported that flavonoids and saponins exhibited antidiabetic properties by stimulating pancreatic beta cells for insulin release and suppressing the transportation and absorption of glucose through the brush border of the small intestine (21).

Apparently, flavonoids and phenolics are the prominent constituents of *C. caudatus* leaves extract. Among all the compounds reported, quercetin (flavonol) is the known inhibitor of the α-glucosidase enzyme, which was previously reported to display good antioxidant activity and antiobesity effects in bioassays and animal studies, respectively. In a cellular analysis using 3T3-L1 preadipocytes, quercetin was found to activate the monophosphate-activated protein kinase (AMPK) signalling in the cells that will impede the formation of adipocytes and cell death. Besides that, quercetin has been reported to reduce oxidative stress while functioning to lower the serum glucose and HbA1c levels in diabetic-induced animal models. It also prevents beta cell death via the mitochondrial pathway and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling, which is crucial in cell survival (56-59). *C. caudatus* was reported to possess superior antioxidant activity (DPPH-IC50 = 21.12 ± 3.20 µg/mL and TPC= 221.61 ± 7.49 mg GAE/g) that may reduce the oxidative stress effects in the cells that subsequently lowers the risk of DM. The RP-HPLC analysis of the ethanolic extract revealed presence of flavonoids in the herbs that may have contributed to this activity (60).

Kaempferol is a flavonoid of the flavonols subgroup consisting of four hydroxyl groups and a ketone group (44) and was detected in *C. caudatus* leaves. It is known as an oxidative stress-reducing agent which potentially inhibits the α-glucosidase enzyme (IC50: 1.16 × 10-5 mol/L) and also found to react in a mixed-mode by partially binding to the active site residues of the observed protein crystal structure. Kaempferol interacts with the residues located at the active site entrance, blocking the substrate entrance, thus resulting in inhibition of the enzyme activity (61). Besides that, the effects of kaempferol in HFD and STZ-induced diabetic mice displayed significant effects in ameliorating hyperglycaemia, hyperinsulinemia, and circulating lipid profile. Kaempferol intake has improved lipolysis, glycogenesis and reversed the impaired insulin-regulated glucose transporter (Glut-4) and AMPK expression in myocytes and adipocyte cells. It can improve glucose tolerance and blood insulin levels associated with increased islet beta-cell mass upon treatment (62).

Rutin typically belongs to the subgroup of flavonols. In this study, it is rutinoside quercetin (O-glycoside) of which the hydroxy group attached to the C ring, which substituted with glucose and rhamnose sugar groups (44). A previous study reported that it was able to improve glucose and insulin level lipid profiles in HFD and STZ-induced type 2 DM animal model. The compound also has the potential to protect pancreatic beta cells by decreasing oxidative stress (63–64). Meanwhile, catechin (flavan-3-ols) which is the most common compound in tea leaves were found to have a high affinity towards the active site of the α-glucosidase enzyme crystal structure with the lowest binding energy of −7.25 kcal/mol with a total of four significant hydrogen bonds and interaction with active site residues of TYR63, ARG197, ASP198, GLU233, ASN324 and ASP 326 (65). Another flavonoid which belongs to the flavone group that is found ubiquitously in edible plants and fruits is luteolin. The hydroxyl moieties of luteolin play an essential role in the inhibitory activity of both α-glucosidase (IC50: 26.15 mM) and α-amylase (IC50: 4.88 mM) enzymes. The compound exhibited a significant therapeutic effect as an antidiabetic agent through the inhibition of protein tyrosine phosphatase (PTPB1) enzyme (IC50: 6.70 µM) that regulates the insulin signalling pathway (66). Another mechanism involved in the luteolin action is the activation of peroxisome proliferator-activated receptor-gamma (PPARγ). PPARγ would improve insulin sensitivity and stimulate the serine/threonine kinase (AKT2) phosphorylation in adipocytes (67).

Isoquercetin is an O-glycoside derivative of flavonoid quercetin which exhibits various pharmacological effects. Supplementation of isoquercetin to STZ-induced diabetic rats indicated notably normalized serum glucose and insulin levels close to standard drug (glibenclamide) effects. The results can be found notably in insulin signalling modulation and carbohydrate metabolizing enzyme genes via regulation of mRNA expression (68). The continual study of isoquercetin supplementation have also regulated the lipid profile effectively via reduction of TG, LDL, very-low-density lipoprotein (VLDL) and total cholesterol levels and improved the HDL level. The positive alteration takes place upon

the activation of AMPK-α and Acetyl-CoA Carboxylase (ACC) in diabetic rats, which subsequently reduces lipid synthesis in hepatocytes. The impairment of the AMPK-α in diabetic rats is known to stimulate the fatty acid syntheses and β-Hydroxy β-Methylglutaryl-CoA (HMG Co-A) reductase activity that leads to disruption in lipid metabolism thus causing the exaggerated lipid profile markers (69). Quercitrin and quercetin 3-O-galactoside (hyperoside) are also an O-glycoside of the flavonoid quercetin. An in silico study using quercitrin and hyperoside displayed their antidiabetic potential via stimulated interaction with four major proteins involved in the mechanism of DM. The study investigated the enzyme found in metabolic tissues (liver, adipose tissue, and central nervous system), namely 11β-hydroxysteroid dehydrogenase type I (11β-HSD1). The inhibition of this cortisone reductase is a targeted treatment of T2DM, which is a glucortinoid-associated disease. The study also analysed glutamine-fructose-6-phosphate amidotransferase (GFAT), which is the key control enzyme that catalyses the formation of glucosamine 6-phosphate. GFAT is responsible to limit the flow of glucose into the hexosamine pathway. Besides that, the PTP1B and Mono-ADP ribosyltransferase-sirtuin-6 (SIRT6) may induce blood glucose levels. It plays a role in mechanisms such as deoxyribonucleic acid (DNA) repair, inflammation, and glycolysis. The compounds displayed high affinity towards the protein docked with low binding energy levels of -9.4, -7.9, -9.0 and -9.3 kcal/mol by quercitrin while quercetin-3-galactoside measured -8.9, -7.8, -9.1, and -8.8 kcal/mol, respectively (70).

Apigenin is a trihydroxyflavone found ubiquitously in vegetables and fruits. It is known to have multiple pharmacological actions, including antidiabetic properties. Apigenin treatment to the STZ-induced diabetic rat group with developing nephropathy, improved oxidative stress and renal dysfunction thus suppressing further development of renal dysfunction. Besides that, apigenin supplementation in HFD and STZ-induced diabetic rats have ameliorated the blood glucose and lipid profiles and downregulated inflammation and oxidative stress by increasing the SOD activity as well as improving glucose tolerance (71–72).

Myricetin is yet another flavonoid of the subgroup flavone with six hydroxyl groups, thus referred to as hexahydroxyflavone (73). The compound is found to improve glucose uptake in adipocytes without a functional insulin receptor. Myricetin-treated STZ-induced diabetic rats displayed regulated hyperglycaemia and insulin resistance (74). It also demonstrated potential antiobesity and antihyperlipidemic activities by decreasing the accumulation of TG in adipocytes (3T3-L1) of rats fed with HFD. Reduced body, visceral fat and plasma lipid were also observed in myricetin-treated rats (75).

Apart from these compounds, phenolic acids viz., chlorogenic, caffeic and ferulic acids are also known to inhibit digestive enzymes (16). An in vitro antidiabetic study reported that both chlorogenic (9.10 and 9.24 µg/mL) and caffeic acid (3.68 and 4.98 µg/mL) have effectively inhibited both the α-glucosidase and α-amylase enzymes with its IC50 value of ranging less than ten µg/mL, respectively (76). Chlorogenic acid was previously reported to have significant effects in the regulation of BW, visceral fat mass, TG, cholesterol, serum insulin and leptin levels, in addition to improved plasma adinopectin levels in obese mice experiment (36). In a cellular study, glucose uptake of active fractions comprising chlorogenic and caffeic acid were investigated. The results showed the synergistic effects of the compounds that modulated glucose metabolism via protein kinase B (Akt) expression on the cell line with insulin resistance, thus delaying the progressing hepatic dysfunction while alleviating its insulin sensitivity (77).

Caffeic acid in the investigation of its antioxidant and antidiabetic effects in STZ=induced diabetic rats showed tremendous potential in reducing measured glucose and improved insulin levels in the treated rat group. The compound exhibited its antioxidant capacity through the regulation of the oxidative stress mechanism associated with cytotoxic action of STZ that induces the formation of reactive oxygen species (ROS) leading to oxidative damages resulting in beta cell destruction that causes insulin suppression (78). Meanwhile, ferulic acid showed improvement in diabetic rats by upregulating glucose intake via the PI3-K pathway. Besides that, it also will regulate oxidative stress mechanism by enhancing catalase and superoxide dismutase enzymes to upregulate glucose intake (79).

Lycopene, a principal carotenoid is reportedly present in the *C. caudatus* leaves. The treatment using lycopene in the form of noisome of 100 and 200 mg/kg have effectively lowered the blood glucose levels in alloxan-induced rats upon treatment of 14 days. The treatment has also effectively reduced the other biochemical parameters, including total cholesterol, triglycerides, very low and low-density lipid (VLDL and LDL) compared to the control group (80). Besides that, the intervention of lycopene in the form of oil solution could stimulate the antioxidant enzyme activity to diminish the oxidative stress action thus regulate the glucose and lipid metabolism in STZ-induced diabetic rats (81).

Lutein is an antioxidant compound belonging to the carotenoids group that is found abundantly in *C. caudatus* leaves. It is a type of xanthophyll with zeaxanthin with proven retinal and macular protection against oxidative stress that contributes to DM. It essentially functions as light filter to protect the eye tissues from damaging ultraviolet rays that closely correlated in overcoming diabetic retinopathy, neuronal injury, age-related macular degeneration (AMD) and cataract (82–84). A recent study reported that the presence of

carotenoids such as lutein as the major constituent in Hibiscus sabdariffa, displayed significant antidiabetic effects of the plant extract by potentially regulating hyperglycaemia in STZ-induced diabetic rats (85). Lutein was also identified as the main pigment in marigold flowers which normalized the glucose levels in alloxan-induced diabetic rats which was characterised based on the reduced malondialdehyde levels in the treated mice. This is probably due to its antioxidant capacity through the inhibition of auto-oxidation of cellular lipids that eventually protects against cellular oxidative damages which subsequently lowers the risk of acquiring DM (86). Conclusively, the various phytoconstituents present in *C. caudatus* plant matrix contributes to its antidiabetic potential. The review suggests that the significant compounds from *C. caudatus* can be developed as an effective therapeutic agent for treating T2DM soon.

CONCLUSION

Recent studies suggest that *C. caudatus* is a medicinal plant that comes with considerable potentials in managing hyperglycaemia in diabetic patients as a functional food. The identified or isolated compounds from *C. caudatus* have the potential to be developed as a nutraceutical and pharmaceutical product. The tradition of consuming *C. caudatus* as a salad or 'ulam' should be continued and encouraged among local people.

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