



Potential of Clinacanthus Nutans as an Alternative Therapeutic Agent for Diabetes Mellitus

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Abstract. Target various aspects of the pathway in DM. One of plant traditionally used in Southeast Asia for diabetes treatment is Clinacanthus nutans (CN). Several studies have proven the pharmacological activity of CN as an antidiabetic. This study aims to review the potential of CN as an antidiabetic and discuss its possible mechanism of action. We present a literature review of original article regarding the antidiabetic effect of CN using invitro and/or invivo models. The article were obtain through Google Scholar database from 2012–2020 using the keywords “Clinacanthus nutans”, “antidiabetic”, and “hypoglycemia”. A total of 39 article were obtained, 25 articles were excluded being not relevant and the remaining 14 articles were selected for the study. CN possess antidiabetic effect through inhibition α -glucosidase, increasing insulin secretion and improving insulin resistance. This effect related to its antioxidant activity. Clinacanthus nutans can be selected as a source of industrial product development for the treatment of DM according to its medicinal value. The mechanism of action is still unclear, so further research are needed.

Keywords: Medicinal plants · Clinacanthus nutans · antidiabetic · antioxidant

1 Introduction

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by deficiency of insulin secretion, insulin action, or both leading to hyperglycemia (ADA, 2019). Chronic hyperglycemia lead to multiple abnormalities including macrovascular complications (coronary heart disease, stroke and peripheral vascular disease) and microvascular complications (end-stage renal disease, retinopathy and neuropathy) (Zheng et al. 2018; Harding et al. 2019). DM has become a metabolic disease with the highest prevalence in the world, according to IDF (2019), the global prevalence of DM was around 463 million (9.3% of the entire population) in 2019 and is estimated to increase to 578 million in 2030 and 700 million in 2045 with a death rate of 4.2 million in 2019.

Although insulin and currently available hypoglycemic drugs can control hyperglycemia, it's not completely prevent long-term vascular complications in diabetic patients (Thrasher, 2017). In addition, some of the side effects of these drugs cannot be tolerated by patients such as weight gain, hypoglycemia, and abdominal discomforts



Fig. 1. Morphology of *C. nutans* leaves (Kamarudin et al. 2017)

(Stein et al. 2013). Therefore, investigation for new antidiabetic agents have continued. Medicinal plants that have been widely used empirically in traditional medicine practices have gained attention as antidiabetics, not just for safer alternative drugs, but also multi-tasking abilities for targeting various aspects in the treatment of diabetes include lowering blood glucose, increasing insulin biosynthesis, improving insulin resistance, enhancing the antioxidant system and prevent long-term complications due to hyperglycemia (Patel et al. 2012).

Clinacanthus nutans, family of Acanthaceae, is widely used in Malaysia, Thailand, and Indonesia as a traditional medicine for treatment of various diseases including herpes infection, cancer, diabetes, and skin disorder (Tan et al. 2020). It's commonly called Sabah Snake Grass in Malaysia, or phaya yo in Thailand, or dandang gendis in Indonesia. Traditionally, it is commonly consumed as raw vegetables, juices, or herbal teas (A. Alam et al. 2016). The leaves of *C. nutans* are pale green, narrow oblong with sharp shoots, 2–12 cm long and 0.5–1.5 cm wide. There are 6–7 pairs of lines that stand out on the leaf surface and are covered by fine hairs (Kamarudin et al. 2017). Many studies have reported the pharmacological activities of *C. nutans* including antiviral (Kunsorn et al. 2013), antibacterial (Arullappan et al. 2014), antivenom (Daduang et al. 2005), antiinflammatory (Mai et al. 2016), anticancer (Wang et al. 2019), antioxidant (Kong et al. 2016), neuroprotective (Azam et al. 2019), analgetic (Zakaria et al. 2019), and antidiabetic (Umar Imam et al. 2019). However, there has not been a comprehensive literature review on the antidiabetic potential of *C. nutans*. In this review, the beneficial effects and proposed mechanisms of *C. nutans* in diabetes are discussed (Fig. 1).

2 Methods

We present a literature review involved research article using Google Scholar database from 2012–2020. Search conducted with the keywords “*Clinacanthus nutans*” “antidiabetic” or “hypoglycemic”. The articles were selected first by the title, then by the summary, and finally by reading the full text. The inclusion criteria are research article on the the antidiabetic effect of *C. nutans* using invitro or invivo models. Articles were excluded if they were review articles, editorial material and book chapters.

3 Result

A total of 39 article were obtained, 25 articles were excluded being not relevant to the scope of this review and the remaining 14 articles were selected for the study. After selecting these articles, we conducted a review by mainly assessing author name, publication year, objective, research model, type of extract and dose, and main findings of each research.

4 Discussion

4.1 Antidiabetic Activity of *C. Nutans* Using Invitro Studies

A search of in vitro studies on the antidiabetic activity of *C. nutans* found 6 relevant articles (Table 1). All studies evaluated the inhibitory activity of CN against α -glucosidase and α -amylase. α -glucosidase is an enzyme that hydrolyze carbohydrates into glucose in the small intestine, whereas α -amylase is the enzyme that hydrolysis of alfa-1,4-glucan bonds in starch, maltodextrins and maltooligosaccharides into simple sugars (dextrin, maltotriose, maltose and glucose) (Tundis et al. 2010). Although this enzymes is not directly implicated in the etiology of diabetes, the inhibition of α -glucosidase and α -amylase can significantly reduce the post-prandial glucose levels and therefore can be an important strategy in the management of metabolic disorders, including type 2 diabetes mellitus (Riyaphan et al. 2018).

Lee et al. (2014) demonstrated that the methanol extracts of *C. nutans* inhibited α -glucosidase activity (leaf 13.57% and stem 17.67%) at concentration of 5 mg/mL. Wong

Table 1. Brief Summary of Invitro Studies on Antidiabetic activity of *C. nutans*

No	Reference	Methods	Study model	Treatment	Inhibitory Effect
1	(Lee et al. 2014)	invitro	α -glukosidase inhibition test	methanol extract	leaf 13.57%, IC50 19.09 μ g/mL stem 17.67%, IC50 19.74 μ g/mL
2	(Wong et al. 2014)	invitro	α -glukosidase inhibition test	aqueos extract	88.2%, IC50 30 μ g/mL
3	(Khoo et al. 2015)	invitro	α -glukosidase inhibition test	ethanol extract	Leaf 41.7%, stem 35.7% IC50 not determined
4	(M. A. Alam et al. 2017)	invitro	α -glukosidase inhibition test	methanol extract	72.16%, IC50 37.47 μ g/mL
5	(Abdullah & Kasim, 2017)	invitro	α -amylase inhibition test	ethanol extract	64.25%, IC59 4.28 μ g/mL
6	(Murugesu et al. 2018)	invitro	α -glukosidase inhibition test	methanol extract	IC50 3,07 μ g/ml

et al. (2014) found that the aqueous extract of *C. nutans* in a higher dose (50 mg/mL) showed high levels of inhibition α -glucosidase activity (88.2%, IC₅₀: 30 mg/mL). Khoo et al. (2015) showed that the ethanol extract of *C. nutans* inhibited α -glucosidase activity up to 41% at concentration of 5 mg/mL. Alam et al. (2017) reported on the α -glucosidase inhibitory activity of *C. nutans* methanol extract showed that butanol fraction had significantly higher α -glucosidase inhibitory activity (72.16%, IC₅₀: 37.47 μ g/mL), which is close to the standard quercetin (positive control) (IC₅₀: 38.54 μ g/mL). Murugesu et al. (2018) demonstrated that the methanol extracts of *C. nutans* with n-hexan and ethyl asetat fraction showed inhibition α -glucosidase activity (IC₅₀ 3,07 μ g/ml). Abdullah & Kasim (2017) demonstrated that the ethanol and aqueous extracts of *C. nutans* inhibited α -amylase activity (64.25%). Based on this study, the methanolic extract of *C. nutans* leaves was the type of extract that showed the best α -glucosidase inhibitory activity, where the butanol fraction showed a greater inhibitory effect. In addition, there was a significant correlation of the α -glucosidase inhibitory with the antioxidant activity and the total flavonoid contents of the fractions (Alam et al. 2017).

4.2 Antidiabetic Activity of *C. Nutans* Using Invitro Studies

In experimental studies with in vivo models (Tab. 3), the effect of *C. nutans* was observed in various doses from 15 mg/kg to 500 mg/kg with different treatment periods between 9 to 28 days. Antidiabetic effect has been shown from *C. nutans* leaves extracted with aqueous, methanol and ethanol solvents. The glucose-lowering effect of *C. nutans* has been reported significantly in several studies, including administration of aqueous extract of *C. nutans* leaves 150 mg/kg for 9 days in mice induced by alloxan 50 mg/kg (Nurulita et al. 2012), administration of ethanolic extract of *C. nutans* leaves 15 mg/kg for 14 days in rats induced by a diet high in fat and fructose (Retnaningsih et al., 2019), and administration of ethanol extract of *C. nutans* leaves 75 mg/kg for 14 days in rats induced by STZ 50 mg/kg (Dewinta et al. 2020).

The effect of *C. nutans* in increasing serum insulin concentration significantly was reported in study by Umar Imam et al. (2019) on administration of leaves aqueous extract 200 mg/kg for 28 days in high fat diet (HFD) and streptozotocin (STZ) induced rats. The other study by Sarega et al. (2016a) on administration of leaves aqueous and methanolic extracts at doses of 500 and 250 mg/kg for 7 weeks in high fat and high cholesterol (HFHC) rats enhances serum insulin. There are no data suggesting that increased insulin secretion is due to improvement in pancreatic β cell dysfunction. Studies on insulin resistance using a homeostatic model have shown that aqueous and methanolic extracts of *C. nutan* leaves can increase insulin sensitivity marked by decreased insulin resistance biomarkers retinol binding protein 4 (RBP4) and mediated through upregulation of the gene encoding insulin receptor substrate (IRS), phosphatidylinositol-3-phosphate (PI3K), adiponectin and leptin receptors (Sarega et al. 2016b).

Oxidative stress has a significant role to trigger insulin resistance and contribute to development of type 2 diabetes (Pitocco et al. 2013). Many studies have been demonstrated the antioxidant properties of *C. nutans* using invitro method (Yong et al. 2013; Arullappan et al. 2014; Wong et al. 2014). The majority study use DPPH method because its an easy, fast, and reliable method that does not require a special device and reactions, as compared to other antioxidant assays (Aksoy et al. 2013). In vivo studies on the

antioxidant activity of *C. nutans* have been reported in 2 articles. Sarega et al. (2016a) demonstrated that the antioxidant activity of *C. nutans* is associated with the ability to modulate the expression of various antioxidant genes including superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase. Umar Imam et al. (2019) showed that *C. nutans* extract at a dose of 200 mg/kg for 4 weeks could significantly reduce markers of oxidative stress and increase total antioxidant levels in rats model of type 2 DM. Based on the data, it appears that the antioxidant activity of *C. nutans* occurs through mechanisms, including the ability to scavenge free radicals and modulate expression various antioxidant enzyme.

Obesity and dyslipidemia are health problems that contribute to impaired glucose homeostasis in diabetes. It affects a large number of people with sedentary lifestyles where physical activity is reduced and calorie intake is high. Free fatty acids promote oxidative stress and increase lipid peroxidation, which are implicated in the etiology of diabetes (Matsuda & Shimomura, 2013). Sarega et al. (2016a) reported that after 7 weeks of *C. nutans* treatment in mice fed a high-fat and high-cholesterol diet, they showed improvements in their lipid profiles, including a decrease in total cholesterol (TC), TG, LDL-C, and VLDL-C levels and an increase in HDL-C levels. Abdulwahid Kurdi et al. (2019) showed that a high-fat diet treated with *C. nutans* (1500 mg/kg) led to significant reductions in body weight and relative visceral fat.

The beneficial effect of *C. nutans* on sorbitol-related complications was evaluated by Umar Imam et al. (2019). The results showed that aqueous extract of *C. nutans* could be reduced the sorbitol contents in the kidney and nerve significantly suggests that it could be used to manage diabetic neuropathy and nephropathy due to sorbitol accumulation in these organs. Diabetes is also associated with complications of the development of atherosclerosis and cardiovascular disease. Administration of *C. nutans* in study by Azemi et al. (2020) could to increase endothelial vasodilation and reduce endothelial contraction through expression of eNOS protein thereby improving endothelial dysfunction in diabetic rats.

4.3 Antidiabetic Mechanism of *C. nutans*

The research articles in this review indicate that *C. nutans* extract has potential as an antidiabetic. The exact mechanism by which *C. nutans* exhibits antidiabetic activity needs to be clarified by further studies, the proposed mechanism is shown in Fig. 2. *C. nutans* reduces the absorption of carbohydrates from the small intestine and prevents a postprandial rise in blood glucose levels. *C. nutans* reduces fasting hyperglycemia possibly due to decreased endogenous glucose production in the liver. *C. nutans* increases insulin secretion from pancreatic β cells. *C. nutans* reduces insulin resistance in peripheral tissues which may be associated with reduced obesity, improved lipid profile, reduced oxidative stress and increased antioxidant enzymes. *C. nutans* prevents diabetes complications due to accumulation of sorbitol in kidney, lens, and nerves and restores endothelial dysfunction in diabetes.

Table 2. Brief Summary of Invitro Studies on Antidiabetic activity of *C. nutans*

No	Reference	Methods	Study model	Treatment	Effect
1	(Nurulita et al. 2012)	in vivo	Mice induced by aloxan 50 mg/kg	Leaves aqueos extract dose 50, 100, and 150* mg/kg for 9 days	↓ FBG
2	(Umar Imam et al. 2019)	In vivo	Rat induced by HFD and STZ 35 mg/kg	Leaves aqueos extract dose 100 and 200* mg/kg for 28 days	↓ FBG ↑ insulin ↓ Total cholesterol, ↓ LDL, ↓ TG, ↑ HDL ↓ liver F2-isoprostane ↑ liver total antioxidant status ↑ aldose reductase in kidney, lens, and nerve ↓ sorbitol dehydrogenase in kidney, lens, and nerve no histologic changes in kidney and liver
3	(Retnaningsih et al. 2019)	in vivo	Rat induced by high fat and fructose diet	Leaves ethanol extract dose 15*, 31, 47 mg/kg for 14 days	↓FBG
4	(Azemi et al. 2020)	in vivo	Rat induced by HFD and STZ 40 mg/kgBB	Leaves methanol extract dose 500 mg/kg for 28 days	↓ FBG ↑ endothelial-dependent vasodilatation ↓ endothelial-dependent contraction ↑ eNOS protein expression
5	(Dewinta et al. 2020)	in vivo	Rat induced by STZ 50 mg/kgBB	Leaves ethanol extract dose 75*, 150, 300 mg/kg for 14 days	↓FBG

(continued)

Table 2. (continued)

No	Reference	Methods	Study model	Treatment	Effect
6	(Sarega et al. 2016b)	in vivo	rat induced by high fat and cholesterol diet	Leaves aqueous and methanol extract dose 500*, 250*, 125mg/kg for 7 weeks	↓ dyslipidemia ↑ serum and hepatic markers of antioxidant status (SOD, GPx) ↓ Serum markers of oxidative stress (F2-isoprostane) ↓ Hepatic markers of oxidative stress (MDA) mRNA levels of hepatic antioxidant genes (SOD, CAT, GPx, and GSR)
7	(Sarega et al. 2016b)	in vivo	rat induced by high fat and cholesterol diet	Leaves aqueous and methanol extract dose 500*, 250*, 125mg/kg for 7 weeks	↓ FBG ↑ Insulin ↓ HOMA-IR ↓ serum RBP4 ↑ serum adiponektin ↓ serum leptin ↑ mRNA levels of insulin resistance-related genes (IRS, PI3K, reseptor adiponektin dan reseptor leptin)
8	(AbdulwahidKurdi et al. 2019)	in vivo	Mice induced by HFD	Leaves methanol extract dose 500,1000,1500* mg/kg for 21 days	↓ body weight ↓ visceral fat ↓ muscle saturated fatty acid compositions

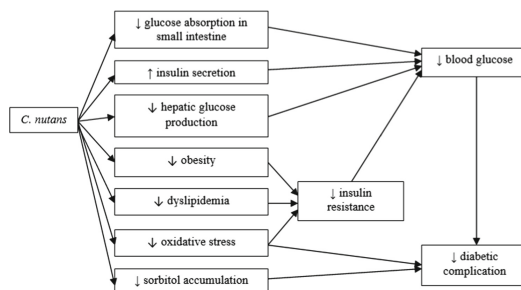


Fig. 2. Schematic pathways for the antidiabetic activity of *C. nutans*, ↑: increase; ↓: decrease.

5 Conclusions

Many studies have shown that *C. nutans* extracts possess antidiabetic effect with the mechanism as α -glucosidase inhibitor, decreasing hepatic glucose production, increasing insulin secretion, and improving insulin resistance. Given the increasing interest in plant resources as potentially cost-effective and safer alternatives, these plants have the potential to be a good source of functional ingredients as antidiabetics. There is a need to further evaluate the potential use of *C. nutans* in modulating cellular signaling pathways in diabetes and also to confirm the bioactive compounds responsible for the observed effects.

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