Antidiabetic activity of *Coccinia grandis* (L.) Voigt: Bioactive constituents, mechanisms of action, and synergistic effects

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**ABSTRACT**

Diabetes mellitus is a disease caused by irregular carbohydrate metabolism in association with an inadequate insulin level and insulin resistance. As synthetic drugs generate undesired side effects, the treatment of diabetes using natural medicines, especially medicinal plants, has become a potential alternative therapy. Medicinal plants contain many secondary metabolites and play a crucial role in diabetes mellitus therapy. For many years, *Coccinia grandis* L. Voigt (family: Cucurbitaceae) has been widely utilized, especially in India and Sri Lanka, as a traditional remedy. All parts of this medicinal plant have promising antidiabetic activity with possible mechanisms of action, i.e., regeneration of β-cells in the pancreas, stimulation of insulin secretion, restoration of antioxidant enzymes, enhancement of glucose uptake, regulation of metabolic enzymes, amelioration of the lipid profile, and inhibition of digestive enzymes. The combination of this plant extract with other plants also results in a synergistic effect that enhances its antidiabetic efficacy and reduces the side effects. In this review paper, we present recent findings regarding the antidiabetic activity of *C. grandis* both *in vitro* and *in vivo*, along with its mechanisms of action. We also discuss the synergistic effect of the combination of *C. grandis* with other plants in order to enhance the antidiabetic potency. Related articles published from 1988 to 2020 in the databases PubMed and Google Scholar were used in this narrative review. This article provides a scientific basis for the antidiabetic activity of *C. grandis*.

**INTRODUCTION**

Diabetes mellitus is a chronic condition caused by abnormal glucose metabolism with hyperglycemia as its main feature. The world population suffering from diabetes (aged 20–79 years) was 463 million in 2019 (9.3% of the world’s total population). It is estimated that this number will rise to 578 million (10.2%) in 2030 and 700 million (10.9%) in 2045 (IDF, 2019). Diabetes is one of the top 10 causes of death worldwide. Approximately 90% of people with diabetes mellitus have the type two form, which is associated with population aging, obesity, and economic advancement, as well as urbanization, which is in turn associated with a more sedentary lifestyle and higher consumption of unhealthy foods (Basu et al., 2013; Hu, 2011; Viljoen and Sinclair, 2011).

Patients with diabetes are more likely than healthy people to develop severe and life-threatening complications, reduced quality of life, and undue family stress. Type 2 diabetes is usually treated with antidiabetic drugs, such as sulfonlureas, metformin, acarbose, thiazolidinediones, and meglitinitides. However, the use of these drugs has disturbing adverse effects, such as nausea, vomiting, diarrhea, dilution anemia, weight gain, improved risk of heart failure and fractures, fever, hypoglycemia, and decreased appetite (Andersen and Christensen, 2016; Gómez-Huelgas et al., 2018; Kancherla et al., 2017; Loke et al., 2009; Seaquist et al., 2013).

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In view of the side effects of the abovementioned medications, the treatment of diabetes has shifted to the use of natural remedies. Herbal medicines are chosen for the treatment of diabetes because they are effective, easy to find, easy to process, free of side effects, and affordable (Arunugam et al., 2013). The phytochemicals contained in herbal medicines are responsible for their antidiabetic activity. It is known that herbal medicines contain phenolics, flavonoids, terpenoids, alkaloids, and other phytochemicals that exert antidiabetic-related effects, such as lowering blood glucose levels, lipid peroxidation, and insulin resistance, increasing insulin levels, inhibiting hexokinase enzyme activity, and acting as antioxidant and anti-inflammatory agents (Modak et al., 2007; Mukherjee et al., 2013). It is currently estimated that 75%–80% of individuals worldwide depend on herbal remedies for some of their healthcare needs (Ekor, 2014; Karunamoorthi et al., 2013; Kumar et al., 2014).

One of several medicinal herbs traditionally used to treat diabetes is Coccinia grandis (L.) Voigt. This plant has been widely used by the people of India and Sri Lanka for generations to treat various diseases (Attanayake et al., 2016). Coccinia grandis contains phytochemicals such as cephalandrine a, cephalandrine b, cephalandrol, lupeol, taraxerol, β-sitosterol, tritriacontane, taraxerone, and stigmast-7-en-3-one (Tupe et al., 2015). Each part of this plant has been studied either as a single extract or even in combination with other plants or with oral hypoglycemic agents for its antidiabetic function. A number of findings have been published on the mechanism of action of C. grandis in lowering blood glucose levels.

Plant extracts have been used not only in single formulas but also in combinations to increase efficacy and decrease side effects. This combination approach provides effective glycemic control for diabetes treatment (Bell, 2013; Sekar et al., 2019). Combinations of two or more extracts often exert synergistic pharmacological effects. In this review, we discuss the antidiabetic effect of C. grandis and provide insight into its mechanism of action. We also address the synergistic impact of combining extracts of this plant with those of other plants or with oral antidiabetic drugs. Electronic databases (PubMed and Google Scholar) were used to search for relevant articles published from 1988 to 2020 with the keywords “antidiabetic/antihyperglycemic activity of Coccinia grandis;” “Coccinia indica;” “Cephalandra indica;” “ivy gourd;” “combination effect;” and “antidiabetic synergistic effect.”

PLANT IDENTITY

Coccinia grandis (L.) Voigt or ivy/little gourd (in English) belongs to the family Cucurbitaceae. It is a creeping plant that can climb quickly over trees, shrubs, and fences (Wasantwisut and Viriyapanich, 2003). According to the scientific nomenclature, some synonyms for C. grandis are Coccinia cordifolia, C. indica, C. indica Naud., and Bryonia grandis (Holstein, 2015). Coccinia grandis originates from tropical areas of Asia and Africa. This plant thrives in Thailand, India, Malaysia, Indonesia, and the Philippines. People in different countries label this plant with specific local names, for example, kundree, olekavi, and telacucha (India), tum leung (Thailand), papasan and boluteke (Indonesia), and pepasan (Malaysia) (Jamwal and Kumar, 2016; Sakharkar and Chauhan, 2017; Wasantwisut and Viriyapanich, 2003). The taxonomic classification of C. grandis is the following (Monalisa et al., 2014):

- **Kingdom:** Plantae.
- **Division:** Tracheophyta.
- **Class:** Magnoliopsida.
- **Order:** Cucurbitales.
- **Family:** Cucurbitaceae.
- **Genus:** Coccinia grandis Wight & Arn.
- **Species:** Coccinia grandis (L.) Voigt.

The leaf structure ranges from pentagon to heart-like, and the leaves, arranged alternately along the length of the stem (Fig. 1), have a hairless upper surface and a hairy lower surface (Pekamwar et al., 2013). The flowers of C. grandis are white, large, and star shaped, while the fruits are soft and green. The fruit is ovate to ellipsoid in shape and becomes bright red when ripe (Ediriweera and Ratnasooriya, 2009). Coccinia grandis is a dioecious plant, so if seeds and fruit are required, both male and female plants should be planted. At 20°C, the seeds normally germinate in 2–4 weeks (Waisundara et al., 2015). Coccinia grandis has been utilized as a herbal medicine in India for hundreds of years. It has also been recorded in the Ayurvedic medical system (Wakte and Patil, 2019).

**PHYTOCHEMICAL CONSTITUENTS**

Coccinia grandis is a plant with bioactive phytochemicals that offer many advantages in the treatment of diabetes mellitus. Some researchers have demonstrated the phytochemical content...
of this plant. Cephalandrine A, cephalandrine B, cephalandrol, β-sitosterol, and triacontane were discovered in the ethanolic extract of leaves and aerial parts of C. grandis (Deokate and Khadabadi, 2011), while rutin, quercetin-3-O-neohesperidoside, kaempferol-3-O-rutinoside, kaempferol-3-O-neohesperidoside, kaempferol-3-O-glucoside, kaempferol-hexoside, oleuropein, and ligstrose were found in the methanolic extract of the leaves (Al-Madhagy et al., 2019). The existence of quercetin in the extract of C. grandis aerial parts was also reported by Randhawa et al. (2015). In the root extract, the presence of lupeol, β-sitosterol, β-amyrin, coccinioside-k, stigmaster-7-en-3-one, flavonoid glycoside ombuin, 3-O-arabinofuranoside, and 3-O-β-((α-l-arabinopyranosyl)-(1→2)-β-d-glucopyranosyl)-(1→3)-β-hydroxylup-20(29)-en-28-oic acid was reported (Deokate and Khadabadi, 2011). The methanolic fruit extract contained 2-methoxy-4-vinylphenol, phenol-2-methoxy-5(1-propenyl), undecanol, 2(3h)-furanone, phenol, 3,7,11,15-tetramethyl-2-hexadecen-1-ol, 2,4-bis(1,1-dimethylethyl), benzofuranone, 2-methyl-z,z-3, 13-octadecadienol 9,12-octadecadienoic acid, hexadecanoic acid methyl ester, β-sitosterol acetate, tocopherol, stigmatossterol, ethisteron, camposteroel, and campessterol. Some phytochemicals found in the aqueous fruit extract were hexadecanoic acid methyl ester, dodecanedioic acid, isosteviol, biphenyl, α-tocopherol, hexadecanoic acid, n-pentadecanoic acid, oleic acid, linoleic acid, and lukianol (Kondhare and Lade, 2017).

Among the phenolic groups, flavonoids are the most abundant and are known to have potential antidiabetic activity (Mukhopadhyay and Prajapati, 2015; Patra and Chua, 2011). Flavonoids comprise more than 4,000 different compounds that occur naturally in plants (Jasmin and Jaitak, 2019). Some flavonoids play a role in reducing hyperglycemia through the increased proliferation of β-cells, stimulation of insulin secretion, reduced apoptosis, and control of liver glucose metabolism (AL-Ishaq et al., 2019). As shown in Figure 2, four flavonoid compounds have been identified in C. grandis extract, namely, quercetin (1), kaempferol (2), ombuin (3), and rutin (4).

One of the flavonoid compounds most studied for its antidiabetic activity is quercetin. This compound is also able to overcome complications related to diabetes mellitus. The mechanism of action by which quercetin and its glycosides exert antidiabetic activity has been reported previously and is presented in Figure 3. In human intestinal Caco-2 cells, quercetin inhibited glucose transporter 2 (GLUT2) and decreased glucose and fructose uptake by 75% (Kwon et al., 2007). Quercetin was also reported to inhibit the activity of two hydrolytic enzymes (α-amylase and α-glucosidase), which degrade carbohydrates to simple sugars. This mechanism delayed the digestion of carbohydrates and controlled postprandial blood glucose (Kumar et al., 2013; Limanto et al., 2019). Pancreatic β-cell protection against oxidative stress is another mechanism by which quercetin exhibits antidiabetic activity. Oxidative stress results from reactive oxygen species (ROS) overproduction and causes damage to the β-cells in the pancreas. The treatment of streptozotocin (STZ)-induced diabetic rats with quercetin protected β-cells directly through reduced levels of nitric oxide and malondialdehyde (MDA) and indirectly through increased antioxidant enzymes activity. In this study, insulin secretion was found to be increased (Adewole et al., 2007). The 5' adenosine monophosphate-activated protein kinase (AMPK) pathway was induced by quercetin glycoside extracted from Vaccinium vitis-idaea (Eid et al., 2010). An increase in glucose transporter 4 (GLUT4) expression was observed in diabetic rats treated with quercetin. This increase in GLUT4 expression stimulated the uptake of glucose in muscle cells (Alam et al., 2014). The liver is one of the organ targets of antidiabetic drugs that lower the blood glucose level. Hyperglycemia occurs with hepatic glucose overproduction in a process called gluconeogenesis. Quercetin suppressed gluconeogenesis in an AMPK-dependent manner by inhibiting the glucose-6-phosphate dehydrogenase (G6PDH) enzyme in the isolated perfused liver and hepatoma H4II cells (Eid et al., 2015; Gasparin et al., 2003). Glucose uptake in the liver occurred by

![Figure 2. Flavonoid compounds found in C. grandis extracts.](attachment:image.png)
stimulating the activity of key enzymes that participated in glycolysis and the pentose phosphate pathway (Yang et al., 2018).

ANTIDIABETIC ACTIVITY

Chronic hyperglycemia is the main characteristic of diabetes mellitus, which is caused by imperfections in the secretion and/or action of insulin (American Diabetes Association, 2009). The presence of insulin as an anabolic hormone can generate carbohydrate, lipid, and protein metabolic abnormalities (Kharroubi and Darwish, 2015). Preclinical studies regarding the antidiabetic activities of C. grandis have been previously reported in the literature. The mechanisms by which C. grandis exerts antidiabetic activity have been proposed and summarized in Table 1. These mechanisms of action include stimulation of insulin secretion, regeneration of β-cells, restoration of antioxidant enzymes, enhancement of glucose uptake, regulation of metabolic enzymes, amelioration of lipid profiles, and inhibition of digestive enzymes. Here we summarize how C. grandis exerts antidiabetic activity via the aforementioned mechanisms of action.

Pancreatic β-cell regeneration and increased insulin secretion

In the pancreatic islets, also known as islets of Langerhans, insulin is produced by β-cells (Da Silva Xavier, 2018). The function of β-cells can be affected by hyperglycemia that involves complex and multifactorial mechanisms. Some evidence suggests that the mechanisms involved include ROS production, gene transcription alteration, and protein-expression-mediated oxidative stress and increased β-cell apoptosis (Alsahl and Gerich, 2010). Regeneration of pancreatic cells and restoration of insulin secretion are assisted by reduced intact free radicals and increased antioxidant enzyme activity. In several studies, C. grandis extract was discovered to decrease blood glucose levels by regenerating β-cells and increasing insulin secretion. According to Sudha et al. (2011), the water, chloroform (60%), and ethanol (70%) fruit extracts of C. grandis [250 mg/kg body weight (b.w.)] lowered the blood glucose levels of diabetic rats induced by alloxan in 7 hours. Pal et al. (2013) found that giving the C. grandis mother tincture (750 μl/kg b.w.) to STZ-induced diabetic rats for 3 weeks stimulated insulin secretion and also β-cell regeneration in the pancreatic islets, thus decreasing blood glucose levels. A mother tincture is a type of homeopathic medicine made from specific plant or animal extracts. In order to make a mother tincture, plant or animal material is extracted with alcohol or water in a particular ratio (Banerjee, 2002; Scheepmaker and Gower, 2011). Enhancement of insulin expression was observed when diabetic rats induced by high-fat-fructose and STZ were given the mother tincture or its active ingredients, i.e., 6-centesimal (6C) and 30-centesimal (30C). In this research, a dose of 20 µl/100 g b.w. was applied twice daily for 30 days. Centesimal is a term of homeopathic dilution in which an amount of the mother tincture is diluted with alcohol or distilled water by a factor of 100 at each stage and then vigorously shaken (“succussion”) in a new vial (Sampath et al., 2013). The administration of the water extract of C. grandis leaves (0.75 g/kg b.w.) orally to diabetic rats induced by STZ for 30 days revealed that the serum insulin, C-peptide, islet diameter, and islet count were increased significantly (Attanayake et al., 2015). The same findings were also confirmed when alloxan-induced rats were given the C. grandis leaf aqueous extract (0.75 g/kg b.w., orally) for 30 days (Attanayake et al., 2019).

Insulin secretion is also affected by the excessive secretion of the growth hormone (GH) produced by the pituitary gland. This hormone inhibits insulin secretion by damaging the pancreatic β-cells. Releasing factors and inhibitory factors (IF) released by hypothalamic neurons are responsible for GH secretion. Rastogi et al. (1988) revealed that the administration of the C. grandis mother tincture (usually prepared as homeopathic therapy, in 41% alcohol v/v) to diabetic rats induced by alloxan

Figure 3. Schematic overview of the antidiabetic activity of quercetin, the main flavonoid in C. grandis. GLUT2: glucose transporter 2, AMPK: 5’ adenosine monophosphate-activated protein kinase, GLUT4: glucose transporter 4, ↑: increase, and ↓: decrease.
| Plant extract                                      | Treated subject                     | Dose (administration route) | Duration | Observed effects                                                                 | References                  |
|---------------------------------------------------|-------------------------------------|----------------------------|----------|----------------------------------------------------------------------------------|-----------------------------|
| Homeopathic mother tincture (in 41% alcohol v/v)  | Diabetic rats induced by alloxan    | 25, 50, 75, 100 µml/100 g b.w. [peroral or intraperitoneal (i.p.)] | 30 days  | ↓ blood glucose, ↑ pancreatic β-cell counts, ↓ blood glucose                      | Rastogi et al. (1988)       |
| Ethanolic (60%) extract of leaves                 | Diabetic rats induced by STZ         | 200 mg/kg b.w. (peroral)   | 90 minutes | ↓ glucose-6-phosphatase activity, ↓ fructose-1,6-bisphosphatase activity, ↑ G6PDH activity, ↑ blood glucose, ↑ hepatic glycogen, ↑ hexokinase activity, ↑ glycogen synthetase activity, ↓ glycogen phosphorylase activity | Shhibib et al. (1993)       |
| Extract of fruits containing pectin               | Normoglycemic rats                  | Fruit extract (2%) along with the diet (peroral) | 45 days  | ↓ blood glucose, ↑ hepatic glycogen, ↓ glycosylated hemoglobin, ↑ total hemoglobin, ↑ plasma insulin, ↑ hexokinase activity, ↑ lipogenic enzymes activity, ↓ gluconegogenic enzymes | Kumar et al. (1993)         |
| Ethanolic (95%) extract of leaves                 | Diabetic rats induced by STZ         | 200 mg/kg b.w. (peroral)   | 45 days  | ↓ serum glucose, ↓ blood glucose, ↓ b.w., ↑ liver glycogen, ↓ TC, TG, VLDL, and LDL, ↑ HDL, ↓ serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase (ALP) | Venkateswaran and Pari (2002) |
| Extract of aqueous stems                          | Rat L8 myoblasts                    | 0.5–2.0 mg/ml              | 24 hours | ↑ 2-DG uptake, ↑ GLUT1 expression                                                  | Purintrapiban et al. (2006) |
| Aqueous leaves extract                            | Diabetic rats induced by alloxan     | Not mentioned (peroral)    | 21 days  | ↓ blood glucose, ↓ TC, TG, VLDL, and LDL                                          | Manjula and Ragavan (2007)  |
| n-Hexane, chloroform, ethyl acetate, and n-butanol fruits extract | Diabetic rats induced by STZ         | 200 mg/kg b.w. (peroral)   | 30 days  | ↓ blood glucose                                                                  | (Shakya, 2008)              |
| Extract of aqueous stems                          | Rat L8 myoblasts                    | 0.5–2.0 mg/ml              | 24 hours | ↑ 2-DG uptake, ↑ GLUT1 expression                                                  | Purintrapiban et al. (2006) |
| Methanolic (95%) aerial parts extract             | Diabetic rats induced by STZ         | 100 and 200 mg/kg b.w. (peroral) | 15 days  | ↓ serum glucose, ↓ blood glucose, ↓ b.w., ↑ liver glycogen, ↓ TC, TG, and LDL, ↑ HDL, ↓ serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase (ALP) | Balaraman et al. (2010)     |
| Hydroalcoholic (1:1) fruits extract               | Diabetic rats induced by alloxan     | 200 mg/kg b.w. (peroral)   | 14 days  | ↓ blood glucose, ↓ urea, ↑ HDL, ↓ TC, TG, VLDL, and LDL                          | Gunjan et al. (2010)        |
| Methanolic (50%) extract of leaves                | α-Amylase enzyme (in vitro)         | 10 ml/g dry weight         | —        | Showed enzyme inhibitory activity                                                 | Sutradhar et al. (2010)     |
| Methanolic extract of leaves                      | Swiss albino mice given 2 g/kg b.w. of glucose after extracts administration | 50–400 mg/kg b.w. (peroral) | 1 hour prior to extracts administration | ↓ blood glucose                                                             | Sutradhar et al. (2011)     |

Continued
| Plant extract                                                                 | Treated subject                                                                 | Dose (administration route)                  | Duration | Observed effects                                      | References      |
|------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------|----------|------------------------------------------------------|-----------------|
| Pet-ether, ethyl acetate, and chloroform fractions of ethanolic leaves extract | Diabetic rats induced by STZ                                                     | 150 mg/kg b.w. (i.p.)                       | 24 hours | ↓ blood glucose, ↓ TC, TG                            | Islam et al. (2011) |
| Ethanolic (64%) leaves extract                                                | Diabetic rats induced by STZ                                                     | 200 mg/kg b.w. (peroral)                    | 90 minutes | ↓ blood glucose, ↓ FFA, ↓ liver arginase activity ↓ blood glucose, ↑ b.w., ↓ glucose uptake in 3T3 cells | Shibib et al. (2012) Pal et al. (2013) |
| Mother tincture                                                              | Diabetic rats induced by STZ                                                     | 750 µl/kg b.w. (peroral)                    | 3 weeks  | ↓ blood glucose, ↑ b.w., ↑ β-cells regeneration, ↓ blood glucose, ↓ glucose uptake in 3T3 cells | Pal et al. (2013) |
| Homeopathic mother tincture                                                   | Diabetic rats induced by high fat, high fructose, and STZ                        | 6-centesimal and 30-centesimal at dose of 20 µl/100 g b.w. (peroral) | 30 days  | ↓ TC, TG, and LDL, ↑ HDL levels, ↑ Akt mRNA and protein, ↑ GLUT4 | Sampath et al. (2013) |
| Aqueous leaves extract                                                        | Diabetic rats induced by alloxan                                                | 0.25–2.00 g/kg b.w. (peroral)               | 4 hours  | ↓ blood glucose, ↑ glucose tolerance, ↓ blood glucose, ↑ glucose tolerance, ↑ b.w., ↓ urine sugar, ↓ kidney index and glomerular filtration rate | Attanayake et al. (2013) Gurukar et al. (2013) |
| Fruits and extract of leaves incorporated to AIN-76 diet                     | Diabetic rats induced by STZ                                                     | 5% and 10% of extract in the diet           | 45 days  | Exhibited enzyme inhibitory activity                | Alagar et al. (2014) |
| Decoction, alcohol maceration, water maceration, and Soxhlet extraction of fruits | α-Glucosidase enzyme (in vitro)                                                 | Various concentrations of extract           | —        | ↓ blood glucose, ↓ TC, ↓ urea, ↓ SGOT, SGPT, and total protein ↓ Hemoglobin A1c (HbA1c), ↓ fructosamine, ↑ islet diameter, islet count, and islet regeneration | Islam et al. (2014) Attanayake et al. (2015) |
| Leaves decoction                                                             | Diabetic rats induced by alloxan                                                | 3 ml/kg b.w. (peroral)                      | 14 days  | Exhibited enzyme inhibitory activity                | Patel and Ishnava (2015) |
| Aqueous extract of leaves extract                                             | Diabetic rats induced by STZ                                                     | 0.75 g/kg b.w. (peroral)                    | 30 days  | Exhibited enzyme inhibitory activity                | Continued |
| Methanolic extract of fruit and callus                                        | α-Amylase enzyme (in vitro)                                                     | Various concentrations of extract           | —        | Exhibited enzyme inhibitory activity                | Continued |
| Plant extract                         | Treated subject                                                                 | Dose (administration route) | Duration | Observed effects                                                                                       | References                           |
|--------------------------------------|---------------------------------------------------------------------------------|-----------------------------|----------|--------------------------------------------------------------------------------------------------------|---------------------------------------|
| Ethanolic leaves extract             | α-Amylase enzyme *(in vitro)*, yeast cells *(in vitro)*, and diabetic rats induced by STZ | 50–500 mg/kg b.w. *(peroral)* | 21 days  | Exhibited enzyme inhibitory activity, ↑ glucose uptake, ↓ blood glucose, ↑ serum insulin, ↑ glycogen and HDL, ↓ TC, TG, LDL, and VLDL, ↑ SOD, CAT, and reduced glutathione, ↓ necrosis, ↑ population and size of islets ↓ blood glucose, ↓ ALT, AST, and ALP, ↓ MDA, ↑ GSH, GR, GPx, and GST, ↑ HDL-C levels ↓ TC, LDL-C, VLDL-C, and TG ↓ blood glucose | Mohammed *et al.* (2016)               |
| Aqueous extract of leaves            | Diabetic rats induced by STZ                                                    | 0.75 g/kg b.w. *(peroral)*  | 30 days  | ↓ blood glucose, ↓ ALT, AST, and ALP, ↓ MDA, ↑ GSH, GR, GPx, and GST, ↑ HDL-C levels ↓ TC, LDL-C, VLDL-C, and TG ↓ blood glucose | Attanayake *et al.* (2018)            |
| Chloroform extract of fruits         | Diabetic rats induced by STZ-nicotinamide                                       | 250 mg/kg b.w. *(peroral)*  | 7 days   | Exhibited radical-scavenging activity, antiglycation potential, and insulinotropic property             | Kaushik *et al.* (2017)               |
| Methanolic extract of fruits         | In vitro antioxidant, antiglycation, cytoprotective effect, and insulin secretion assays developed to the extract | Various concentrations     | —        | ↓ serum glucose, ↑ serum insulin, ↓ TBARS, nitrite, and advanced glycation end product’s levels, ↑ SOD and GSH | Meenatchi *et al.* (2017)             |
| Mother tincture and its potencies of 6C and 30C | Diabetic rats induced by STZ-nicotinamide                                     | 2 ml/kg b.w. orally *(peroral)* | 30 days  | ↓ serum glucose, ↑ serum insulin, ↓ TBARS, nitrite, and advanced glycation end product’s levels, ↑ SOD and GSH | Kishore and Singh (2017)             |
| Aqueous leaves and stems extract     | α-Amylase and α-glucosidase *(in vitro)*                                       | Various concentrations     | —        | Exhibited enzyme inhibitory activity ↓ blood glucose, ↓ HbA1c, ↑ insulin, ↑ glycogen, ↑ hexokinase activity, ↑ G6PDH, ↓ glucose-6-phosphatase, ↓ fructose-1,6-bisphosphatase ↑ serum insulin, ↑ C-peptide, ↑ islets counts, ↑ β-cells regeneration ↓ blood glucose, ↑ b.w., ↑ renal function, ↓ TC, TG, LDL, and VLDL, ↓ HDL, ↓ TBARS level, ↑ GSH and SOD | Pulbutr *et al.* (2017)               |
| Ethanolic extracts of fruits (mature unripe) | Diabetic rats induced by STZ                                                  | 125–750 mg/kg b.w. *(peroral)* | 30 days  | ↑ hexokinase activity, ↑ G6PDH, ↓ glucose-6-phosphatase, ↓ fructose-1,6-bisphosphatase ↑ serum insulin, ↑ C-peptide, ↑ islets counts, ↑ β-cells regeneration ↓ blood glucose, ↑ b.w., ↑ renal function, ↓ TC, TG, LDL, and VLDL, ↑ HDL, ↓ TBARS level, ↑ GSH and SOD | Packirisamy *et al.* (2018)           |
| Aqueous leaves extract               | Diabetic rats induced by alloxan                                               | 0.75 g/kg b.w. *(peroral)*  | 30 days  | ↑ C-peptide, ↑ islets counts, ↑ β-cells regeneration ↓ blood glucose, ↑ b.w., ↑ renal function, ↓ TC, TG, LDL, and VLDL, ↑ HDL, ↓ TBARS level, ↑ GSH and SOD | Attanayake *et al.* (2019)            |
| Mother tincture and its potencies of 6C and 30C | Diabetic rats with nephropathy induced by STZ                                | 2 ml/kg b.w. *(peroral)*  | 75 days  | ↓ TC, TG, LDL, and VLDL, ↑ HDL, ↓ TBARS level, ↑ GSH and SOD | Kishore and Singh (2019)             |
with doses of 25–100 µml/100 g b.w. for 30 days was observed to normalize blood glucose levels and maintained the levels for 14–20 days after drug withdrawal. Additionally, the pancreatic β-cell count was also reported to reach the normal range. These effects were probably caused by the release of IF, which inhibited the secretion of GH from the adenohypophysis, thus regenerating and restoring the β-cell count.

**Restoration of antioxidant enzymes**

Excessive ROS production induces oxidative stress, which is a major factor in the development of diabetes and its complications (Asmat et al., 2016). ROS, including free radicals, can cause oxidation of proteins, peroxidation of lipids, and damage to the enzyme system and cellular organelles (Bansal and Bilaspuri, 2011; Kishore and Singh, 2017). Therefore, an extract with the ability to scavenge free radicals is required in order to minimize oxidative stress (Roy et al., 2013). Preclinical antidiabetic studies revealed that peroral administration of STZ induces oxidative stress by selectively targeting β-cells of the pancreas via plasma membrane GLUT2 and causes β-cell destruction. In rats, STZ causes hyperglycemia and oxidative stress (Mao et al., 2015). In an experiment, the methanolic extract of *C. grandis* fruits scavenged free radicals [1,1-Diphenyl-2-picrylhydrazyl (DPPH)] with the half maximal inhibitory concentration (IC₅₀) value of 165.69 mg/ml (Meenatchi et al., 2017). The extract was also able to scavenge H₂O₂ and superoxide anion radicals. The scavenging activity was found to increase with increasing extract concentration. The existence of phenolic and flavonoid compounds in the *C. grandis* fruit extract was found to be responsible for its antioxidative activity.

Oxidative stress may occur due to a mismatch between the antioxidative protective systems in the human body and the formation of ROS, including free radicals. Reduced glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) are the antioxidant enzymes that have been reported to protect the human body against free radicals (Halliwell, 2009; Oguntibeju, 2019). The levels of these enzymes decreased in diabetic rats, as compared with those in nondiabetic rats. Diabetic rats also had a higher content of thiobarbituric acid-reactive substances (TBARS), which may be attributed to a rise in oxygen free radicals (Kishore and Singh, 2019). Attanayake et al. (2018) discovered that the aqueous extract of *C. grandis* leaves administered to diabetic rats induced by STZ for 30 days was able to decrease the concentration of MDA and to increase the activity of reduced glutathione (GSH), glutathione reductase (GR), glutathione S-transferase (GST), and glutathione peroxidase (GPx) in liver homogenates. These results demonstrated that the extract scavenged free radicals that inactivated metabolic enzymes. The mother tincture of *C. grandis* and its dilutions 6C and 30C (2 ml/kg b.w.) given orally to STZ-nicotinamide-induced diabetic rats for 30 days increased the activities of antioxidant enzymes (GSH and SOD) and decreased TBARS level (Kishore and Singh, 2017). The same result was also found when the mother tincture of *C. grandis*, 6C, and 30C (2 ml/kg b.w.) were given to diabetic rats induced by STZ with nephropathy for 75 days (Kishore and Singh, 2019).

**Enhancement of glucose uptake**

Glucose disposal is mainly deposited into skeletal muscles, and this process is insulin dependent. Insulin is well known for assisting glucose utilization in muscle cells. To promote the uptake of glucose, insulin recruits GLUT4 to the plasma membrane. Purintrapiban et al. (2006) revealed that water extract of *C. grandis* enhanced the uptake of 2-deoxyglucose (2-DG) in rats L8 myotubes for 16 hours of incubation in a dose-dependent manner. In addition, they revealed that the *C. grandis* water extract promoted glucose transport by increasing the amount of GLUT4 (an insulin-dependent protein highly expressed in fat tissue and skeletal muscle) on the cell surface and increased the synthesis of the glucose transporter 1 (GLUT1) protein. Sampath et al. (2013) studied the effect of the *C. grandis* mother tincture on high-fat-fructose- and STZ-induced diabetic rats at a dose of 20 µl/100 g b.w. for 30 days. Increased GLUT4 messenger ribonucleic acid (mRNA) was observed in the cytosol, plasma membrane, and gastrocnemius muscle. This led to the increase in the GLUT4 level and enhancing glucose uptake activity.

**Regulation of metabolic enzymes**

A low insulin level can affect the catalysis of metabolic reactions by hepatic enzymes. The main enzymes in the gluconeogenesis pathway are glucose-6-phosphatase and fructose-1,6-bisphosphatase. When rats developed diabetes, the activity of these enzymes increased substantially. As a result, the concentration of glucose in the blood was elevated. Oral administration of the *C. grandis* leaf ethanolic extract (60%) at a dose of 200 mg/kg b.w. was reported to depress glucose-6-phosphatase and fructose-1,6-bisphosphatase enzyme activity in diabetic rats induced by STZ after 18 hours of fasting. This extract was also reported to activate G6PDH in the glucose metabolism pathway (the hexose monophosphate shunt pathway), which resulted in an increase in glucose oxidation (Shibib et al., 1993). In another study, STZ-induced diabetic rats were administered an ethanolic (95%) extract of *C. grandis* leaves (200 mg/kg b.w.) for 45 days. This extract was found to inhibit the glucose-6-phosphatase and fructose-1,6-bisphosphatase enzymes in the gluconeogenic pathway and to improve glucose uptake by stimulating hepatic hexokinase in the glycolytic pathway (Venkateswaran and Pari, 2002).

Hexokinase is an insulin-dependent enzyme that plays a key role in the homeostasis of glucose. This enzyme is involved in the glycolytic pathway and metabolism of glucose by adenosine triphosphate to produce glucose-6-phosphate. When hexokinase activity increased, glucose utilization in glycolysis was also increased. The activity of this enzyme was significantly reduced when rats developed diabetes. Consequently, the concentration of glucose in the blood was increased. Kumar et al. (1993) investigated the influence of the *C. grandis* fruit extract (2% along with the diet) on the activity of hexokinase in normoglycemic rats for 45 days. The results showed that pectin from fruit extracts increased glycolysis by activating hexokinase enzyme activity and enhanced the rate of glycogenesis. They also found that pectin from the fruit extracts increased the glycogen synthase activity and decreased the glycogen phosphorylase activity in glycogenolysis. Increased hexokinase and G6PDH activity and increased glycogen content have also been reported by Packirisamy et al. (2018). They revealed that ethanolic extracts of fruits (mature unripe) given orally to STZ-induced diabetic rats at doses of 125–750 mg/kg b.w. for 30 days inhibited the action of glucose-6-phosphatase and fructose-1,6-bisphosphatase.
Amelioration of lipid profiles

Diabetes and dyslipidemia are related remarkably. When rats develop diabetes, the lipid profile is impaired by hyperglycemia, which is accompanied by abnormalities in lipoprotein metabolism. This results in an increase in triacylglycerol (TG), total cholesterol (TC), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) and a decrease in high-density lipoprotein (HDL) due to the mobilization of excessive fat from adipose tissues (Bhat et al., 2012). In normal rats, insulin inhibits lipolysis and reduces free fatty acid (FFA) release by suppressing lipase activity. However, the activity of lipase is increased in diabetic rats. Consequently, it stimulates the release of FFA. Thus, more acetyl-CoA and cholesterol are produced during β-oxidation of FFA (Nasirian et al., 2019). Several studies have shown that giving diabetic rats an extract of C. grandis improves their lipid profiles. Manjula and Ragavan (2007) reported decreases in blood glucose, TC, TG, VLDL, and LDL in alloxan-induced diabetic rats when the C. grandis aqueous leaf extract was given. A similar result was also obtained by Balaraman et al. (2010), who administered a 95% ethanolic extract of C. grandis aerial parts to STZ-induced diabetic rats in doses of 100 and 200 mg/kg b.w. for 15 days. Furthermore, a hydroalcoholic (1:1) fruit extract of C. grandis at a dose of 200 mg/kg b.w. for 14 days was reported to increase HDL and decrease TG, LDL, VLDL, and TC levels in alloxan-induced diabetic rats. Attanayake et al. (2018) showed that oral administration of the aqueous leaf extract of C. grandis for 30 days in STZ-induced diabetic rats resulted in the reduction of TC, Low-density lipoprotein cholesterol (LDL-C), Very low-density lipoprotein cholesterol (VLDL-C), and TG levels and elevation of High-density lipoprotein cholesterol (HDL-C) level. Most recently, the mother tincture and its dilution at 6C and 30C (2 ml/kg b.w.) ameliorated the lipid profile, including TC, TG, LDL, VLDL, and HDL, in STZ-induced diabetic rats (Kishore and Singh, 2019).

Inhibition of digestive enzymes

Reducing postprandial hyperglycemia by inhibiting carbohydrate-degrading enzymes in the gastrointestinal tract is indeed one of the therapies targeted to diabetes mellitus. Extracts with enzyme inhibitory activity delay carbohydrate digestion and prolong the overall digestion time of carbohydrates, resulting in a decrease in glucose absorption (Sy et al., 2017). The hydrolysis of starch to maltose, maltotriose, α-(1-4)-oligoglucons, and α-(1-6)-oligoglucons is catalyzed by the α-amylase enzyme. The mixture of oligosaccharides is degraded into glucose by the α-glucosidase enzyme. Therefore, reducing glucose absorption in the digestive tract by inhibiting the activity of these carbohydrate-degrading enzymes is one of the therapeutic approaches for managing diabetes mellitus (Sudha et al., 2011).

The C. grandis leaf extract was reported to have potent α-amylase and α-glucosidase inhibitory activities. Jaiboon et al. (2010) revealed that the methanolic (50% v/v) extract of C. grandis leaves inhibited α-amylase enzymatic activity. The inhibitory activity of α-amylase by the ethanolic extract of C. grandis leaves was also reported by Mohammed et al. (2016) with an IC_{50} of 78.47 ± 0.18 µg/ml. This activity was higher than that of ethyl acetate and the n-hexane extracts, with IC_{50} values of 94.65 ± 0.15 and 110.27 ± 0.04 µg/ml, respectively. The fruit extract of C. grandis obtained by various methods of extraction, i.e., decoction, alcohol maceration, water maceration, and Soxhlet extraction, showed inhibition of α-glucosidase activity (Alagar et al., 2014). The methanol extract of C. grandis fruits, callus, and different combination mixtures of callus at a concentration of 1.0 mg/l inhibited α-amylase enzymatic activity with inhibition percentages of 54.29%, 75.72%, and 80.00%, respectively (Patel and Ishnava, 2015). Pulburt et al. (2017) revealed that the aqueous extract of leaves and stems of C. grandis significantly inhibited α-amylase activity with IC_{50} of 8.09 ± 0.72 and 8.06 ± 1.27 mg/ml, respectively. It also inhibited the action of α-glucosidase with IC_{50} values of 77.66 ± 9.16 µg/ml and 0.75 ± 0.11 mg/ml, respectively.

SYNERGISTIC EFFECT AND COMBINATION OF EXTRACTS

The antidiabetic activity of a plant extract might be increased by combining it with other extracts and/or drugs that have similar activity. The synergistic effect of these combinations can increase efficacy and decrease side effects. Synergism is the effect that occurs when the combined effects of two or more drugs are greater than the sum of their individual effects. This occurs because the phytochemical compounds in the combined extracts act on different targets in the pathogenic process; consequently, the overall therapeutic efficacy is increased (Rasoanivoh, 2011). The combination index (CI) has been used frequently to determine the interactions between the components of the combined extracts. This approach was introduced by Chou and Talalay using median effect principle (Chou and Talalay, 1984) and was computerized later using ComputSyn software (Chou, 2006). The formula used for the calculation of the CI was as follows:

\[
CI = \frac{D_{100}}{E_{100}} + \frac{D_{200}}{E_{200}},
\]

where \(D_{100}\) and \(D_{200}\) are the concentrations of each extract/drug in combination that produced an x effect and \(E_{100}\) and \(E_{200}\) are the concentrations of each extract/drug alone that produced the same effect. Synergy, additivity, and antagonism interactions are implied by CI values of <1, 1, and >1, respectively (Wong et al., 2019).

The combination of C. grandis extract with other extracts/drugs has been mentioned in several publications (Table 2). The combination of C. grandis leaves and the Abroma augusta root aqueous extract (300 mg/kg b.w.) exhibited antihyperglycemic and antihyperlipidemic activities better than the single plant extract in STZ-induced albino rats for 8 weeks. These results provide evidence of a synergistic interaction between C. grandis and A. augusta (Eshrat, 2003). The synergistic interaction was also reported by Mallick et al. (2007), who combined the C. grandis leaf extract and Musa paradisiaca root extract. Both plant materials were extracted in a 2:3 ratio with water and methanol. The combined extract (1:1) at a dose of 80 mg/100 g b.w. was administered orally to diabetic rats induced by STZ for 14 days. The combined extract exhibited higher antihyperglycemic activity than the single extract in terms of reducing the level of fasting blood glucose and raising the glucose tolerance and the level of serum insulin. In addition, the combined extract greatly increased glucose-6-phosphatase, G6PDH, hexokinase, and glycogen levels in the liver. Further research conducted by Mallick et al. (2009)
Table 2. The combination of C. grandis extracts and synthetic drugs.

| C. grandis extracts | Combination with | Diabetic model animals | Dose (administration route) | Duration | References |
|---------------------|------------------|------------------------|-----------------------------|----------|------------|
| Water extract of leaves | Water extract of A. augusta roots | Diabetic rats induced by STZ | 300 mg/kg b.w. (peroral) | 8 weeks | Eshrat (2003) |
| Water-methanol water extract of leaves | Water-methanol extract of M. paradisiaca roots | Diabetic rats induced by STZ | 80 mg/0.5 ml olive oil/100 g b.w. (oral gavage) | 14 days | Malick (2007) |
| Water-methanol water extract of leaves | Water-methanol extract of M. paradisiaca roots | Diabetic rats induced by STZ | 80 mg/0.5 ml olive oil/100 g b.w. (oral gavage) | 14 days | Malick et al. (2009) |
| Water extract of fruits | Water extract of M. citrifolia fruits | Diabetic rats induced by alloxan | 300 mg/kg b.w. (peroral) | 30 days | Prakash et al. (2010) |
| Ethanolic extract of leaves | Glibenclamide | Diabetic rats induced by alloxan | 100, 150, and 200 mg/kg b.w. (peroral) | 45 days | Eliza and Usha (2011) |
| Petroleum ether-methanol extract of leaves | Petroleum ether-methanol extract of Salvadora oleoides leaves | Diabetic rats induced by alloxan | 150 mg/kg b.w. (peroral) | 15 days | Saklani et al. (2012) |
| Extract of leaves from the Green Chem industry, Bangalore (Batch No. CIL/12005) | Acarbose | Diabetic rats induced by -HFD- low-dose STZ | 200 mg/kg b.w. (peroral) | 8 weeks | Kohli and Kumar (2014) |
| Extracts of whole plant methanolic | T. foenum-graecum (L.) methanolic extracts | Alloxan-induced diabetic rats | 125 mg/kg b.w. (C. grandis) and 250 mg/kg b.w. (T. foenum-graecum) (peroral) | 21 days | Ruby et al. (2014) |
| Aqueous leaves extract | Aqueous extract of A. bilimbi L. fruits | In vitro study | Ratios of 1:3, 1:1, and 3:1 | — | Putra et al. (2020) |
| Ethanolic extract of leaves | Pioglitazone | Diabetic rats induced by HFD-STZ | 200 mg/kg b.w. (peroral) | 7 weeks | Basavarajappa et al. (2020) |

indicated that the combination of the C. grandis leaves and M. paradisiaca root aqueous-methanol extract was able to modulate the protein involved in the regulation of metabolic disorders as well as diabetes. Interestingly, it also showed a protective effect against diabetes by increasing the capacity of β-cell regeneration. The aqueous extract of C. grandis and Morinda citrifolia fruits (300 mg/kg b.w.) reduced serum glucose and increased serum insulin in alloxan-induced diabetic rats in 30 days (Prakash et al., 2010). Synergism was also reported by other researchers who combined whole plant methanolic extracts of C. grandis and Trigonella foenum-graecum L. Alloxan-induced diabetic rats were given this combined extract at doses of 125 mg/kg b.w. (C. grandis) and 250 mg/kg b.w. (Trigonella foenum-graecum L.) for 21 days (Ruby et al., 2014). The level of blood glucose was found to be decreased significantly. This finding suggested that the combined extract was more active than the single extract. Saklani et al. (2012) found that giving alloxan-induced diabetic rats a petroleum ether-methanol extract of C. grandis and Salvadora oleoides leaves (150 mg/kg b.w.) for 15 days decreased blood glucose levels, compared with administration of the standard drug glipizide. Furthermore, the combined extract had an major impact on lipid profiles, alanine aminotransferase/aspartate amino transferase (AST) activity, and serum creatinine and urea levels. Recently, Putra et al. (2020) reported that the aqueous extract of C. grandis leaves and Averrhoa bilimbi fruits showed higher in vitro DPPH radical-scavenging and α-amylase inhibition activities than that of the single extract.

In addition to the combination with other plant extracts, C. grandis was also combined with antidiabetic drugs as reported by Eliza and Usha (2011), who combined the ethanolic leaf extract of C. grandis at doses of 100, 150, and 200 mg/kg b.w. with the antidiabetic drug glibenclamide (0.125 mg/kg b.w.). Alloxan-induced diabetic rats were given the extract-drug combination orally at 15 days intervals. After 45 days of therapy, the extract-drug combination lowered the concentration of blood glucose and normalized TC and TG levels. Additionally, GSH and lipid peroxide levels were also reduced. The C. grandis leaf extract (200 mg/kg b.w.) combined with acarbose (5 mg/kg b.w.) reduced blood glucose levels compared with the single extract and drug administered to STZ-induced diabetic rats with a high-fat diet (HFD) for 8 weeks. This combination also showed stronger antioxidant activity (SOD, CAT, TBARS, and GSH) than the single extract and drug (Kohli and Kumar, 2014). The combination effect of the C. grandis ethanolic leaf extract and pioglitazone was recently reported by Basavarajappa et al. (2020). The combination of extract (200 mg/kg b.w.) and pioglitazone (7 mg/kg b.w.) was given orally to HFD-fed STZ-induced diabetic rats for 7 weeks. They discovered that the extract-drug combination normalizes blood glucose levels and lipid profiles and decreases oxidative stress more efficiently than a single extract and pioglitazone alone. In rats treated with the extract-drug combination, an improved renal protection effect was also observed.

CONCLUSION

This review provides comprehensive information regarding the activity of C. grandis as an antidiabetic remedy. This plant is a promising agent for treating diabetes mellitus. The mechanism of action of these plant extracts in lowering
blood glucose levels has been elucidated, i.e., by pancreatic β-cell regeneration, insulin secretion stimulation, antioxidant enzyme restoration, glucose uptake enhancement, metabolic enzyme regulation, lipid profile amelioration, and digestive enzyme inhibition. The combination of the *C. grandis* extract with other plant extracts and antidiabetic drugs showed a synergistic effect that is beneficial for increasing efficacy and safety.

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**AUTHORS’ CONTRIBUTIONS**

I Made Wisnu Adhi Putra initiated and drafted the review article. Nanang Fakhirudin, Arief Nurrochmad, and Subagus Wahyono conducted revisions and reviews on the initial draft prior to submission to the journal website.

**CONFLICT OF INTEREST**

All authors declare no conflicts of interest.

**ETHICAL APPROVAL**

This article does not contain any studies with human participants or animals performed by any of the authors.

**LIST OF ABBREVIATIONS**

ALP: Alkaline phosphatase; AMPK: 5’ adenosine monophosphate-activated protein kinase; AST: Aspartate amino transferase; b.w.: Body weight; CAT: Catalase; Cl: Combination index; 2-DG: 2-Deoxyglucose; DPPH: 1,1-Diphenyl-2-picylhydrazyl; FFA: Free fatty acid; G6PDH: Glucose-6-phosphate dehydrogenase; GLUT1: Glucose transporter 1; GLUT2: Glucose transporter 2; GLUT4: Glucose transporter 4; GH: Growth hormone; GSH: Reduced glutathione or glutathione with sulfhydryl group; G6PDH: Glucose-6-phosphate dehydrogenase; GR: Glutathione reductase; GST: Glutathione S-transferase; HDL: High-density lipoprotein; HFD: High-fat diet; IC50: Half maximal inhibitory concentration; IF: Inhibitory factors; i.p.: Intraperitoneal; LDL: Low-density lipoprotein; MDA: Malondialdehyde; mRNA: Messenger ribonucleic acid; ROS: Reactive oxygen species; SGPT: Serum glutamic pyruvic transaminase; SGOT: Serum glutamic oxaloacetic transaminase; SOD: Superoxide dismutase; STZ: Streptozotocin; TC: Total cholesterol; TBARS: Thiobarbituric acid-reactive substances; TG: Triacylglycerol; VLDL: Very low-density lipoprotein.

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