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Anti-diabetic potential of ivy gourd (*Coccinia grandis*, family: Cucurbitaceae) grown in Sri Lanka: A review

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Abstract
Leaves of ivy gourd; *Coccinia grandis* (L.) Voigt (Family: Cucurbitaceae) is one of the well-known leafy vegetables, which has been consumed by Sri Lankans for centuries. The therapeutic potential of ivy gourd against diabetes is brought mainly by its anti-hyperglycemic, β-cell regenerative, antihyperlipidemic and antioxidant properties. In addition, the optimum effective therapeutic dose of the aqueous *C. grandis* extract was found to be safe in terms of hepatotoxicity, renotoxicity, hematotoxicity *in vivo*. The scientific investigations confirmed the effectiveness of this leafy vegetable for the development of potential nutraceuticals against diabetes mellitus.

Keywords: Anti-diabetic potential, *Coccinia grandis*, standardization, toxicity studies

Introduction
Diabetes mellitus has become a major global epidemic over the past few decades. The prevalence of diabetes has been increased worldwide and has reached alarming levels in many countries around the world. It is estimated that 415 million people (6.4% of the adult population worldwide) were affected by diabetes in 2015, and the number is projected to increase to 642 million in 2040. Accordingly, it is predicted to become the 7th leading cause of death in the world by the year 2040 [1].

In the past couple of decades, evidence from prospective observational studies and clinical trials has converged to support the importance of individual nutrients, foods, and dietary patterns in the prevention and management of diabetes mellitus. Medicinal plants have long been used as medications or/and as simple dietary adjuncts to the existing therapies since antiquity. Before the introduction of insulin in 1922, the treatments for diabetes mellitus relied mainly on the recommendations of herbal preparations of edible medicinal plants [2]. However, from the past to the present, the dietary recommendations for diabetes have widened, with the appreciation that fiber rich food such as leafy vegetables would be able to enhance the glycemic control of patients with diabetes and thereby prevent the progression of the disease into diabetic complications [3-5]. However, in this sense, the investigation of anti-diabetic activity of edible medicinal plants is imperative, as with proven *in vivo* efficacy these would be recommended as dietary adjuncts to the conventional therapies and more importantly are able to attribute for the development of potential sources of nutraceuticals.

A multitude of herbs, spices, and other plant materials have been described in the management of diabetes mellitus in Sri Lanka [6]. However, several edible medicinal plants have been attributed a special value in the diet of Sri Lankans. Ivy gourd; *Coccinia grandis* (L.) Voigt (Family: Cucurbitaceae) is one of the well-known leafy vegetables, which has been consumed by Sri Lankans for centuries. It is also known as scarlet gourd in English; Kowakka, Kobowakka, Kem-wel in Sinhala; Kovai, Kwai in Tamil. The plant is widely distributed in Southern, Western and North Central regions in the country. It is a perennial climber with single tendrils and glabrous leaves. Generally, the leaves have five lobes and are 6.5–8.5 cm long and 7–8 cm wide [7]. Even though that the reputed effects of leaf extract of *C. grandis* have not been evaluated critically, it is widely used for the glycemic control by the local population. Accordingly, the results of a cross sectional survey using an interviewer based questionnaire clearly showed that the leaves of *C. grandis* has been commonly used as a complementary and alternative medicine by patients with diabetes mellitus in Sri Lanka [7]. A number of scientific reviews are published on pharmacological properties of *C. grandis* grown in different geographical locations in the world however, to date a comprehensive report on anti-diabetic potential of *C. grandis* of Sri Lankan origin has not been published. The present review aims to provide a comprehensive summary of the investigations carried out on the anti-diabetic and toxicological effects of the leaves of Ivy gourd grown in Sri Lanka in order to corroborate its proposed anti-diabetic potential in patients with diabetes mellitus.

Anti-hyperglycemic activity: Hyperglycemia is the fundamental biochemical derangement in diabetes mellitus, causing oxidative and nitrosative stress, activation of inflammatory pathways and endothelial dysfunction, leading to vascular complications [8-10]. However, the effective blood glucose control is primarily targeted in the management of diabetes mellitus. Investigations carried out by Attanayake and coworkers [11, 12] demonstrated that the leaf extract of *C. grandis* of Sri Lankan origin exerted both acute and long term antihyperglycemic effects in healthy, alloxan induced and streptozotocin induced diabetic rats. The optimum therapeutic dose of the aqueous leaf extract of *C. grandis* upon a glucose load was 0.75g/kg in healthy and diabetic rats. Leaf extract of *C. grandis* at the optimum effective dose lowered the blood glucose concentration gradually during a period of four hours in diabetic rats. The highest reduction (33%) in the blood glucose concentration was observed in the second hour after the administration of *C. grandis* extract in streptozotocin induced diabetic rats. In addition, Munasinghe and coworkers [13] reported a phase 1 clinical trial of an ingestion of a meal containing 20 g of leaves of *C. grandis* mixed with a measured amount of scraped coconut and table salt were able show acute hypoglycemic effects in a selected group of healthy subjects. The acute antihyperglycemic activity of *C. grandis* may is due to a reduction in the absorption of glucose in the small intestine, stimulation of glucose induced secretion of insulin from the pancreatic β cells, enhancement of uptake of glucose by peripheral tissues etc. [14]. (Ndong, *et al*., 2007). The long term antihyperglycemic activity is also evident in *C. grandis* treated diabetic rats. The diabetic rats treated with the optimum therapeutic dose of the aqueous extract of *C. grandis* exhibited a remarkable glycemic control as evident by a reduction in the percentage of HbA_{1C} in streptozotocin induced diabetic rats[15]. Accordingly, the concentration of fasting serum fructosamine, insulin and C-peptide were decreased significantly in diabetic rats. The results reported by Attanayake *et al*. [15] corroborate with the findings on antihyperglycemic efficacy of *C. grandis* grown in India [16-18].

B-cell regenerative potency: The optimum pancreatic β-cell function is essential for the regulation of intracellular glucose homeostasis. Several studies have provided the evidence that loss of functional β-cell mass through apoptosis and impaired proliferation consequent to hyperglycemia is considered as a hallmark of diabetes mellitus [19]. Regulation of functional β-cell mass has been considered as a critical therapeutic challenge in patients with the disease [20]. However, islet cell regeneration has gained much interest and has been considered as a strategy to restore the loss of β-cell mass in diabetes mellitus. Stimulation of β-cell proliferation/regeneration may have an impact on the insulin-producing cells in the pancreas [21]. One such approach to foster restoration and regeneration of β-cells is from putative exogenous sources as edible medicinal plants [22]. Accordingly, the extract of *C. grandis* of Sri Lankan origin showed β-cell regeneration as evident through an increase in the number of insulin secreting β-cells in streptozotocin induced diabetic rats. An increase in the diameter of small, medium and large islets were found in *C. grandis* treated diabetic rats and it was confirmed that the functional mass of the islet and the entire regenerative capacity of the pancreas increased with the treatment of *C. grandis* extract in diabetic rats [15]. In contrast, none of the species of *C. grandis* except the variety found in Sri Lanka reported the β cell regenerative potency *in vivo* to date.

Anti-hyperlipidemic activity: Lipid abnormalities are postulated to be major causes for complications associated with diabetes mellitus. Indeed, dyslipidemia in diabetes mellitus is generally comprised with low levels of high-density lipoprotein cholesterol (HDL-C), high levels of low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) [23]. Several studies have revealed that a positive correlation between dyslipidemia and development of premature atherosclerosis, coronary insufficiency and myocardial infarction in diabetic subjects [9, 22]. Thus, effect of natural products in the management of diabetic complications has recently received considerable attention, highlighting the importance of edible leafy vegetables as regulators of metabolism of carbohydrate and lipids [24]. Recent studies by Attanayake and coworkers have demonstrated that a significant reduction in the concentration of serum TC, TG, LDL-C and an elevation in the concentration of HDL-C in streptozotocin induced diabetic rats on the 30th day of the study [15]. This is similarly mentioned by other authors who observed potential antihyperlipidemic effects in serum lipid parameters in diabetic rats with the leaf extract of *C. grandis* of Indian origin [25, 26]. The favorable effects of aqueous leaf extract of *C. grandis* on serum lipid parameters in addition to the glycemic control would be useful in the development of nutraceuticals targeting diverse disease pathologies of diabetes mellitus. The increase in the concentration of HDL-C by *C. grandis* is of therapeutic advantage as it improves the glycemic control as well as reduces the cardiovascular risk associated with diabetes mellitus. The strong anti-hyperlipidemic effect by the administration of *C. grandis* in diabetic rats could be through its control on hyperglycemia or/and direct actions on the absorption of intestinal cholesterol and biosynthesis of cholesterol as suggested by many authors [26, 27].

Anti-oxidant activity: Oxidative stress is one of the major factors underlying the resistance for insulin in disease pathogenesis of diabetes mellitus [28]. Elevated free fatty acids, glycation of proteins, other circulating factors, leptin and simultaneous decline of cellular antioxidant defense mechanisms in patients with diabetes contribute to cause an overproduction of reactive oxygen species [9].

Edible medicinal plant extracts with strong antioxidative properties have been the recent focus in diminishing cellular oxidative stress in diabetes mellitus. The increase in reactive oxygen species may lead to disruption of cellular functions, oxidative damage to membranes and lipid peroxidation that consequently lead to the occurrence of diabetic complications. In addition, it has been shown that dietary supplementation with natural antioxidants such as vitamins C and E, melatonin and flavonoids attenuates the oxidative stress in diabetic subjects [29]. The overall experimental data reported by Attanayake *et al*. [30] indicated that the administration of leaf extract of *C. grandis* was able to improve the activities of antioxidant enzymes such as glutathione reductase (EC 1.6.4.2), glutathione peroxidase (EC 1.11.1.9), glutathione S-transferase (EC 2.5.1.18), increase the concentration of reduced glutathione and decrease the concentration of malondialdehyde as a product in the lipid peroxidation in diabetic rats. In addition, the *in vitro* glycation induced protein cross-linking inhibitory effects of the leaf extract of *C.*

grandis was also proven [31]. The *in vivo* antioxidant activity is further corroborated by the relatively high *in vitro* antioxidant activity of *C. grandis* compared determined using three *in vitro* assays of 2,2-diphenyl-2-picrylhydrazyl hydrate (DPPH) radical scavenging activity, ferric reducing power (FRAP) and nitric oxide (NO) inhibition [32]. The *in vivo* antioxidative activity of *C. grandis* may be due to the presence of wide range of phytochemicals principally due to high content of polyphenolic and flavonoid compounds as suggested by Attanayake *et al*. [32].

Safety profile

Chemical standardization: Standardization of crude plant extracts involves the process of prescribing a set of standards or inherited characteristics, constant parameters, definitive quality and quantitative values that carry an assurance of quality, safety and reproducibility [33]. The *C. grandis* grown in Sri Lanka has a very low amount of acid insoluble ash content, and moderate level of total ash content indicates the purity of the leaves of *C. grandis* leaves that could be useful in human consumption and development of nutraceutical products. According to the recent report by Attanayake *et al* [34] heavy metals were not detected in *C. grandis* leaves of Sri Lankan origin.

***In vivo* toxicity studies:** The use of edible medicinal plants for therapeutic purposes has been increasingly popular as they are believed as beneficial and free of side effects [35, 36]. However, the rationale for the utilization of plant food has rested largely on long-term clinical experience with little or no scientific data on safety. Attanayake and coworkers reported that the administration of *C. grandis* at a range of doses (0.25 g/kg-2.00 g/kg) in healthy Wistar was well tolerated by test animals, suggesting it's *in vivo* safety. Further, the long term administration of the extract to Wistar rats for 28 days was not associated with adverse effects reflected in the general condition, growth, relative weight of organs, clinical biochemical, hematological values and more importantly did not cause abnormalities in histopathology of body tissues [37]. However, a proper clinical evaluation may be required to define a safe dosage in humans precisely.

Conclusion: This is the first scientific review that describes the potential anti-diabetic activities and toxicological effects of *C. grandis* grown in Sri Lanka. The fact that the aqueous leaf extract of *C. grandis* exert anti-hyperglycemic, anti-hyperlipidemic, antioxidant activities *in vivo* merits its use in the development of potential nutraceuticals against diabetes mellitus. However, there is an urgent need for the determination of its clinical efficacy on diabetic subjects through well-defined and adequately powered randomized controlled clinical trials before the recommendation of ivy gourd as an effective dietary supplement for patients with diabetes mellitus.

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