Story of Young Innovators in Health Sciences

A novel herbal capsule for the management of type 2 diabetes mellitus

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Overview of the research or innovation: The emerging epidemic of type 2 diabetes mellitus (T2DM) is a major health burden in the world. According to recent estimates, nearly half a billion people are living with diabetes mellitus globally. Despite the availability of several hypoglycemic drugs for the management of hyperglycemia in patients with T2DM, the growing impact of diabetes and its associated complications lead to one death per every eight second. *Coccinia grandis* (Linn.) Voigt (Family; Cucurbitaceae) is an edible perennial climber commonly found in Sri Lanka. From time immemorial, it has been widely used as an ingredient in Sri Lankan traditional herbal medicine for the treatment of several diseases including diabetes mellitus. Preclinical studies conducted by our research group showed promising antidiabetic effects of the aqueous leaf extract of *C. grandis in vivo* and *in vitro*.

Purpose/objectives of the research

The present innovation was aimed to develop an herbal capsule *C. grandis* and to determine the clinical utility in terms of efficacy and safety in patients with newly diagnosed T2DM.

Methods

The plant of *C. grandis* was authenticated by comparing authentic samples at National Herbarium, Royal Botanical Gardens, Peradeniya. The aqueous leaf extract was prepared, freeze dried and filled into gelatin capsules (500 mg per one capsule) to prepare the herbal capsule *C. grandis.* Newly developed herbal capsule *C. grandis* was standardized and its proximate and nutrient composition were determined. A three month long, randomized, double blind, placebo controlled clinical trial was conducted involving a total number of 158 patients with newly diagnosed T2DM, who attended the University Medical Clinic, Teaching Hospital, Karapitiya, Galle, Sri Lanka, to determine the safety and effectiveness of the herbal capsule *C. grandis*. Changes of glycemic parameters, lipid profile parameters, oxidative stress markers, inflammatory markers and toxicity parameters were determined at the baseline (month=0) and at the end of the intervention (month=3). Ethical clearance for the study was granted by Faculty of Medicine, University of Ruhuna, Sri Lanka (14.06.2017:3.9). The clinical trial protocol was registered in the Sri Lanka Clinical Trials Registry, Sri Lanka (SLCTR/ 2018/012).

Findings

In the process of standardization, it was revealed that none of the heavy metals (Hg, Pb, Cd, As) and microbial contaminants (aerobic plate count, total coliform, *Escherichia coli, Saccharomyces cerevisiae, Staphylococcus aureus, Salmonella*) were present beyond the upper limits defined by the World Health Organization. Chemical fingerprint profile including thin layer chromatogram, Fourier-transform infrared spectrum and liquid chromatography-mass spectrum showed characteristic peak patterns for the content of herbal capsule *C. grandis* which will be useful in the scaleup development of the herbal capsule in the commercialization. Preliminary phytochemical screening showed the presence of polyphenols, flavonoids, tannins, alkaloids, saponins, steroids and triterpenoids in the herbal capsule *C. grandis*. Proximate analysis revealed that the content of moisture, total ash, acid insoluble ash, water soluble ash, carbohydrate, protein, fat and fiber as 6.3±0.2, 42.9±0.1, 0.2±0.02, 22.4±0.8, 26.7±0.3, 29.8±0.4, 0.3±0.0 and 0.3±0.1 % respectively in the herbal capsule *C. grandis*. Nutrient composition analysis revealed the presence of vitamin B_1 and B_2 as 0.52±0.01 and 0.38±0.02 mg/100 g respectively and minerals of Ca and Mg as 3.7 and 0.2 mg/kg respectively in the herbal capsule *C. grandis*, showing the beneficial effects as a nutraceutical in addition to the therapeutic value. Overall, findings of the clinical trial showed significant mean±SD changes of glycemic parameters from the baseline to the end of the intervention in the test and the placebo groups as 0.66±0.52 and 0.06±0.64% for glycated hemoglobin ($p<0.001$), 1.91±2.95 and -1.28±9.32 mIU/L for insulin ($p<0.001$), 0.02±0.03 and -0.01±0.03 mmol/L for fructosamine ($p<0.001$), 1.43±0.55 and 0.04±0.48 mmol/L for fasting plasma glucose concentration ($p<0.001$), 1.73±1.31 and -0.37±3.22 for insulin resistance quantified by homeostatic model assessment ($p<0.001$). Significant mean±SD changes of lipid profile parameters from the baseline to the end of the intervention in the test and the placebo groups were 0.16±0.17 and -0.06±0.41 mmol/L for triglyceride ($p<0.001$), 0.07±0.08 and -0.04±0.20 mmol/L for very low density lipoprotein cholesterol ($p<0.001$). Significant mean±SD changes of oxidative stress markers were -3.25±3.93 and 1.42±4.84 U/L for glutathione reductase ($p<0.001$), 12.75±33.35 and -1.45±41.93 nmol/dL for malonaldehyde ($p=0.025$). Significant mean±SD changes of inflammatory marker; interleukin-6 from the baseline to the end of the intervention in the test and the placebo groups was 5.89±11.49 and 0.46±13.11 pg/mL ($p=0.002$). Hematological parameters (FBC), renal (creatinine), and liver (ALT, AST, ALP, γ-GT) safety parameters and blood pressure were within the normal physiological reference ranges at the base line and end of the intervention.

Conclusions

Standardization process and well define proximate and nutrient composition enhance the overall quality of the herbal capsule *C. grandis*. Administration of the herbal capsule *C. grandis* (500 mg per day) for three months for patients with newly diagnosed T2DM significantly improved the glycemic control, lipid alterations, antioxidant and anti-inflammatory status with well tolerated safety.

Practical implications

Standardized herbal capsule *C. grandis* with well-defined proximate and nutrient composition and mechanism of action will be an excellent phytomedicine or a nutraceutical with clinically proven safety and efficacy for it to be used in the early-stage management of T2DM and its complications.

Novelty

This is the first commercially viable herbal product developed from the aqueous leaf extract of *C. grandis*. Our research work proved the safety and clinical utility of the herbal capsule *C. grandis* against mild hyperglycemia, lipid abnormalities, oxidative stress and inflammation in newly diagnosed patients with T2DM for the first time.

Benefit to the society

Management of T2DM is hampered in developing countries like Sri Lanka by inadequate healthcare services, especially in the rural and semi urban localities. The cost of care, demand for consumables, and shortage of healthcare professionals skilled in treating diabetes and its related complications present a large and growing challenge for the public healthcare system in Sri Lanka. Development of new herbal drugs with proven clinical efficacy and safety will be able to manage T2DM at the initial stage and will be able to reduce the occurrence of diabetic complications. This will aid in reducing the mortality caused by diabetes and its related complications and enhance the quality of life of patients with T2DM. This approach can be successfully employed in cost-cutting strategies in the healthcare system and also in reducing the economic burden of the nation. Indeed, the positive results of the study will complement the efforts in reaching the national health needs of the general public.

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