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EVALUATION OF ANTIDIABETIC ACTIVITY OF *LEUCOMERIS SPECTABILIS* EXTRACT IN ALLOXAN-INDUCED DIABETIC RATS

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ABSTRACT

The objective of the study is to investigate the hydro alcoholic leaves extract of *Leucomeris spectabilis* (Asteraceae) for hypoglycemic effects in normal and diabetic rats. Acute oral toxicity study indicated that HAE was safe up to a dose of 2000 mg/kg body weight of rats and screened for antidiabetic activity in alloxan (120 mg/ kg, i.p.) induced diabetic rats for 21 days along with phytochemical analyses of HAE were also carried out. *In-vivo* evaluation of the extracts decreased blood sugar levels with significant improvement in blood glucose level, serum marker enzymes (SGPT, SGOT and ALP) and the content at the end of 1, 2 and 3rd weeks after HAELC treatment. The results suggest of antidiabetic activity study revealed that HAE possesses significant ($p < 0.05$) hypoglycemic activity compared to diabetic rats group. The results showed that the hydroalcoholic leaves extract has significantly most of effect in 200mg/kg.

Keywords: *Leucomeris spectabilis*, Leaves, Acute oral toxicity, Alloxan, Ant-diabetic activity.

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1. INTRODUCTION

Traditionally, herbs used for the treatment of many disease and disorders in which herbal medicines are the synthesis of therapeutic usefully for stage of life of practicing physicians of indigenous system of medicine for over hundreds of years while nutraceuticals are nutritionally or medicinally enhanced foods with health benefits of recent origin and marketed in developed countries[1]. The marketing of the former under the category of the latter is unethical. Herbal medicines are also in great demand in the developed world for primary health care because of their efficacy, safety and lesser side effects [2]. In this era of rapid industrial development, ever increasing population growth rate throughout the world.

Diabetes mellitus (DM) is the most common endocrine disease worldwide and is a prevalent serious chronic metabolic disease which result due to no production of insulin causing type 1 DM or due to partial and/or insufficient production of insulin causing type 2 DM. Furthermore, insulin resistance cause hyperglycemia and diabetes due to the inability of the cells to use insulin properly and efficiently. Some to the serious complication of diabetes include nephropathy, retinopathy, and neuropathy, foot ulcers among other symptoms [3, 4, 5]. As per the reports published by WHO in 2016; about 173 million people suffer from diabetes mellitus. The number of people with diabetes mellitus in Indonesia is ranked the fourth largest number of people with DM, after India, China, and the United States, which is about 8.4 million people. The global prevalence of diabetes has increased from 4.7 to 8.5% i.e. 108 million in 1980 to 422 million in 2014. Diabetes mellitus (DM) is characterized by chronic hyperglycemia and alterations in carbohydrate, lipid and

protein metabolism, associated with absolute or relative deficiencies in insulin secretion and/or insulin action [6, 7].

It consists of several types, one of which is noninsulin dependent diabetes mellitus (type 2 DM). This type of DM is more common, reaching 90–95% of the population with DM and is a long-lasting malady of energy metabolism involving impaired glucose breakdown as well as reduced insulin action [8, 9]. This increasing trend in type 2 DM has become a serious medical concern worldwide that prompts every effort in exploring for new therapeutic agents its progress [10].

Natural resources provide a huge and highly diversified chemical bank from which we can explore for potential therapeutic agents by bioactivity-targeted screening. The high prevalence of diabetes as well as its long-term complications has led to an ongoing search for hypoglycemic agents [11,12].

The treatment of hyperglycemia in diabetic patients is oral hypoglycemic agents. The last two decades have witnessed the introduction of many classes of these agents, and their optimal use and side effects are gradually recognized. Seven approved major classes of oral anti-hyperglycemic agents are currently available: MET, SU, glinides (GLN), thiazolidinediones (TZD), alpha-glucosidase inhibitors (AGI), dipeptidyl peptidase-4 inhibitors (DPP-4I), and the most recent sodium glucose cotransporter-2 inhibitors (SGLT-2I)[13]. Although a number of pharmacological approaches to the treatment of NIDDM are currently available, it is clear that none is ideal for the treatment of a great majority of NIDDM patients. Thus development of newer therapeutic approach remains highly desirable [14].

In view of the side effects associated with the treatment by insulin and synthetic drugs which are available at present, searching for effective and safer hypoglycemic plant drugs is going on all over the world. Herbal medicines play a vital role in this part to prevent side effects [15].

Therefore, researchers try to explore the potential antidiabetic agents with the mechanism of action of α-glucosidase inhibition in several plant species from four families: Apocynaceae, Clusiaceae, Euphorbiaceae, and Rubiaceae. The four families were chosen because members of some species have been scientifically proven to have antidiabetic activity. Today explore much other family show antidiabetic activity [16]. The literature survey on journal, library and other of *Leucomeris spectabilis* plant uses, activity or full details has not found.

2. MATERIALS AND METHODS

2.1. *Plant material*

The leaves of *Leucomeris spectabilis* were collected from Bareilly, near Uttrakhand border hills, Uttar Pradesh, India. It was authenticated by Dr. Ashok Kumar, Department of Botany, IFTM University, Moradabad, Uttar Pradesh, India.

2.2. *Preparation of extracts*

Leucomeris spectabilis leaves were made free from the adherent foreign material and air-dried, coarsely powdered and packed into soxhlet apparatus and extracted using hydro alcoholic solvent. The extraction was carried out for about 40hr. The extract obtained was dried at 45°C in hot air oven till green colored semisolid mass was obtained. The yield obtained was 18.5% and the semisolid extract was stored in a refrigerator at 4°C until further use [17].

2.3. *Phytochemical screening*

Preliminary phytochemical screening of the HAE was carried out for detection of the presence of various phyto-constitutents like alkaloids, glycosides, flavonoids, phenolic compounds, tannins, saponins, proteins, amino acids and steroids [18].

2.4. Animals

Albino rats of either sex weighing between 150-200gm were used for this investigation. Housed individually in polypropylene cages, maintained under standard conditions (12 h light and 12 h dark cycle, 25±30°C, 35–60% relative humidity), and the protocols related with animal experiment were approved by Institutional Animal ethics committee (IAEC). All the chemicals were of AR grade and procured from CDH (P) Ltd, New Delhi.

2.5. Acute Toxicity Tests

Acute toxicity studies were conducted by using albino rats of either sex. Over-night fasted rats were randomly divided into five groups of six animals each. Rats of different groups were administered 2000 mg/kg b.w. of the HAE. One group was maintained as Normal control and was given vehicle alone. The animals were observed individually symptoms of toxicity and mortality if any, and then periodically for the next 24 h, and then at every 24 h for any signs of acute toxicity over a period of 14 days. The acute toxicity study was done as per OECD guideline-425. Acute oral toxicity studies revealed the nontoxic nature of aqueous extract of *Leucomeris spectabilis*. There was no morbidity observed or any profound toxic reactions found a dose of 2000 mg/Kg p.o. which indirectly pronouns the safety profile of the plant extract. The doses 100 and 200 mg/kg b.w were selected for the evaluation of anti-diabetic activity.

2.6. Anti-diabetic activity in Alloxan-induced diabetic rats.

Diabetes was induced in overnight fasted animals by a single intra peritoneal (i.p) injection of Alloxan monohydrate120 mg/ kg b.w. was dissolved in normal saline. The solution should be fresh and prepared just prior to the administration. The animals confirmed as diabetic (after 72 h of Alloxan injection) by the elevated plasma glucose levels (200– 300 mg/dl) was used for the experiment.

The animals were divided randomly into five groups of six rats in each group.

Group I rats served as Normal control were given vehicle (3% tween 80 v/v in normal saline 10 ml/kg b.w) alone.

Group II rats served as Positive control (120 mg/kg b.w Alloxan diabetic control) and were administered with vehicle alone.

Group III rats were received the standard drug, metformin hydrochloride (100 mg/kg b.w.).

Group IV and V rats were treated with HAE at 100 mg/kg b.w. and 200 mg/kg b.w., respectively.

Treatments doses were given orally using a cannula once daily for a period of 21 days. Blood was collected from the tail vein each time for the determination of glucose levels on 0, 7, 14 and 21 day. Blood glucose levels were measured by the GOD-POD method [19,20].

2.7. Statistical analysis

Values are represented as mean± SEM of three replicate studies. Statistical analysis was performed using the Graphpad 5.0 statistical software package, for Windows. Statistical differences at 5% level of probability ($p < 0.05$) between the groups were analyzed by one-way ANOVA followed by Dunnett's test.

3. RESULTS

3.1. Phytochemical screening

The results of preliminary phytochemical screening revealed the presence of phyto-constitutents in plant leaves (Table 1).

3.2. Acute toxicity study

No sign and symptoms of acute toxicity and mortality up to 2000 mg/kg body weight dose were observed during the whole experimental period. The body weight and food consumption were normal compared to vehicle treated rats. For further studies, the doses were fixed as 100 and 200 mg/kg body weight.

Table 1: Preliminary phytochemical tests to identify the presence of various phytochemicals in Hydro-alcoholic extract of *Leucomeris spectabilis* leaves.

S.N.	Phytochemical Parameters	HAELS
1.	Alkaloids	+
2.	Carbohydrates	+
3.	Glycosides	+
4.	Proteins	-
5.	Tannins & Phenolic compounds	+
6.	Flavonoids	+
7.	Steroids	-
8.	Amino Acids	+
9.	Fats And Oils	-
(+): Presence, (-): Absence		

3.3. Effect of HAE on blood glucose levels in diabetic rats

Alloxan treated diabetic rats were increase the levels of blood glucose in comparison to normal rat values. The diabetic rats treated with metformin (100 mg/kg) also showed significantly considerable lowering effect in blood glucose level when compared to diabetic treated rats.

In diabetic rats, the blood glucose level (Fig. 1) were significantly decreased. After 7, 14, 21 days of treatment with HAE at 100 and 200 mg/kg. The activity of HAE was found lesser than that of metformin (100 mg/kg) treated group. Results of the effect of metformin and HAE on blood glucose levels in normal and diabetic rats are depicted in Table 2.

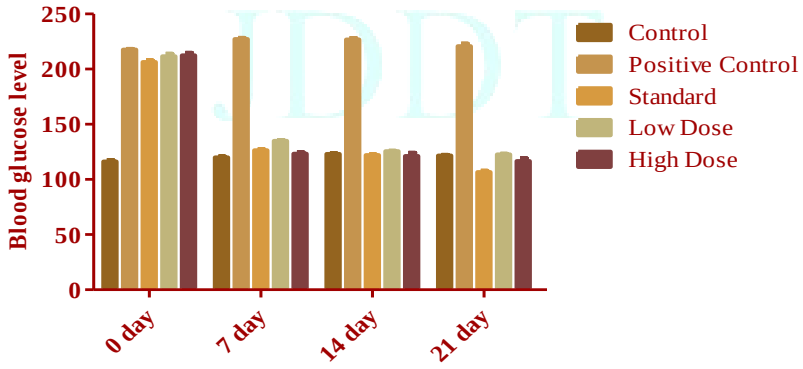

Figure 1: Effects of HAELC on blood glucose level at 0, 7, 14, 21 days.

Table 2: Effect of repeated dose treatment of *Leucomeris spectabilis* leaves on blood glucose level in alloxan-induced diabetic rats

Group	Dose	Blood glucose level (mg/dl) (Mean ± SEM)			
		0 day	7 day	14 day	21 day
I Normal Control (Tween 80 3%)	10 ml/kg	116.16±1.24**	119.83±0.792**	123.00±0.632**	121.5±0.670**
II Positive Control (Alloxan)	120 mg/Kg	217.50±0.763	227.16±1.07	226.83±1.24	220.8333±2.24
III Standard (Metformin)	100 mg/Kg	206.33±1.40*	126.33±0.843*	122.00±0.632*	106.5±1.33*
IV Hydro-alcoholic Extract (Low Dose)	100 mg/Kg	211.50±2.32*	134.83±0.600*	125.50±0.428*	122.5±0.763*
V Hydro-alcoholic Extract (High Dose)	200 mg/Kg	212.33±2.33*	123.16±1.22*	121.16±2.79*	116.5±2.57*

All values are expressed in mean ± SEM. Statistical analysis of data was carried out by one way ANOVA followed by Dunnett's test. *($p<0.05$) when compared with the Positive Control (Diabetic control) group.

3.4. Effect of HAE on SGOT, SGPT, ALK-Phosphate, total serum bilirubin, bilirubin direct, bilirubin indirect, serum total protein, serum albumin and globulin in diabetic rats:.

The results indicated from (Fig. 2 and 3).

Table 3: Effect of HAE of *Leucomeris spectabilis* leaves on SGOT, SGPT, and ALK-Phosphate in normal and diabetic rats

Groups	Dose	SGOT	SGPT	ALK-Phosphate
I Normal Control (Tween 80 3%)	10 ml/kg	211.35±1.42*	131.04±1.22*	402.6±0.807***
II Positive Control (Alloxan)	120 mg/Kg	450.2±2.06	352.77±1.06	754±0.899
III Standard (Metformin)	100 mg/Kg	173.04±0.747*	134.04±0.611*	375.35±1***
IV Hydro-alcoholic Extract (Low Dose)	100 mg/Kg	254.99±1.48*	176.38±1.11*	491±1.48***
V Hydro-alcoholic Extract (High Dose)	200 mg/Kg	205.92±0.768*	155.82±1.17*	414.85±0.949***

All values are expressed in mean ± SEM. Statistical analysis of data was carried out by one way ANOVA followed by Dunnett's test. *($p<0.05$) when compared with the Positive Control (Diabetic control) group.

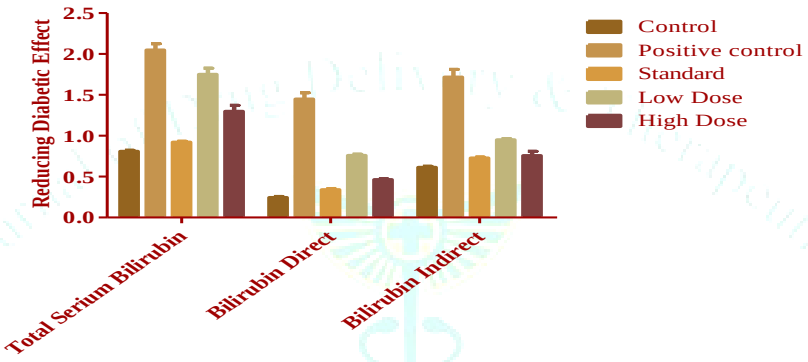

Figure 2: Effects of HAELC on biochemical parameter as Total Serum Bilirubin, Bilirubin direct and Bilirubin indirect.

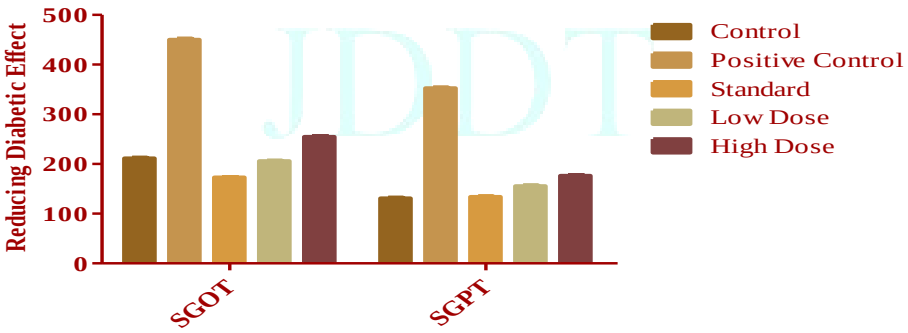

Figure 3: Effects of HAELC on biochemical parameter as SGOT and SGPT.

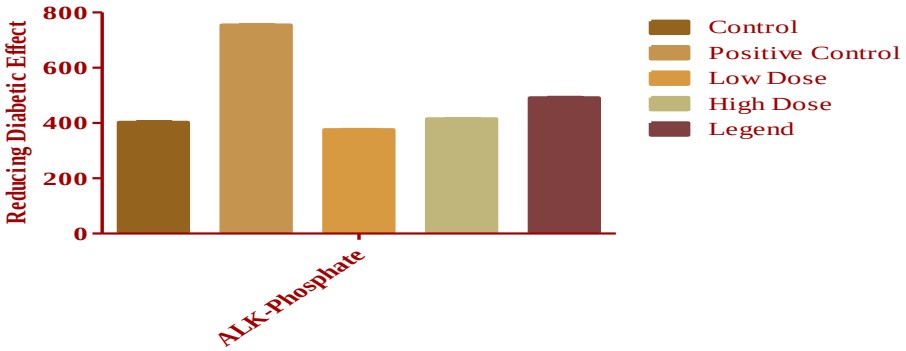

Figure 4: Effects of HAELC on biochemical parameter as ALK-Phosphate.

It is increase in activities of SGOT, SGPT and ALK-Phosphate in diabetic rats, The diabetic rats treated with Metformin 100 mg/kg, p.o., and HAE (100 & 200 mg/kg)given considerable lowering effect on the levels of serum marker enzymes SGOT, SGPT and ALK-Phosphate were compared to diabetic control rats (Table 3). The biochemical parameter results indicated (Fig. 4), there was increase in activities of total bilirubin, bilirubin direct and bilirubin indirect level in diabetic rats. The diabetic rats treated with Metformin 100 mg/kg, p.o., and HAE 200 mg/kg given considerable decreasing effect on the level of total serum bilirubin, bilirubin direct and bilirubin indirect, but the dose or HAE 100 mg/kg given no significant effect on level of this parameter were compared to diabetic control rats. In which increase in activity of serum total protein, serum albumin and globulin level in diabetic rats. The diabetic rats treated with Metformin 100 mg/kg, p.o., and HAE 200 mg/kg given significant effect on the level of serum total protein, serum albumin and globulin were compared to diabetic rats. In which the dose of HAE 100 mg/kg given no significant effect on level of serum total protein, serum albumin and globulin (Fig. 5, 6 and 7) were compared to diabetic rats (Table 4)

Table 4: Effect of HAE of *Leucomeris spectabilis* leaves on Serium Bilirubin, Bilirubin Direct, Bilirubin Indirect, Total Protein, Serium Albumin and Serium Globulin in normal and diabetic rats.

Groups	Dose	Serium Bilirubin	Bilirubin Direct	Bilirubin Indirect	Total Protein	Serium Albumin	Globulin
I Normal Control (Tween 80 3%)	10 ml/kg	0.81±0.012*	0.245±0.012*	0.613±0.013*	5.8±0.096609ns	3.2±0.089***	2.6±0.096***
II Positive Control (Alloxan)	120 mg/Kg	2.05±0.076	1.45±0.076	1.72±0.094	6.1±0.139044	3.9±0.106	3.4±0.141
III Standard (Metformin)	100 mg/Kg	0.922±0.011*	0.34±0.011*	0.728±0.011*	5.2±0.121106***	3.0±0.077***	2.3±0.106***
IV Hydroalcoholic Extract (Low Dose)	100 mg/Kg	1.75±0.076ns	0.76±0.015ns	0.95±0.012ns	5.8±0.106ns	3.7±0.139ns	3.0±0.152ns
V Hydroalcoholic Extract (High Dose)	200 mg/Kg	1.29±0.074*	0.46±0.009*	0.75±0.051*	5.5±0.096609**	3.4±0.096**	2.6±0.106***

All values are expressed in mean ± SEM. Statistical analysis of data was carried out by one way ANOVA followed by Dunnett's test. *($p<0.05$) when compared with the Positive Control (Diabetic control) group.

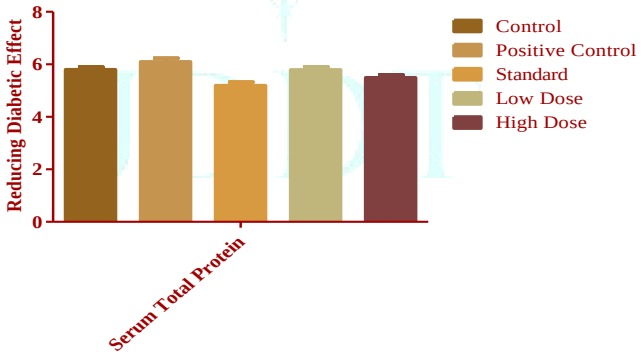

Figure 5: Effects of HAELC on biochemical parameter as Serum total protein.

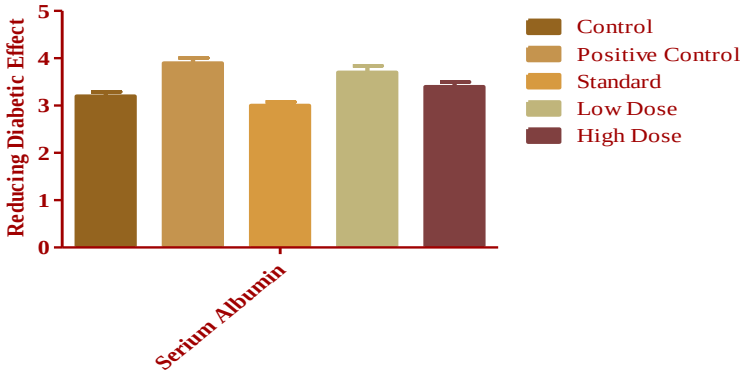

Figure 6: Effect of HAELC on biochemical parameter as Serum Albumin.

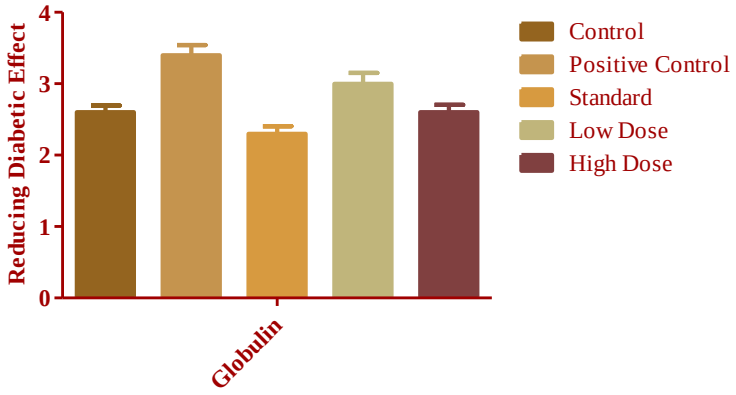

Figure 7: Effects of HAELC on biochemical parameter as Globulin.

4. DISCUSSION

Hydro-alcoholic extract (HAE) of *Leucomeris spectabilis* leaves did not demonstration toxicities in the dose of (2000 mg/kg b.w.) experimentally on animals which indicated the safety of bioactive phytochemical present in the extract. The *intra-peritoneal* administration of Alloxan leading to decreased in release of insulin which ultimately results show induces of diabetes mellitus in rats. The treated group of metformin and HAE demonstrated significant decrease the level of blood glucose when compared with diabetic rat son 0, 7, 14 and 21 days of treatment. The serum marker enzymes SGOT, SGPT and AKL-Phosphate are important markers of liver function. The rise in the activities of SGOT, SGPT and ALK-Phosphate in plasma of diabetic rats due to the outflow of these enzymes from the liver cytosol into the blood stream which was an sign of the hepatotoxic effect in liver. The serum biochemical parameters total bilirubin, bilirubin direct, bilirubin indirect, serum total protein, serum albumin and globulin increases show the deficiency of this content in plasma which was sign of toxicity causable effect in the body of parameter. The biochemical parameter increase in activities of total bilirubin, bilirubin direct, bilirubin indirect, serum total protein, serum albumin and globulin level in diabetic rats. The diabetic rats treated with Metformin 100 mg/kg, p.o., and HAE 200 mg/kg given considerable decreasing effect on the level of total serum bilirubin, bilirubin direct, bilirubin indirect, serum total protein, serum albumin and globulin but the dose or HAE 100 mg/kg given no significant effect on level of this parameter were compared to diabetic control rats [4,19,20,21].

5. CONCLUSIONS

The present study concludes that HAE of *Leucomeris spectabilis* showed potent hypoglycemic activity in diabetic rats compared to positive control (alloxan) induced rats and exhibited antidiabetic effect potentially on 0, 7, 14 and 21 days of treatment with significant improvement in blood glucose level. The serum marker enzymes SGOT, SGPT, ALK-Phosphate and the content total serum bilirubin, bilirubin direct, bilirubin indirect, serum total protein, serum albumin and globulin show reducing effect when compared to diabetic rats group. This effect may be due to the presence of glycosides, flavonoids, alkaloids and other constituents present in the leaves which could act synergically or independently in enhancing the activity of glycolytic and gluconeogenic enzymes. The result suggests that it is worth undertaking further studies on possible usefulness of the *Leucomeris spectabilis* leaves in diabetes mellitus. The phytochemical analyses need be executed in order to identify the possible flavonoid components having antidiabetic activity.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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