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AMELIORATIVE POTENTIAL OF ETHANOL LEAF EXTRACT OF ANNONA CHERIMOLA IN ALLOXAN-INDUCED DIABETIC RATS

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ABSTRACT

Diabetes mellitus (DM) is a chronic disease characterized by a relative or absolute lack of insulin secretion or insulin inaction. The study investigated the effect of *Annona cherimola* leaf extract on the liver and kidney function indices of alloxan-induced diabetic rats. A total of twenty (20) albino rats of both sexes weighing about 100g to 200g were used for the study, while eighteen (18) mice were used for the acute toxicity study. The animals were randomly divided into five (5) groups of four (4) rats each; Group 1 was not induced nor treated (normal control), group 2 was induced but not treated (untreated control), group 3 was induced and treated with 100 mg/kg b.w. of metformin (standard control), and groups 4 and 5 were induced and treated with 100 and 200 mg/kg b.w. of the extract respectively. The induction of diabetes was achieved by intraperitoneal injection of alloxan monohydrate (150 mg/kg b.w.). The oral administration (treatment) was done once per day using gavages for fifteen (15) days, and the blood glucose level was checked every three (3) days. The result indicated the extract possessed significant ($p < 0.05$) antidiabetic effect on groups 4 and 5 compared to the untreated group. A significant ($p < 0.05$) increase in serum total cholesterol (TC) and triglyceride (TAG) was also observed in groups 4 and 5 compared to the untreated group. In conclusion, this research showed that the ethanol leaf extract of *Annona cherimola*possess a potent ameliorative effect in alloxan-induced diabetic rats.

Keywords: *Annona cherimola*, blood glucose, diabetes mellitus, metformin, alloxan

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that is characterized by a relative or absolute lack of insulin secretion or insulin inaction, resulting in hyperglycaemia, hyperlipedemia, hyper-aminoacidemia, and hypo-insulinaemia (Altan, 2003). Chronic diabetes condition may lead to a variety of complications such as neuropathy, nephropathy and retinopathy and increased risk of cardiovascular diseases. Research figures suggest the worldwide prevalence of diabetes is 9.2% in women and 9.8% in men, with approximately 347 million people suffering from the disease worldwide in 2008 (Danaei*et al*., 2011). DM is considered one of the oldest known diseases to humans and was first reported in Egyptian manuscript some 3000 years ago (Ahmed, 2002). According to the World Health Organization (WHO), diabetes mellitus is a chronic metabolic disease characterized by elevated levels of blood glucose, which leads overtime to damage of the heart, vasculature, eyes, kidneys and nerves. In 1936, the distinction between type 1 and type 2 DM was clearly made (Roden and Shulman, 2019). *Annona cherimola* (Cherimoya) which literally means "cold seeds" is a small domesticated tree that produces edible fruits which are conical and heart shaped. The leaves which are ovate-lanceolate appear glabrous on the ventral surface and pubescent dorsally (Anaya-Esparza *et al*., 2017). The fruits of Cherimoya are the only part of the plant that has gained commercial importance, as they are consumed fresh. However, the fruits of Cherimoya are used traditionally to treat a number of ailments (Albuquerque *et al*., 2016). Recent studies have revealed that different parts of Cherimoya such as stem back, leaves and fruit are rich in bioactive compounds, with high content in polyphenols and alkaloids (Quílez *et al*., 2018). In particular, similarly to other species belonging to Annona genus, leaves of Cherimoya were found to be a potential source of bioactive compounds (Díaz-de-Cerio *et al*., 2018), and are currently ingredients in traditional medicine preparation and folkloric teas for the treatment of gastric, intestinal, cardiovascular, skin, and eye diseases (Arunjyothi*et al*., 2011). These leaves are also traditionally used in Mexico, South America, India and the Azores to prepare a decoction for treating diarrhea, intestinal worms, respiratory diseases, hyperlipidemia, hyperglycemia, anxiety, convulsions, and agitation (Arunjyothi *et al*., 2012).

Studies on this plant have confirmed the traditional uses of the leaves for therapeutic purposes, and their extracts were found to be an excellent source of bioactive compounds, such as flavonoids, tannins, alkaloids, phytosterols, and terpenoids (Díaz-de-Cerio *et al*., 2018). Despite the long usage history of these preparations without significant evidence of toxicity and the empirical presence of bioactive compounds, the antidiabetic potential of *A. cherimola* leaves have been poorly explored.

Treatment of diabetic patients (types 1 and 2) involves the use of antidiabetic agents, which are grouped as non-insulin (including the biguanides (e.g. metformin), sulfonylureas (e.g. glyburide), SGLT-2 inhibitors (e.g. dapagliflozin), bile acid sequestrants (e.g. colesevelam), amylin mimetic (e.g. pramlintide), dopamine-2 agonist (e.g. bromocriptine), DPP-4 inhibitors (e.g. sitagliptin), GLP-1RAs (e.g. exenatide), thiazolidinedione (e.g. rosiglitazone), and α-glucosidase inhibitors (e.g. Acarbose and voglibose)) and insulin therapies (e.g. human insulin and analogs) (Skyler *et al*., 2017). However, these agents are expensive and may be associated with serious side effects (Yang *et al*., 2019).

Herbal products or plant products are rich in phenolic compounds, flavonoids, terpenoids, coumarins, and other constituents which show a reduction in blood glucose levels (Jung *et al*., 2006; Ji *et al*., 2009). Due to their perceived effectiveness, fewer side effects in clinical trials, and relatively low costs, herbal drugs are prescribed (Verspohl, 2002). Thus, the primary aim of the present research was to investigate the effect of *Annona cherimola* (Annonaceae) ethanol leaf extract on blood glucose levels, liver and kidney function indices and lipid profile in alloxan-induced diabetic rats.

MATERIALS AND METHODS

Chemicals

All chemicals and solvents used for the study were of analytical grade and highest purity. The Alloxan monohydrate and Metformin used for the induction and treatment of diabetes were products of Sigma, St Louis, Germany and Hovid Bhd, Malaysia respectively.

Collection of Plant Sample

Leaves of *A. cherimola* were collected from the premises of Anglican Cathedral, Lokoja, Kogi State, Nigeria. The taxonomic identification of the plant sample was done by a Botanist.

Preparation of Extract

The leaves of *A. cherimola* were shade-dried at ambient temperature and then pulverized into powder using a grinding machine. The powder (124g) was macerated in 400 ml of ethanol and allowed to stand for 72 hours at room temperature. The mixture was filtered with Whatman No. 1 filter paper and the filtrate was concentrated using rotary evaporator to get a semi-solid extract. The semi-solid residue was weighed and preserved for use.

Experimental Animals

A total of twenty (20) albino rats of both sexes with their weight ranging from 100g to 200g were used for the study, while eighteen (18) mice were used for acute toxicity study of the plant extract. All the animals used were sourced from the animal house of the Department of Zoology, University of Nigeria, Nsukka. The rats were acclimatized to laboratory environment (at ambient temperature) with a 12 hours light-dark cycle for 7 days prior to experimentation (animal house, Department of Science Laboratory Technology, School of Applied Sciences, Kogi State Polytechnic, Lokoja). During the experimental period, the animals were fed *ad libitum* with standard grower's mash rat pellets (Livestocks Feeds Plc, Ikeja - Lagos, Nigeria) and water.

Phytochemical Screening

The extract obtained was screened in order to determine the presence of phytochemical constituents such as alkaloids, flavonoids, tannins, saponins, steroids and cardiac glycosides, with standard qualitative phytochemical methods as described by Harborne (1973) and Trease and Evans (2002).

Acute Toxicity Study

The acute toxicity profile of the extract was carried out according to the method of Lorke (1983).

Induction of Diabetes

Diabetes was introduced into the rats by intraperitoneal injection of alloxan monohydrate (150 mg/kg b.w.) according to published protocols. Blood samples were collected by tail blood vessel puncture for fasting blood sugar (FBS) test. After 2 days, FBS test indicated diabetes was effectively induced and treatment with the standard drug, and different doses of extract commenced.

Animal Grouping and Treatment

The animals were randomly divided into five (5) groups of four (4) rats each (n = 4). Group 1 was not induced nor treated (normal control), group 2 was induced but not treated (Untreated control), group 3 was induced and treated with 100 mg/kg b.w of metformin (standard control), and groups 4 and 5 were induced and treated with 100 and 200 mg/kg b.w. of extract (low and high dose) respectively. The oral administration (treatment) was done once per day by the use of gavages for fifteen (15) days. Normal saline was used as the vehicle.

Body Weight

The animals were weighed prior to the commencement of the experiment (Day 0) using electric weighing balance and subsequently every three (3) days till the end of the experiment. The final body weight of rats in all groups was measured prior to their sacrifice.

Blood Collection

After fifteen (15) days of treatment, the rats were fasted overnight and sacrificed under chloroform anaesthesia. Blood samples were collected via cardiac puncture and then dispensed into labelled empty vacutainer tubes. Blood samples for each rat were centrifuged at 4000 rpm (Wisperfuge centrifuge, model 1384) for 10 minutes. To obtain sera, the supernatant was collected into respective labelled sample tubes for analyses.

Blood Glucose Test

After intraperitoneal injection of 150 mg/kg b.w of alloxan, to confirm establishment of diabetes in rats, blood was collected from overnight-fasted rats 2 days post-induction using the tail-tip amputation method. Tails of rats were first wiped clean with sterile cotton dipped in 10% ethanol. Fasting blood sugar was measured using glucometer (Accu-Answer).

Estimation of Kidney and Liver Function Indices

Creatinine concentration was determined according to the method described by Syal*et al*. (2013). The colored compound, creatinine alkaline picrate is formed when creatinine reacts with piric acid, and the change in absorbance is proportional to the creatinine concentration. The total protein was estimated using the method described by Nayyar *et al*. (2012). Protein in plasma or serum sample forms a blue colored complex when treated with cupric ions in alkaline solution. The intensity of the blue color formed is proportional to the protein concentration. Enzymatic determination of urea was carried out according to the method in a practical guide described by Kumar and Gill (2018). Alanine aminotransferase (ALT) was assayed using the method described by Gowda *et al*. (2009). Total bilirubin was estimated base on Vanden Bergh reaction. In this reaction, bilirubin reacts with diazotized sulfanilic acid to produce azobilirubin which is purple in color. Intensity of color is directly proportional to the amount of bilirubin in the serum according to the modified method of Jendrassik-Grof as described by Choosongsang *et al*. (2011).

Estimation of Lipid Profile

The concentration of serum lipid profile was determined using the following methods: total cholesterol by Abell *et al*.

(1952), triacylglycerols by Tietz (1990), high-density lipoproteins by Albers *et al*. (1978) and low-density lipoproteins by Friedewald*et al*. (1972).

Statistical Analysis

Statistical analysis was carried out using Statistical Product and Service Solution, version 21 (SPSS 21.0). Statistical differences were evaluated using a one- and two-ways analysis of variance (ANOVA), followed by Duncan's multiple range test to detect significant differences among the mean values of the dfferent groups. Difference were considered significant at $p < 0.05$ (i.e at 95% confidence interval).

RESULTS

Phytochemical Composition of Ethanol Leaf Extract of *Annona cherimola*

The phytochemical screening of ethanol extract of *Annona cherimola* leaves revealed the presence of tannins, glycosides, alkaloids and saponins, while flavonoids was absent as shown in Table 1. This revealed that the plant under study is a rich source of tannins, glycosides and alkaloids, being the most abundant in the evaluated sample.

Acute Toxicity ofEthanol Leaf Extract of *Annona cherimola*

The acute toxicity study showed that there was no mortality in any of the animals in both phases for the period of the investigation (24 hrs) as shown in Table 2.

Effect of Ethanol Leaf Extract of *Annona cherimola* on Body Weight

The changes in body weight of the animals during the experimental procedure and the weight difference in each group are shown in Table 3. The final weight was measured prior to the sacrifice of the animals at the end of the experiment. In contrast to the Group 4 that showed a significant ($p < 0.05$) increase in body weight at Days 6, 9,12 and 15, compared to the Days 0 and 3, there was no significant ($p > 0.05$) difference in body weight amongst the groups throughout the study period.

Effect of Ethanol Leaf Extract of *Annona cherimola* on Blood Glucose Level

The intrperitoneal injection of alloxan significantly ($p < 0.05$) increased blood glucose level of the rats in the treatment groups compared to the normal control (Table 4). Though, there was no significant ($p>0.05$) difference in the untreated group throughout the experimental procedure, the increases in the blood glucose levels were reduced by treatment of the rats with standard drug and different doses of the extract. The peak reduction effect of the treatment was observed in the standard group. There was a significant ($p < 0.05$) reduction of blood glucose level down the row with the reduction day-dependent.

Table 1: Phytochemical Constituents of Ethanol Leaf Extract of *Annona cherimola*

Constituent	Test	Result
Tannins	Ferric chloride	++
Glycosides	Fehling's solutions	++
Alkaloids	Dragendorff's	++
Saponins	Emulsion	+
Flavonoids	Ammonium	-

Key: ++ = Highly present, + = Moderately present, - = Absent

Table 2: Acute Toxicity (LD_{50}) Profile of Ethanol Leaf Extract of *Annona cherimola*

Phase I	Dose (mg/kg)	Mortality
Group 1	10	0/3
Group 2	100	0/3
Group 3	1000	0/3
PhaseII		
Group 1	1600	0/3
Group 2	2900	0/3
Group 3	5000	0/3

Table 3: Effect of Ethanol Leaf Extract of *Annona cherimola* on Body Weight (g)

Group	Day 0	Day 3	Day 6	Day 9	Day 12	Day 15
1	120.01 ±46.78^{b}	116.76 ±47.73^{a}	118.06 ±47.13^{a}	117.07 ±44.67^{b}	122.50 ±45.98^{c}	122.79 ±44.33^{b}
2	86.59 ±7.44^{ab}	94.55 ±15.01^{a}	85.90 ±21.45^{a}	72.68 ±14.58^{a}	60.47 ±5.26^{a}	73.76 ±20.96^{a}
3	81.50 ±25.68^{ab}	78.15 ±18.89^{a}	86.11 ±20.64^{a}	95.38 ±21.48^{ab}	95.18 ±23.10^{abc}	99.03 ±22.88^{ab}
4	62.45 ±13.21^{a}	74.54 ±8.71^{a}	103.83 ±22.56^{a*}	109.23 ±28.52^{ab*}	105.61 ±23.25^{bc*}	117.69 ±27.14^{ab*}
5	86.75 ±22.9.59^{ab}	99.50 ±20.79^{a}	97.42 ±23.49^{a}	75.62 ±9.15^{ab}	73.36 ±5.59^{ab}	74.74 ±12.95^{a}

Values are expressed as mean ± SD, (n = 4). Values in the same column having different superscripts differ significantly ($p < 0.05$). Values in the same row having asterisk (*) as superscripts differ significantly ($p < 0.05$).

Table 4: Effect of Ethanol Leaf Extract of *Annona cherimola* on Blood Glucose Level (mg/dL)

Group	Day 0	Day 3	Day 6	Day 9	Day 12	Day 15
1	108.75 ±3.10^{a}	108.50 ±4.43^{a}	108.50 ±3.32^{a}	108.75 ±3.77^{a}	108.00 ±1.41^{a}	110.00 ±2.94$^{a\,b}$
2	388.24 ±50.56^{b}	391.24 ±62.26^{d}	378.24 ±21.51^{c}	362.25 ±31.56^{d}	359.24 ±33.87^{d}	358.33 ±50.56^{c}
3	386.50 ±157.31^{b}	136.50 ±33.16^{a*}	104.25 ±15.97^{a*}	95.50 ±9.33^{a*}	87.25 ±13.43^{a**}	84.50 ±11.73^{a**}
4	324.0± 138.58^{b}	263.50 ±52.90^{b}	281.50 ±118.33^{b}	184.00 ±50.94^{b*}	172.50 ±45.32^{b*}	158.00 ±40.86^{b*}
5	333.25 ±23.23^{b}	365.50 ±6.35^{c*}	340.25 ±22.81^{b}	271.50 ±75.03^{c}	245.50 ±55.27^{c}	159.25 ±48.47^{b**}

Values are expressed as mean ± SD, (n = 4). Values in the same column having different superscripts differ significantly ($p < 0.05$). Values in the same row having asterisk (*) as superscripts differ significantly ($p < 0.05$).

Effect of Ethanol Leaf Extract of *Annona cherimola*on Kidney and Liver Function Indices

The intraperitoneal injection of alloxan significantly ($p < 0.05$) decreased the serum ALT, total protein and TBB, and significantly ($p< 0.05$) increased serum creatinine concentrations compared to the normal control as shown in Table 5. There was no significant ($p > 0.05$) changes in urea concentration after induction compared to the normal control. The administration of standard drug to the animals significantly ($p < 0.05$) decreased the serum ALT concentration compared to the untreated. There was no significant ($p > 0.05$) difference in serum ALT concentration of animals treated with different doses of extract compared to the untreated group. Treatment of the animals with different doses of the extract showed significant ($p < 0.05$) increase in serum total protein concentrations. In contrast to the rats treated with different doses of the extract that showed significant ($p < 0.05$) decrease in serum TBB, the administration of the standard drug significantly ($p < 0.05$) increase the level of TBB compared to the untreated control.

Effect of Ethanol Leaf Extract of *Annona cherimola*on Lipid Profile

The intraperitoneal injection of alloxan significantly ($p< 0.05$) increased serum TC, TAG, HDL, and LDL compared to the normal control (Table 6). The significant ($p < 0.05$) increase in serum lipid profile were reduced by the treatment of the rats with standard drug and different doses of the extract. Though, there was no significant ($p>0.05$) difference in the serum TC level of the high dose (200 mg/kg b.w) treated rats compared to the standard control, the low dose (100 mg/kg b.w) treated rats showed significant ($p<0.05$) decrease in serum TC level compared to the standard control and the high dose treated rats. In contrast to the LDL, the HDL and TAG were restored after treated with high extract dose compared to the normal control.

Table 5: Effect of Ethanol Leaf Extract of *Annona cherimola*on Kidney and Liver Function Indices

Group	ALT(U/L)	Total Protein(g/dL)	TBB(mg/dL)	Urea(mg/dL)	Creatinine(mcmol/L)
1	27.25±1.71^{c}	79.50±1.29^{b}	9.20±0.37^{c}	7.35±0.47^{b}	54.25±3.86^{b}
2	21.50±2.38^{b}	69.25±1.26^{a}	5.95±0.31^{b}	8.08±0.51^{c}	61.75±2.99^{c}
3	16.75±0.96^{a}	66.75±1.71^{a}	9.48±0.62^{c}	8.83±0.59^{d}	67.50±2.08^{d}
4	21.25±1.89^{b}	81.50±3.11^{c}	14.70±0.80^{d}	7.18±0.30^{b}	43.00±1.63^{a}
5	22.25±0.96^{b}	83.25±2.22^{c}	4.25±0.45^{a}	6.28±0.49^{a}	61.25±2.22^{c}

Values are expressed as mean ± SD, (n = 4). Values in the same column having different superscripts differ significantly ($p < 0.05$). ALT = Alanine amino transferase; TBB = Total bilirubin.

Table 6: Effect of Ethanol Leaf Extract of *Annona cherimola* on Lipid Profile(mg/dL)

Group	TC	TAG	HDL	LDL
1	119.50±1.29^{b}	101.50±2.08^{c}	42.50±2.08^{a}	53.00±2.16^{b}
2	153.00±2.38^{d}	111.25±1.71^{d}	51.25±1.71^{b}	79.25±1.71^{d}
3	130.25±1.71^{c}	87.50±1.29^{b}	52.00±2.16^{b}	56.50±5.45^{b}
4	110.25±2.21^{a}	74.50±2.65^{a}	50.00±1.83^{b}	46.75±3.30^{a}
5	133.50±3.11^{c}	103.50±2.65^{c}	44.25±1.71^{a}	68.75±3.59^{c}

Values are expressed as mean ± SD, (n = 4). Values in the same column having different superscripts differ significantly ($p < 0.05$). TC = Total cholesterol; TAG = Triacylglycerol; HDL = High density lipoprotein; LDL = Low density lipoprotein.

DISCUSSION

The phytochemical analysis of the ethanol leaf extract of *Annona cherimola* revealed the presence of secondary metabolites such as tannins, glycosides, alkaloids, and saponins (Table 1). The presence of alkaloids corroborates with the report of Manninoet *al*. (2020) on the chemical profile and biological activity of Cherimoya (*Annona cherimola*) and Atemoya (*Annona atemoya*) leaves, that

phytochemical analysis of *A. cherimola* showed large amounts of alkaloid compounds. Further studies on the characterization of bioactive compounds of *A. cherimola* leaves by Díaz-de-Cerio*et al*. (2018) also reported the presence of glycosides in the leaf extract. In contrast to our findings, recent studies by Iacopetta *et al*. (2022) showed the presence of flavonoids in *A. cherimola* leaf extract. This variation could be due to differences in the methods adopted for phytochemical screening. Given its phytochemical composition, *A. cherimola* is known to be eaten as a food and used in folkloric medicine. As reported by Calzada *et al*. (2017), local populations use this plant for the treatment of diseases such as gastrointestinal disorders, worms, and diarrhea, as well as diabetes. The toxicity study has allowed the determination of the safe dose of the ethanol leaf extract of *A. cherimola* administered orally. The acute toxicity study showed no mortality in any of the animals in both phases for the period of the investigation (Table 2). A study reported by Kennedy *et al*. (1986) showed that substances with LD_{50} values of 5000 mg/kg administered by oral route without any signs of toxicity (changes in locomotion or respiration) are regarded as being safe or practically non-toxic. Hence, ethanol leaf extract of *A. cherimola* may be considered non-toxic.

In this study, alloxan was used to establish diabetesin the experimental rats; this is as a result of its specific pancreatic β-cell toxicity (Viana *et al*., 2004). Upon injection of alloxan into rats, it is biotransformed by hepatic metabolic enzymes via reduction into dialuric acid. This acid is reoxidized back to alloxan establishing a redox potential leading to the production of superoxide radicals, which dismutate to form hydrogen peroxide (H_2O_2). The peroxide forms reactive hydroxyl radicals (OH^-) through the Fenton reaction (Szkudelski, 2001). These reactive oxygen species result in the rapid destruction of pancreatic β-cells, leading to insufficient insulin, and in turn, induced diabetes in rats. This study showed a significant ($p < 0.05$) decrease in body weight of the diabetic rats compared to normal control which could be a result of adjustments in metabolism caused by the exogenous substances (alloxan) administered. This is in line with the result of the study reported by Khaleel *et al*. (2015) that rats induced with diabetes are known to lose body weight, which could be a result of protein degradation, and the inability to provide gluconeogenesis amino acid linked to insulin deficiency, which results in muscle wasting and tissue breakdown in diabetic rats according to Anand *et al*. (2008). The administration of different doses of ethanol extract of *A. cherimola* leaf to the diabetic rats restored their body weight (Table 3). This could be attributed to insulin secretion enhanced by the bioactive componentspresent in the extract.

The diabetic rats showed a significant ($p < 0.05$) increase in blood glucose levels (Table 4). These increments could be due to insufficiency in insulin culminating from the destruction of pancreatic β-cells. Boye*et al*. (2020) reported that diabetes is one of the metabolic disorders characterized by chronic hyperglycemia culminating from dysregulated glucose metabolism secondary to defects in pancreatic β-cell function. However, treatment of diabetic rats with a standard drug and different doses of extract for the period of the experiment significantly ($p < 0.05$) decreased the blood glucose level in diabetic rats compared to normal control. Biological activities of the plant products used as alternative medicines for the treatment of diabetes are related to their chemical composition. Plant products are rich in phytochemicals which show a reduction in blood glucose levels (Jung *et al*., 2006; Ji *et al*., 2009).

The establishment of diabetes in the experimental rats caused significant ($p < 0.05$) changes in serum kidney and liver function indices compared to the normal control (Table 5). This confirms the already established observation by Kazumi *et al*. (1978) that diabetogenic substances cause spontaneous recovery from high blood glucose levels by the development of functioning insulinoma and a high incidence of kidney and liver tumours. Similarly, the intraperitoneal injection of alloxan significantly ($p < 0.05$) increased serum TC, TAG, HDL, and LDL compared to the normal control (Table 6). These could probably be a result of extensive oxidative stress and lipid peroxidation which are the by-products of reactions between glucose and biological molecules, as previously reported by Rehman and Akash (2017). However, the significant ($p < 0.05$) increase in serum lipid profile was reduced by the treatment of the rats with standard drug and different doses of the extract. The decrease could be attributed to the antioxidant potential of the bioactive constituents of the extract as substantiated by the report of Shemishere *et al*. (2020) on phytochemical screening and free radical scavenging activities of plant extract. Phytochemicals derived from plants exhibit many biological properties which account for their health benefits and a justification for their use in food and medicine. Kang *et al*. (2011) reported that phytochemicals exert their effects by interacting with diverse cellular components including membrane transporters, protein kinases, ROS, lipoxygenases, and some transition metals.

CONCLUSION

Several researchers have shown that different parts of Cherimoya such as stem bark, leaf, and fruit possess an interesting phytochemical profile, with bioactive compounds that are beneficial to human health. Because diabetes mellitus is one of the metabolic disorders that may lead to a variety of complications such as neuropathy, nephropathy, retinopathy, and increased risk of cardiovascular diseases, it will be important to have an effective alternative remedy, with minimal side effects in clinical experience and relatively low costs for the prevention and treatment of this disease. The present study using ethanol leaf extract of Cherimoya conveys important information that may justify its medicinal uses.

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