

Research Paper

Evaluation of the Antidiabetic Properties of Hydro-Alcoholic Extract and Its Fractions from *Physalis peruviana* L. Leaves on Streptozotocin-Induced Diabetic Wistar Rats

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To cite this article:

Felicien M. Kasali, Charles Ntungwen Fokunang, Joseph Ngoupayo, Estella Tembe-Fokunang, Bathelemy Ngameni, Borgia Njinkio, Frederick Kechia, Justin N. Kadima, Tsague Marthe, Oyono Victor, Wilfred Mbacham, Bonaventure Tchaleu Ngadjui. Evaluation of the Antidiabetic Properties of Hydro-Alcoholic Extract and Its Fractions from *Physalis peruviana* L. Leaves on Streptozotocin-Induced Diabetic Wistar Rats. *Journal of Diseases and Medicinal Plants*. Vol. 2, No. 6, 2016, pp. 67-73. doi: 10.11648/j.jdmp.20160206.12

Received: July 10, 2016; **Accepted:** July 20, 2016; **Published:** November 21, 2016

Abstract: The purpose of this study was to investigate the antidiabetic activity of extracts from leaves of *Physalis peruviana* L. used in the Eastern part of the Democratic Republic of the Congo used against diabetes. Different fractions with hexane, ethyl acetate and residue were obtained from the hydroalcoholic extract of *Physalis peruviana* leaves. The antidiabetic evaluation of hydroalcoholic and its fractions was evaluated in diabetic rats by a single administration of streptozotocin (50 mg/kg body weight) intravenously. The Reference group received glibenclamide (6.5 mg/kg body weight) and each test group received 100 mg/kg of body weight. Those groups were compared with a control group which received only a Tween 20 solution (1 ml per 100 g body weight). Serum biochemical profiles were evaluated by some blood markers including serum glucose, serum alanine transaminase (ALT), serum aspartate transaminase (AST) serum creatinine, total protein, triglyceride, total cholesterol, HDL-cholesterol and LDL-cholesterol. Antidiabetic profile evaluation showed no significant variation ($P < 0.05$) in blood glucose between groups after 28 days of treatment. There was no significant difference in the biochemical markers change including creatinine, ALT, AST, total protein, triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol. The hydroalcoholic extract from the leaves of *Physalis peruviana* L. and its fractions showed antidiabetic activity suggesting future detailed studies for new chemical entities lead drug discovery.

Keywords: *Physalis peruviana*, Antidiabetic, Hydroalcoholic Extract, Streptozotocin, Biochemical Parameters, Wistar Rats

1. Introduction

Diabetes mellitus is a chronic metabolic disorder attributed by hyperglycemia, glucosuria and negative nitrogen balance and is primarily caused due to absolute deficiency or deprecated production of insulin. It is the most prevalent disease in the world affecting 25% of the population and afflicts 150 million people and is predicted to rise to 300 million by 2025 [1]. It has already been established that chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and eventually the failure of organs, especially the eyes, kidneys, nerves, heart and blood vessels. It has an adverse effect on carbohydrate, lipid and protein metabolism resulting in chronic hyperglycemia and abnormality of lipid profile. These lead to series of secondary complications including polyurea, polyphasia, ketosis, retinopathy as well as cardiovascular disorder [2]. The pathogenesis of diabetes mellitus and possibility of its management by the oral administration of antidiabetic agents, including those from folk medicines, have stimulated great interest in recent years [3].

The use of herbal medicines for the treatment of diabetes mellitus has gained importance throughout the world and there is an increased demand to use natural products with antidiabetic activity due to the side effects associated with the use of insulin and oral hypoglycemic agents [4]. In recent years, herbal medicines have started to gain importance as a source of hypoglycemic agents [5]. Furthermore, after the recommendation made by WHO on diabetes mellitus, investigations on hypoglycemic agents from medicinal plants have become more important [6]. More than 800 plant species have been found important sources for the discovery and development of new types of antidiabetic molecules [7].

The study showed that Asian and African continents have 56% and 17% share of the worldwide distribution of therapeutic herbal plants, respectively [8].

Physalis peruviana is a medicinal plant widely used in folk medicine for treating diseases such as malaria, asthma, hepatitis, dermatitis, cancer, diuretic, rheumatism, antispasmodic, diuretic, antiseptic, sedative, analgesic, cataract-cleaning, antidiabetic, and anti-parasitic properties [9]. Many medicinal properties have been attributed to the Cape gooseberry, including antiasthmatic and antiseptic, and it is a strengthener for the optic nerve, a treatment for throat affections, and aids in elimination of intestinal parasites, amoebas, as well as albumin from kidneys. It has an anti-ulcer activity and it is effective in reducing cholesterol level [10]. The Cape gooseberry (*Physalis peruviana* L.) is a species within the Solanaceae family widely used for medicinal and commercial purposes. It is native in the Andean region, primarily Colombia, Peru, Ecuador and is now cultivated in many regions throughout the world [11, 12].

Ethnopharmacological surveys conducted in many countries have documented a considerable inventory of plants used to treat diabetes [13]. In a survey conducted in

the Eastern part of the Democratic Republic of the Congo (DRC) a number of traditional healers pointed out the use of *Physalis peruviana* L. fruit and leaves for this purpose [14].

The present study was undertaken to complete antidiabetic investigations with the hydroalcoholic extract and its fractions in normal and streptozotocin-induced diabetic rats

2. Materials and Methods

2.1. Study Sites

The present study was undertaken respectively at the laboratories of Pharmacognosy (Faculty of Medicine and Pharmacy, Official University of Bukavu/Republic Democratic of Congo) and Chemical study of Medicinal Plants, Bacteria, Fungi and Endophytes (Faculty of Sciences of University of Yaoundé 1, Cameroon), Phytochemical laboratory of Higher Teachers' Training College (Faculty of Sciences, University of Yaoundé 1) and laboratory of Toxicological and Pharmacological studies (Faculty of Medicine and Biomedical Sciences/ University of Yaoundé 1). This study was conducted during the period between September 2015 and April 2016.

2.2. Plant Material

The leaves of *Physalis peruviana* L. (Solanaceae) were collected at Lwiro (Center for Research in Natural Sciences, Democratic Republic of Congo) situated at 50 Km from Bukavu (South Kivu, Democratic Republic of Congo). They were identified by Mr. Gentil IRAGI of Botany department of this center and compared with voucher specimen N°2044. The leaves were air-dried and powdered by maceration for analysis.

2.3. Preparation of Hydroalcoholic Extract and Its Fractions

800 g of the powdered leaves of *Physalis peruviana* were macerated with 6 L of 70% EtOH[15]for 48 hours and the combined filtrate (using the Whatman filter paper N°1) was evaporated under reduced pressure using a rotary evaporator. A dried extract with a yield of 28.95% was obtained. One part of the filtered hydroalcoholic extract was stored in a refrigerator at 4°C. Another part of this extract was soaked in hexane and decanted into a funnel. The hexane fraction was concentrated in a rotary evaporator (BÜCHI 461 water Bath). This operation was repeated several times until total exhaustion (the solution has become colorless). The same operations were carried out with ethyl acetate. The residue from this fraction was concentrated under reduced pressure using a rotary evaporator. The following yields were obtained: 3.19% and 25.06% respectively for hexane and ethyl acetate.

2.4. Animals

Healthy male albino Wistar rats (body weight 175 ± 10.6 g)

at the age 2-3 months were used in the study. The rats were maintained under standard laboratory conditions at 27.75 ± 1°C, and normal photo period [12 h dark/12 h light] were used for the experiment. The rats were acclimatized to the laboratory conditions a week prior to experiment.

The experimental protocol and the maintenance of the experimental animals was done in accordance with the regulations of the OEDD guide since in Cameroon the ethics committee focuses only on clinical studies. The animal experiment protocols were carried out in accordance with the guidelines of the ICH on preclinical pharmaceutical testing in mouse [16].

2.4.1. Induction of Diabetes

Diabetes was induced in fasted rats injecting 50 mg/kg streptozotocin (Sigma, France) in the tail vein. STZ was dissolved in 0.1 M citrate buffer (pH 4.5) [17]. Streptozotocin induces diabetes within 3 days by destroying the beta cells [18]. After 48 hours of STZ administration, blood glucose level of each rat was determined [19]. Before induction, all rats were fasted 12 hours [20]. Rats with serum glucose level above 300mg/dl were considered as diabetic [21].

2.4.2. Experimental Protocol

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

Group 1: Untreated rats (Control), received vehicle alone (1% tween 20, 1ml per orally)

Group 2: Rats treated with 6.5 mg/kg of Glibenclamide (Reference drug)

Group 3: Rats treated with 100 mg/kg of Hydroalcoholic extract of *Physalis peruviana*

Group 4: Rats treated with 100 mg/kg of hexane fraction of *Physalis peruviana*

Group 5: Rats treated with 100 mg/kg of ethyl acetate fraction of *Physalis peruviana*

Group 6: Rats treated with 100 mg/kg of residue fraction of *Physalis peruviana*

All rats were administered single dose of drug (orally) daily for 28 days. Daily administration was through a gastric gavage by introducing a gastric tube [22]. The day of administration of first dose was considered the zero day of treatment.

At the end of the experimental period, all animals were deprived of food overnight and then sacrificed by cervical decapitation after anesthetized by ether inhalation [23]. Blood

was collected in tube for the estimation biochemical parameters.

2.4.3. Determination of Blood Glucose Levels

Blood samples were collected from the tail vein of overnight fasted rats one day 0 (start of treatment), 7th, 14th, 21st and 28th day (end of treatment) [24] for determination of blood glucose levels using GlucoPlus® Active Glucometer.

2.5. Serum Biochemical Analysis

Blood samples were collected from tail vein of the mice into Eppendorff tubes. The blood samples were then centrifuged at 2000 ×g for 10min at 4°C for the preparation of serum. Serum glutamate oxaloacetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT), serum alkaline phosphatase (SALP), creatinine and total protein, using a commercial Diagnostic Kit (Chronolab, France). Concentrations of total cholesterol (TC), triglycerides (TG), and HDL-cholesterol were measured with enzymatic assay kit (Genzyme Diagnostics) (Gutierrez *et al.* 2014). LDL-cholesterol was calculated as the remaining difference of total cholesterol and HDL [25].

2.6. Statistical Analysis

All results were expressed as mean ± SEM (standard deviation) for each sample. Statistical analysis was performed using GraphPad Prism 5.02 statistical package (GraphPad Software, USA). The data were analyzed by one way analysis of variance (ANOVA) followed Turkey’s multiple comparison posttest. Differences between groups were considered to be significant at P < 0.05.

3. Results

3.1. Antidiabetic Study

The group treated with 100 mg/kg of Hydroalcoholic extract of plant Exp I, group treated with 100 mg/kg of hexane fraction of plant Exp II, group treated with 100 mg/kg of ethyl acetate fraction of plant Exp III, group treated with 100 mg/kg of residue fraction of plant Exp IV on Day 0: First day of treatment, showed no significant difference at (* p<0.05), but high significant at (**p<0.001).

Table 1. Blood glucose concentrations measured at different weeks (in mg/dL).

Treatment	Control	Reference	Exp. I	Exp. II	Exp. III	Exp. IV
Day 0.	90.0±7.1	402±36.4***	437.5±30.4***	480.8±13.8***	443.8±40***	445.2±31.3***
Day 7	114.6±21.2	398±43.3***	465.7±37.9***	429±26.2***	504.4±36***	507±51.8***
Day 14	106.2±6.2	495±25.5***	473±40.4***	451.4±37.6***	463.2±33***	458.3±48.3***
Day 21	73.8±26.6	231±26.9	261.8±35*	214±25.3	493.3±47***	467.8±49.1***
Day 28	67.2±13.5	139.5±53	191±37.7	247±23.7	265±29	156±26.6

The values are expressed as mean ± SEM of respective groups (n=5). The blood glucose values of groups were compared with normal control animals, values ***p< 0.001, **p< 0.01, *p< 0.05.

The blood sugar levels measured in experimental and normal rats at the 0, 7, 14, 21 and 15 days of treatment are

given in these different figures 1. At the first day of treatment, the administration of Streptozotocin increased highly significantly ($P < 0.01$) the levels on blood sugar as compared to normal rats. This level is maintained sufficiently high until 21 days.

On 21 day, oral administration of the glibenclamide (6.5 mg/Kg body weight) and hexane fraction (100mg/kg body weight) decreased blood sugar level (not significant variation with control group). At the end of treatment (day 28), it observed a decrease in the all groups. Non-significant difference in all groups (Fig. 1).

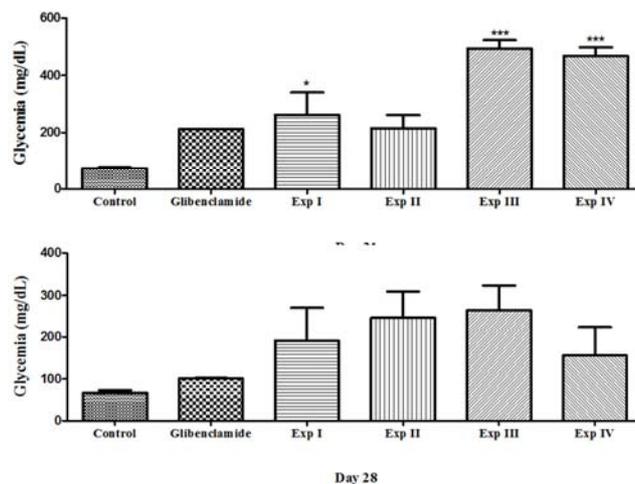
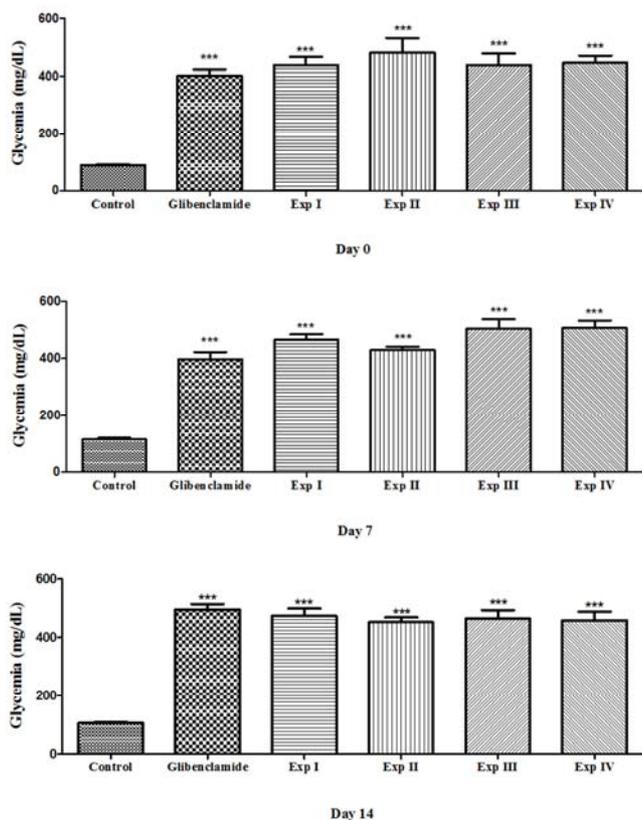


Figure 1. Experimental data from rats treated compared to control during four weeks of exposure, at day 0, 7, 14, 21 and 28 respectively.

3.2. Serum Biochemical Analysis

Exp. I: Group treated with 100 mg/kg of Hydroalcoholic extract of plant; *Exp. II:* Group treated with 100 mg/kg of hexane fraction of plant; *Exp. III:* Group treated with 100 mg/kg of ethyl acetate fraction of plant; *Exp. IV:* Group treated with 100 mg/kg of residue fraction of plant was to show changes in the values of blood biochemical markers as presented in the Table 2.

At the dose 100mg/kg used to test the antidiabetic effect, the values ALAT, ASAT, triglycerides, and HDL-cholesterol remained in normal ranges for glibenclamide and hydroalcoholic extract with its fractions. Meanwhile, the creatinine and total protein values are increased respectively high and very significant ($p < 0.01$) and High Significant ($p < 0.001$) in the group treated with hexane fraction. The value of total cholesterol was decreased in reference group while it was much decreased in the group treated to hexane fraction where it noted a very decreased of LDL-cholesterol. This value was decreased ($p < 0.01$) in rats treated with hydroalcoholic extract, residue of ethyl acetate and in the reference group (Table 2).

Table 2. Serum Biochemical Analysis.

Biochemical parameters	Control	Reference	Exp. I	Exp. II	Exp. III	Exp. IV
Creatinine (mmol/L)	201.5±20	309.9±23.5	309.7±24.3	781.7±75.4***	177.0±22.6	354.0±25.0
ALAT (U/L)	27.7±2.2	27.2±1.6	28.7±2.2	21.7±2.7	33.1±2.1	23.9±2.7
ASAT (U/L)	25.6±2.0	25.1±1.3	21.1±1.3	20.2±0.4	21.5±2.2	28.8±1.7
Total protein (g/dL)	9.07±1.7	6.6±0.9	6.44±1.0	3.6±1.8**	6.4±0.8	6.45±1.3
Triglycerides (mmol/L)	1.38±1.1	0.54±0.1	0.64±0.2	0.65±0.2	0.62±0.1	0.76±0.1
Total cholesterol (mmol/L)	13.14±1.6	7.56±0.3*	8.35±2.5	5.70±1.5**	10.25±2.0	8.07±1.5
HDL-cholesterol (mmol/L)	0.62±0.05	0.15±0.03	0.17±0.01	0.18±0.01	0.08±0.004	0.18±0.02
LDL-cholesterol (mmol/L)	12.29±1.2	7.35±0.2*	6.99±2.5*	6.12±1.4**	8.14±1.8	7.46±1.7*

The values are expressed as mean ± SEM of respective groups ($n=5$). The serum biochemical values of groups are compared with normal control animals, values *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

4. Discussion

These analytical figures show the glycaemic evolution in rats treated to hydroalcoholic extract and its fractions (100mg/kg

body weight) and those treated to 6.5mg/kg body weight of glibenclamide (reference drug) all compared to normal rats which received a 1% of Tween 20 solution (1ml per 100kg/body weight).

Four-eight hours after diabetes induction by a single dose of streptozotocin (50mg/Kg bw), the animals of all treatment groups (reference and experimental) with a high significant variation of level glucose ($p < 0.001$). Glycaemia has been increased from 90 ± 7.1 mg /dL (normal animals) to 402 mg/dL (reference), 437.5mg/Dl (Exp. I), 480.8 mg/dL (Exp. II) 443.8 mg/dL (Exp. III) and 445.2 mg/dL (Exp. IV). It is known that, the single high-dose streptozotocin induced diabetes mellitus in rats that arises from irreversible destruction of the β -islet cells of the pancreas, causing degranulation or reduction of insulin secretion resulted in hyperglycemia and decreased body weight [26].

Insulin is a hormone secreted by the pancreas that metabolizes and stores carbohydrates, proteins and fats. Insulin transport glucose from blood into different cells of the body. When the pancreas produce low level of insulin or improperly work of insulin, the glucose stays in the blood cells, which makes the blood sugar level high [27].

At twenty-first day, the administration of hydroalcoholic extract caused significant ($p < 0.5$) reduction of blood glucose levels. The blood glucose values in reference group and animals treated to hexane fraction were non-significant varied compared to control group. Indeed, according basal glycaemia in different groups, it was observed a reduction of 42.53%, 40.02% and 47.17% respectively reference, experimental I and experimental II groups. Oral antidiabetic sulfonylurea drug (As glibenclamide) exerts their effects by stimulation of beta cells in the pancreas to produce more insulin [28]. At the twenty-eighth day blood glucose level was normalized is in the other groups (ethyl acetate and its residue). At the end of the treatment maximum reduction (64.95%) was observed in group treated to ethyl acetate residue.

According many preceding studies, extracts from *Physalis peruviana* showed *in vivo*, the antidiabetic activity. *Physalis peruviana* fruit efficiency *in vitro* as an antidiabetic and antihypertensive dietary supplement was demonstrated [29]. It reduced significantly ($p < 0.05$) blood glucose and serum insulin ($p < 0.05$) in alloxan-induced diabetic rats [30]. A study showed that the extract of *Physalis* fruit reduced significantly blood glucose levels in diabetic rats [31]. The effect of intestinal carbohydrate inhibition *in vitro* has been demonstrated [32] and their antioxidant effect [33]. However, at 100mg/Kg of *Physalis peruviana* leaves showed an important antidiabetic effect in guinea-pig [13]. At a dose of 200 mg/kg body weight, this extract demonstrated a potential diabetic effect in alloxan (120mg/kg) induced diabetic guinea-pigs for 28 days of treatment [7].

Daily administration of 100 mg/kg body weight of the hydroalcoholic extract of plant and its fractions, during 28 days, induced positive changes in serum biochemical markers.

Serum creatinine is a good indicator of kidney function because any elevated serum is associated with failure of nephron function [34]. Therefore, our results showed that daily administration of *Physalis peruviana* is not affected in general, renal functions. However, the hexane fraction provoked very significantly her elevation. By synergy with the other fractions did not affect serum creatinine. The value of

creatinine significantly decreased ($p < 0.01$ and 0.001) in all diabetic groups of rats treated with hydroalcoholic extract (70%) from fruit of *Physalis peruviana*, alone or treated with chromium [31]. A study showed the increased levels of creatinine and urea in the serum of CCl_4 intoxicated rats as compared to control rats. The study recorded significant ($p < 0.05$) decrease in the levels of creatinine and urea in all treated groups of *Physalis peruviana* and Liv-52 pre-treated groups [35]. Transaminases are important enzymes in hepatic toxicity study [22].

Our results showed that treatment with hydroalcoholic extract and its fractions did not affect of ALT and AST activities, suggesting that they have no toxic effect on these enzymes. Consequently, *Physalis peruviana* prevent the progression of liver dysfunction induced by chronic hyperglycemia. The normal level of ALT and AST reflects the normal liver cells. The normal value of hepatic biochemical markers revealed the safety profile of the plant on its chronic use [36].

It was also reported that the simultaneous treatment with silymarin and *P. peruviana* had prevented a significant increase in levels of ALT, AST and ALP [37].

Serum total protein did not decrease significantly, except for the group treated with the hexane fraction which logically explained by its low creatinine level. The structural proteins are known to contribute to body weight [38].

The most frequently observed lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia [39] and contribute to diseases of the coronary artery.

Our biochemical results related to lipid metabolism showed that the hydroalcoholic extract and its fractions have reduced the levels of blood triglycerides and cholesterol levels (a very significant reduction of the hexane fraction). These results suggest that the plant would have a significant potential also in the treatment of coronary diseases, which are secondary complications of diabetes [40]. They are in relationship with the transaminases results, which are operated in the balance cardiac as necrosis marker (mainly AST) combined with other assays. A serum triglycerides increase is attributed to insulin deficiency [41].

A study confirmed the reduction ($p < 0.05$) in serum cholesterol and triglycerides in mice subjected to hyperlipidemia treated to *Physalis peruviana* [42].

In fact, we thought that *Physalis peruviana* would act, as glibenclamide (sulfonamide) by stimulating insulin secretion observed in all treated groups consequent a significant reduction in blood glucose.

5. Conclusion

In conclusion, our present study demonstrated that the hydroalcoholic of *Physalis peruviana* L. and its fractions has antidiabetic effects in comparing to glibenclamide (reference drug). Biochemical profiles in treated animals suggested its use in diseases related to diabetes complications. Further investigation is needed for development of this plant into a pharmaceutical product for the treatment of diabetic.

Acknowledgements

The authors thank Intra-ACP program through AFIMEGQ Project. Also, we grateful all personal of Chemical study of Medicinal Plants, Bacteria, Fungi and Endophytes laboratory (Faculty of Sciences of University of Yaounde 1/Cameroon), Phytochemical laboratory of Higher Teachers' Training College (Faculty of Sciences, University of Yaounde 1), laboratory of Toxicological and Pharmacological studies (Faculty of Medicine and Biomedical Sciences/ University of Yaounde 1) and Mr. Gentil IRAGI of Department of Biology (Center for Research in Natural Sciences, NSRF/Lwiro) in Democratic Republic of Congo, for authentication of the plant.

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