Sumerianz Journal of Biotechnology, 2021, Vol. 4, No. 3, pp. 126-132
ISSN(e): 2617-3050, ISSN(p): 2617-3123
Website: https://www.sumerianz.com
DOI: https://doi.org/10.47752/sjb.43.126.132

Original Article Open Access

Hypoglycemic Activities of Ethanolic Leave Extract of *Acalypha Wilkesiana* in Streptozotocin-Induced Diabetic Wistar Rats

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Article History
Received: July 9, 2021
Revised: September 13, 2021
Accepted: September 16, 2021
Published: September 19, 2021

Abstract

Diabetes is a rampant metabolic disorder of insulin deficiency or resistance. In support of the alternative therapy quest, this study investigates the antidiabetic actions of ethanolic leave extract of *Acalypha wilkesiana (A. wilkesiana)* in diabetic rats. The study was conducted in 3 phases using streptozotocin (50mg/kg) induced diabetic adult Wistar rats. In phase one, 18 diabetic rats were divided into 3 groups (n=6) and treated with distilled-water (10ml/kg), glimepiride (0.1mg/kg) and ethanolic leave extract of *A. wilkesiana* (250mg/kg) respectively. On separate 18 diabetic rats (phase two), 5% glucose (10ml/kg) was administered after treatments as in phase one. Blood glucose was measured at 0 and 30-minute intervals for 180 minutes in both phases. On another 18 diabetic rats (phase three), similar treatments were given daily for 14 days. Blood glucose was measured at day 0, 3 days after induction, 3, 7, 10, and 14 days treatments. ANOVA was carried out with $p < 0.05$ as significant. The results showed progressively hypoglycemic actions significant from the 90^{th} minute with glimepiride (285.17±12.09mg/dl) and the 120^{th} minute with the extract (279.83±14.88mg/dl) through 180 minutes compared to control in 1^{st}-phase. There was a significant obliterating effect on glucose-induced hyperglycemia in a time-dependent manner at 90^{th} through 180^{th} minutes after glucose loading in glimepiride and extract-treated groups compared to control (2^{nd} phase). Streptozotocin-induced decreased body weight was improved in glimepiride and extract-treated groups by days 7 and 14 and there was a significant steady duration-dependent decrease in blood glucose from the 3^{rd} to 14^{th} day of treatments compared to control. The findings suggest that ethanolic leaves extract of *A. wilkesiana* possesses antidiabetic action probably through stimulation of pancreatic β-cells or improves insulin action.

Keywords: Diabetes; Hyperglycemia; Glimepiride; *Acalypha wilkesiana* extract; Streptozotocin.

1. Introduction

Metabolic syndrome is a cluster of several metabolic abnormalities, including central obesity, insulin resistance, hypertension, dyslipidemia, and hyperglycemia, that has become a major public health challenge [1]. Diabetes is the most common metabolic disorder worldwide and is a major risk factor for cardiovascular disease [2]. Diabetes is a chronic disease caused by inherited and/or acquired deficiency in pancreatic insulin production, or by insulin ineffectiveness when produced [3] and these deficits cause increased blood glucose concentrations and eventually damaged blood vessels, nerves, and many-body systems [4]. Recent data of the International Diabetes Federation reported over 366 million people worldwide as diabetic and this is likely to increase to 552 million or over by the year 2030 [5]. In Africa, more than 14 million people have diabetes, accounting for about 4.3% of adults, and is responsible for about 401,276 deaths in 2012 in the region [6]. West Africa recorded the highest number of Diabetes Mellitus (DM) cases with Nigeria (3.2 million diabetics) occupying the first positions [7].

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At present, different approaches for controlling diabetes include the use of modern synthetic antidiabetic drugs and lifestyle modification [7]. However, these synthetic drugs have characteristic profiles of serious side effects like hypoglycemia, weight gain, gastrointestinal discomfort, nausea, liver and heart failure, and diarrhea [8] and are rather costly for the majority of African populations [7]. Despite the availability of different types of oral hypoglycemic agents for diabetes treatment, there is increasing demand for the use of natural herbal products with anti-diabetic activity [9] because these products not only improve glucose metabolism of diabetic individuals, but also lipid metabolism, antioxidant status, and capillary function [10]. Several medicinal plants and herbs have been studied and validated for their hypoglycaemic potential in experimental animal models for diabetes [11] and in clinical studies involving diabetic patients [12, 13]. Thus, medicinal plants and herbs have continued to provide valuable therapeutic agents for both modern and traditional medicine systems [14]. To support the quest for alternative therapies in the treatment of diabetes, we investigated oral glucose tolerance after glucose loading and antidiabetic activities of ethanolic leave extract of *A. wilkesiana* in streptozotocin-induced diabetic rats.

2. Materials and Methods

2.1. Collection, Processing, and Extraction of Plant Materials

Samples of *Acalypha wilkesiana* leaves were collected from Benin City in Edo State, Nigeria, and authenticated at the Herbarium Unit of Forestry Research Institute, Ibadan, Oyo State, Nigeria. The leaves were plucked, sorted, air-dried for 7 days, and then pulverized and packaged in air-tight polyethylene bags. 200g of the powder leaf was added into a container of 1.5L of 70% ethanol and used to prepare the ethanolic extract as described in the slightly adjusted method of Majekodunmi and Nubani [15].

2.2. Experimental Animals

Fifty-four (54) adult male Wistar rats (average weight of 140 -180g) were obtained from the animal house of the College of Medicine, Ambrose Alli University, Ekpoma. The rats were housed at room temperature on a 12-hour dark-light cycle and acclimatized for 14 days with *ad libitum* access to food (rat chow; Vital Feed Nig. Ltd, Jos, Nigeria) and water.

2.3. Induction of Diabetes

Diabetes was induced in 24 hrs fasted adult male Wistar rats by intraperitoneal injection with a single dose of 50mg/kg body weight of freshly prepared streptozotocin (STZ) dissolved in 0.10M citrate buffer (pH 4.5). The dose of STZ was based on previous studies by Mythili, *et al.* [16] and Szkudelski [17]. To stave off the hypoglycemia during the first day after the STZ injection, diabetic rats were given 5% glucose solution orally as reported by Sugumar, *et al.* [18]. Rats with blood glucose levels higher than 300mg/dl after three days (72 hrs) of STZ injection were considered diabetic as previously reported by El-Khateeb, *et al.* [19] and used for the studies.

2.4. Phase One Experiment (Hypoglycemic Activity in Diabetic Rats)

Eighteen (18) diabetic rats (150g-170g) were used in this 1st phase experiment. They were isolated from the other diabetic rats and fasted for 12 hours and divided to three groups (n = 6) and treated as follows:

Group 1: Diabetic control group; treated with 10ml/kg of distilled water.

Group 2: Standard drug group; treated with 0.1mg/kg of Glimepiride.

Group 3: *A. wilkesiana* extract group; treated with 250mg/kg ethanolic leaves extract.

2.5. Phase Two Experiment (Oral Glucose Tolerance Study in Diabetic Rats)

In the 2nd phase experiment, replicates of groups 1, 2, and 3 as treated in phase one further received 10ml/kg of 5% glucose water 30 minutes after treatments as in phase one. The blood glucose levels were measured at 0 min, 30 min, 60 min, 90 min, 120 min, 150 min, and 180 min to determine hypoglycemic and oral glucose tolerance activities in the diabetic rats. Blood glucose levels were determined using an Accu-check glucometer by Roche Diagnostic.

2.6. Phase Three (Chronic Anti-Diabetic Study in Diabetic Rats)

In the 3rd phase experiment, replicates of groups 1, 2, and 3 like in phase one were treated for 14 days. Blood glucose levels were determined at baseline (before diabetic induction), 3 days after induction of diabetes, 3, 7, 10, and 14 days after treatments.

2.7. Statistical Analysis

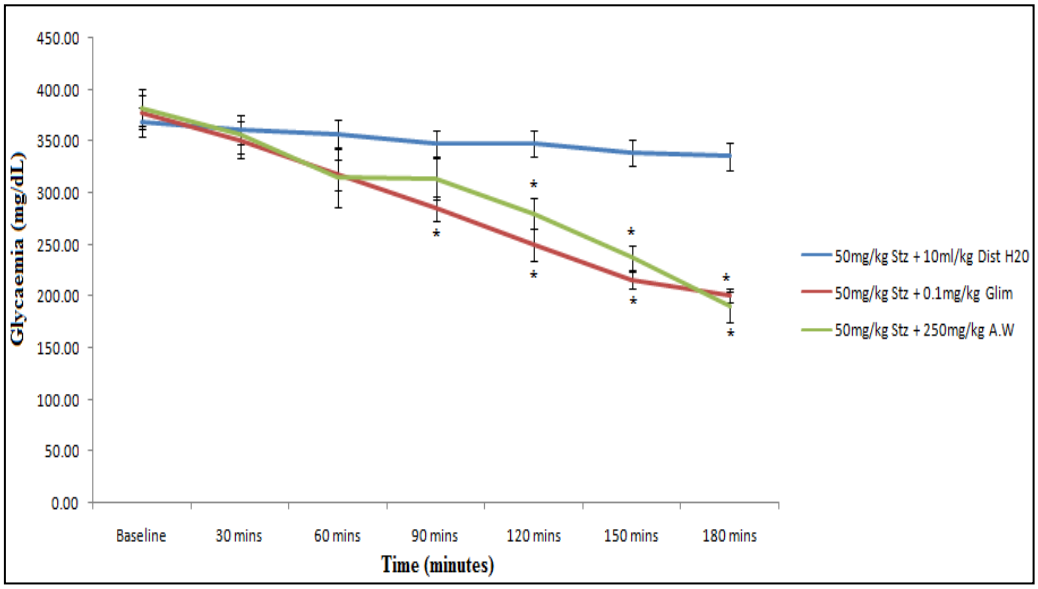
Data were analyzed using statistical tools from SPSS (version 20) and reported as means ± SEM. One-way analysis of variance (ANOVA) was used to analyze the experimental data and Duncan's multiple test range was used to compare the group means obtained after each treatment. Differences were considered significant when $P \leq 0.05$.

3. Results

3.1. Hypoglycemic Effect of the Ethanolic Leaves Extracts of *Acalypha wilkesiana* in STZ Induced Diabetic Rats

Figure 1 shows the time course of hypoglycemic effect of ethanolic leave extract of *Acalypha wilkesiana* treated compared to standard drug-treated and untreated control groups in diabetic adult male Wistar rats. Blood glucose level was similar at baseline and decrease progressively in all the groups. However, it was significantly lower at 90 minutes (285.17±12.09mg/dl) through 180 minutes in the glimepiride group while in the ethanolic leaves extract *A. wilkesiana* treated group it decreased significantly at the 120 minutes (279.83±14.88mg/dl) through 180 minutes when compared with the control.

Figure-1. Comparing the hypoglycemic effect of ethanolic leaves extract *A. wilkesiana* and glimepiride with untreated control in STZ induced diabetic rats

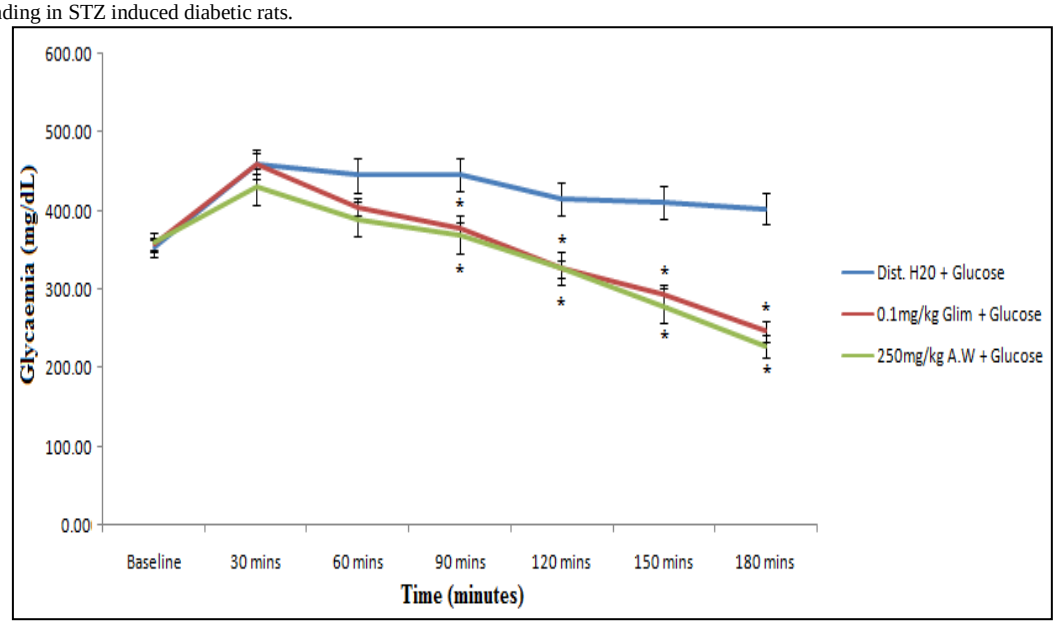


Values are Mean ± SEM; n = rats, * indicates significant difference at $p<0.05$ compared with untreated control; H_2O =water, Dist = distilled, Glim = Glimepiride treated, 250mg/kg A.W = *Acalypha wilkesiana* treated.

3.2. Oral Glucose Tolerance Activity of Ethanolic Leaves Extract *A. wilkesiana* in STZ Induced Diabetes Rats

Figure 2 compares the time course of oral glucose tolerance in ethanolic leaves extract of *A. wilkesiana* and glimepiride treated groups compared with untreated control after glucose loading in diabetic rats. There was a similar blood glucose level at baseline and 30 minutes after glucose loading in all the groups. However, at 60 minutes glucose level was not significantly decrease in the ethanolic leaves extract *A. wilkesiana* (389.00±22.04mg/dl) and glimepiride treated groups (405.67±11.09mg/dl) compared with the control (445.00±22.83mg/dl) but significant decrease ($p<0.05$) in a time-dependent manner by the 90th minutes through 180 minutes after glucose loading compared to the control.

Figure-2. Time course of oral glucose tolerance in untreated, glimepiride and ethanolic leaves extract of *Acalypha wilkesiana* treated after glucose loading in STZ induced diabetic rats.

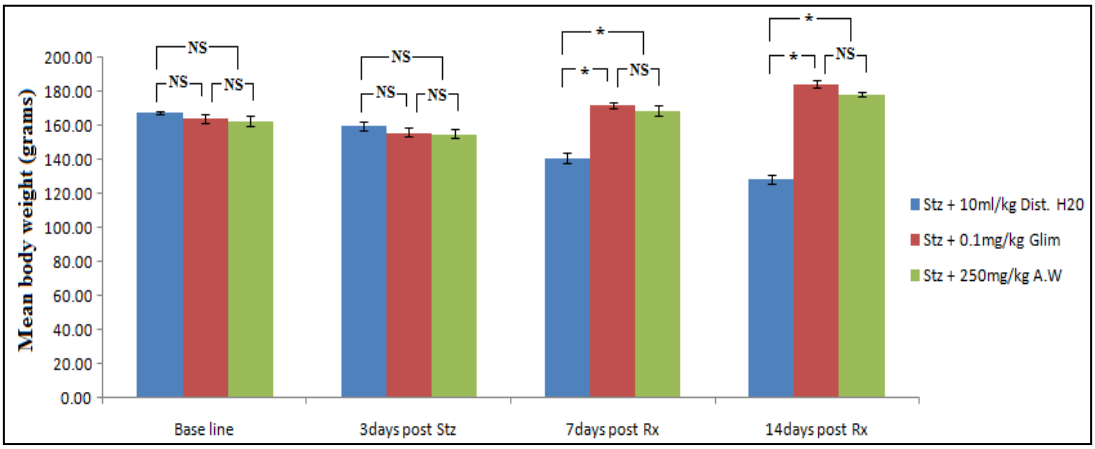


Values are Mean ± SEM; n = rats, * indicates significant difference at p<0.05 compared with untreated control, H_2O =water, Dist = distilled, Glim = Glimepiride treated, 250mg/kg A.W = *Acalypha wilkesiana* treated.

3.3. Bodyweight Variations in Treated and Untreated STZ Diabetic Rats

Figure 3 compares the mean body weight in ethanolic leaves extract *A. wilkesiana* and Glimepiride treatments with untreated control in STZ induced-diabetic rats. Mean body weights were similar at baseline and decreased similarly 3 days post-induction of diabetes in all the groups. However, mean body weights increased significantly (p<0.05) in ethanolic leaves extract *A. wilkesiana* and Glimepiride treated groups at 7 and 14 days post treatments compared to the untreated diabetic control.

Figure-3. Comparing the mean body weight of ethanolic leaves extract of *Acalypha wilkesiana* treatments and glimepiride treatments with untreated control in STZ induced-diabetic rats.

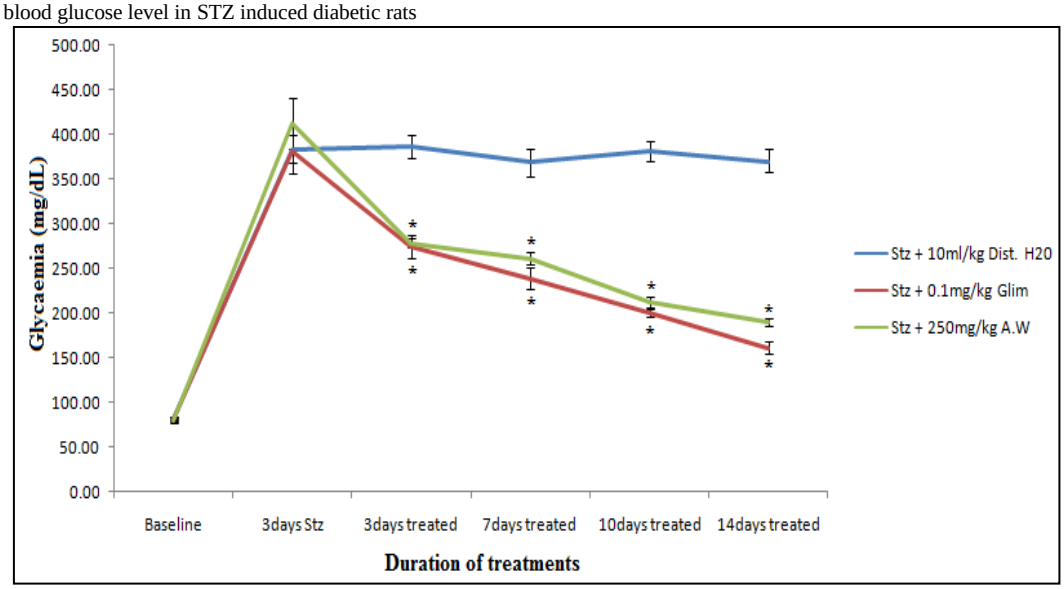


Values are Mean ± SEM; n = 6 rats, * indicates p<0.05, NS indicates not significant (p>0.05), H_2O = water, Dist = distilled, Glim = Glimepiride treated, 250mg/kg = *Acalypha wilkesiana* treated.

3.4. Chronic Hypoglycemic Effect of the Ethanolic Leaves Extracts of *A. wilkesiana* in Treated and Untreated STZ Induced Diabetic Rats

Figure 4 compares the effects of 14 days treatments with ethanolic leaves extract of *A. wilkesiana* and glimepiride treatment with untreated control on blood glucose level of diabetic rats. There was a significant steady duration-dependent decrease (p<0.05) in blood glucose level in the ethanolic leaves extract *A. wilkesiana* treated and glimepiride treated groups from the 3rd day to the 14th day of treatments compared to the control untreated group. Glimepiride treatment had greater but not significant (p>0.05) blood-glucose-lowering capacity than the ethanolic leaves extract *A. wilkesiana* from the 3rd day to the 14th day of treatment.

Figure-4. Comparing the effects of 14 days treatment with ethanolic leaves extract of *A. wilkesiana* and glimepiride with untreated diabetic control on blood glucose level in STZ induced diabetic rats



Values are mean ± SEM; n = 6 rats, * indicates <0.05 compared with untreated control, H_2O =water, Dist = distilled, Glim = Glimepiride treated, 250mg/kg A.W= *Acalypha wilkesiana* treated.

4. Discussion

The use of plant parts and extracts in herbal or traditional medicines is not an uncommon practice in Nigeria as well as in several countries, particularly Africa Shapiro and Gong [20] and Asia Chacko [21]. Considering the current prevalence and health risk of several diseases, particularly diabetes, there is no doubt that several medicinal plants have been tried and given some beneficial claims even if not yet scientifically proven. Worrisome, there is

documentation of several drawbacks of currently available drug regimens for diabetes management and thus the need for safer and effective anti-diabetic drugs [22, 23].

This study revealed the ethanolic leaves extract of *A. wilkesiana* to exhibits hypoglycemic effect in diabetic rats, inhibit glucose-induced hyperglycemia in diabetes rat, and in the long run cause reduction in glucose level with chronic administration that is comparable with glimepiride; a standard diabetic drug. Glimepiride is a type 2 diabetes therapeutic drug and can also be used in type-1 diabetes [24]. It induces a blood hypoglycemic action by promoting endogenous insulin secretion by pancreatic β-cells stimulation [25]. Judging by this, the observed similar hypoglycemic action and glucose lower effect of ethanolic leaves extract of *A. wilkesiana* with glimepiride may suggest that the leaves extract cause its antidiabetic effect by stimulating the pancreatic β-cells to secrete insulin. Thus, the observed suppression of glucose level after glucose loading and reduction in blood glucose level by the ethanolic extract of *A. wilkesiana* in diabetic rats indicate the extract to have glucose reducing properties and as such anti-diabetic. The antidiabetic effect of *A. wilkesiana* has been reported by several studies. Fonkoua, *et al.* [26], have reported the hypoglycaemic effect of 400mg/kg hydroethanolic extract of *A. wilkesiana* in streptozotocin-diabetic rats. Also, Al-Attar [27] has reported a duration-dependent decrease in blood glucose in streptozotocin-induced diabetic rats with an aqueous extract of *A. wilkesiana* leaves.

This anti-diabetic action of ethanolic leaves extract of *A. wilkesiana* may be due to the bioactive constituents present in the extract. This assertion is in line considering the reports by Bnouham, *et al.* [28], Kumar, *et al.* [29], and Mogale [30] that phytochemicals in plants are responsible for blood-glucose-lowering and anti-diabetic activities. Flavonoids and tannins isolated from antidiabetic medicinal plants have been documented to stimulate secretion of insulin or possess an insulin like-effect [31] and inhibit alpha-amylase [32]. Other bioactive compounds such as alkaloids and others found in the extract of *Acalypha wilkesiana* leaves have been documented to lower glycemic effects [33]. Thus, the antidiabetic action by the ethanolic leaves extract of *A. wilkesiana* in this study is possibly due to the active phytochemical components which include alkaloids, flavonoids, and tannins which we previously reported to be among the phytochemicals in the ethanolic leaves extract of *A. wilkesiana*.

On body weight, it was observed in this study that diabetes induced by STZ has a reducing effect on body weight. The observed decrease in body weight agrees with the study by Okoro [34] and Oyedemi, *et al.* [35]. However, considering the study by Thulesen, *et al.* [36], that STZ induces autoimmune destruction of pancreatic β-cells which in turn, according to Rajkumar, *et al.* [37], has been linked to the degradation of structural proteins and muscle wasting, the reduction in body weight caused by the STZ in this study is in accordance. However, the STZ induced decreased in body weight were reversed to baseline level in the ethanolic leaves extract *A. wilkesiana* and standard drug treatments at day 14. Specifically, there were duration-dependent improvements in body weight with plant extract treatment that is comparable with the standard drug. Thus, the administration of the extracts reversed the decrease in body weight seen in the diabetic state. These findings indicate that ethanolic leave extract of *A. wilkesiana* treatment possesses the ability to manage as well as controlling diabetes-induced muscle wasting and adipogenesis. This effect may be interconnected to the protein and fat contents of the *A. wilkesiana* leave.

5. Conclusion

Conclusively, this study showed that the ethanolic leaves extract of *A. wilkesiana* possesses antidiabetic potentials, hypoglycemic actions and inhibits postprandial hyperglycemia in diabetic rats. The mechanism of this antidiabetic action by ethanolic leaves extract of *A. wilkesiana* may be via increased secretion of insulin through stimulation of pancreatic β-cells by the active phytochemical content of the plant. Further studies are recommended to identify and isolate the phytochemical components with this action as this may be a promising anti-diabetes agent(s).

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