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Anti-hyperglycaemic Effect of Methanolic Extract of Tridax Procumbens in Alloxan-Induced Diabetic Wistar Rats

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Abstract

Plant based herbs have historically been a significant source of pharmaceutical molecules for the treatment of metabolic illnesses like diabetes mellitus. This research was aimed at assessing the antihyperglycaemic effect of Tridax procumbens plant on alloxan-induced diabetic wistar rats. The whole plant of T. procumbens was collected within UDUTH, Sokoto premiss, dried under shade and extracted with absolute methanol by maceration for 72 hours with an obtainable percentage yield of 6.9%. The dried mass was used for preliminary phytochemical, acute toxicity and pharmacological analysis. Diabetic rats were treated with 250 mg/kg of metformin, 250 mg/kg and 500 mg/kg body weight of T. procumbens extract for 14 consecutive days. At the end of the experiment blood samples were collected into sample containers to assess the hypoglycaemic effect of the methanolic extract of T. procumbens plant by analyzing fasting plasma glucose and fasting lipid profile level for all experimental animals and compared with diabetic control. The pancreas for all groups were harvested for histological examination. Preliminary phytochemical analysis of methanolic extract of T. procumbens indicated the presence of alkaloid, steroids, flavonoids, tannins and saponin compounds and the LD50 was greater than 5000mg/kg. The methanolic extract of whole plant of at 250 and 500 mg/kg shows significant decrease ($p<0.05$) in fasting plasma glucose and some lipid profile parameter (TG, TC, LDL-C, and AI) except for (HDL-C) which significantly increased ($p<0.05$) when compared with diabetic control. The pancreas histology for groups treated with extract of T. procumbens at dose 250 and 500 mg/kg shows absence of islet cells. Methanolic extract of Tridax procumbens plant has a blood glucose lowering potentials against alloxan-induced diabetic wistar rat. However, chronic toxicity studies and molecular phytochemical studies should be conducted to access the pancreatic effect over time and its active components.

Keywords: Anti-hyperglycaemic effect, Methanolic Extraction, Tridax Procumbens, Alloxan-Induced Diabetic, Wistar Rats.

Introduction

Diabetes is a condition that affects how proteins, fats, and carbohydrates are metabolized. It is linked to a malfunction in the pancreatic synthesis of insulin or a lack of insulin sensitivity or activity, which causes type 1 or type 2 diabetes mellitus, respectively (Mezil and Abed, 2021). About 90–95% of people with diabetes mellitus (DM) have type 2 diabetes mellitus (T2DM), which is the most common kind of disease. T2DM is characterized by insulin resistance in the liver and peripheral tissues as well as insufficient insulin production due to malfunctioning pancreatic β-cells (Nolan *et al.,* 2011).

One of the biggest threats to public health worldwide is diabetes, which has a negative impact on both socioeconomic development and public health. Most developed and developing countries have seen an increase in the prevalence of diabetes in recent decades, despite the fact that incidence has begun to deteriorate in some of them (Patterson *et al.,* 2019). According to the

International Diabetes Federation (IDF), 451 million persons worldwide had diabetes in 2017, and if no effective preventive measures are taken, this figure is expected to increase to 693 million by 2045 (Cho *et al.,* 2018).

Historically, people have used medicinal plants to cure, prevent, and manage a variety of illnesses in humans, including infections, oxidative stress, diabetes and inflammation. (Khumalo *et al.,* 2022). Based on differences in chemical structure, several phytochemicals that have anti-diabetic activities are present in medicinal plants and have been categorized into broad groups (Velu *et al.,* 2018; Gonfa *et al.,* 2021). For a very long time, oral herbal medicines has been used to treat diabetes mellitus because plant-based products are typically thought to be less toxic with fewer side effects than synthetic drugs as it was once used to treat infections, diabetes, malaria, wound healing, and other metabolic problems (Beck *et al.,* 2018).

Tridax procumbens (T. procumbens), also referred to as coat buttons or Tridax daisy, is a flowering plant that is a member of the Asteraceae family. Naturalized in tropical Asia, Africa, Australia, India and Nigeria, the plant is native to tropical America. It's a wild herb found all over India. In addition, it can be found around waste areas, riverbanks, meadows and referred to as Mbuli by the Igbo people of south-eastern Nigeria, Harantama in Hausa (northern Nigeria) and Igbalode in Yoruba (western Nigeria) (Babayi *et al.,* 2018).

Plant-based chemicals have historically been a significant source of pharmaceutical molecules for the treatment of metabolic illnesses like diabetes mellitus and estimated to have been used by at least four billion individuals who reside in underdeveloped nations (Choudhury *et al.,* 2018). Scientists are in search for newer drugs in plants and their extracts which can really be helpful in treating diseases. Fortunately, an increasing number of individuals are seeking herbal remedies with less adverse implications to assist in managing diabetes. Although there are medications available to manage diabetes, interest in alternative traditional cures is growing as usage of herbal remedies is also experiencing an increased demand globally and scientists are becoming more interested in it as a potential source of new drugs due to several drawbacks with current diabetes medications, such as their high cost, limited availability, and associated side effects (Inzucchi *et al.,* 2015).

Materials and Methods

Plant Collection and Identification

Fresh *Tridax procumbens* plants were collected within doctor's quarter UDUTH, Sokoto state. It was identified and authenticated at herbarium unit of department of pharmacognosy, Faculty of Pharmaceutical Science, Usmanu Danfodiyo University, Sokoto with voucher number PCG/UDUS/Aste/0007. The specimen was preserved and kept in the Herbarium for reference purposes.

Preparation of Plant Extract

The leaves of *Tridax procumbens* were dried under shade and grinded in electrical grinder to coarse powder. 400 grams of the grinded powdered leave of *Tridax procumbens* was soaked in three liters (3L) of absolute methanol for 72 hours on a mixer container to ensure maximum extraction by maceration technique at room temperature followed by periodic stirring. The resulting crude extract was filtered using Whatman number 1 filter paper and the filtrate was concentrated in an oven at 40oC to obtain green crude extract. The extract yield was expressed in percentage by dividing the quantity of dried mass obtained after extraction by the total weight of the dried powder dissolved and multiplying by one hundred to obtain 6.9%.

$$\text{Percentage Yield} = \frac{\textit{yield obtained}}{\textit{total powder dissolved}} \times 100$$

Phytochemical Analysis

The phytochemical screening of the extracts was conducted using standard procedures described by Trease (1989) where the extract was subjected to phytochemical screening for various constituents such as alkaloids, flavonoids, saponins, tannins and steroids by Dragendroff reaction, Alkaloid, Froth test, Ferric chloride test and Liebermann Burchard test.

Experimental Animals

Adult Wistar rats weighing 110-150 g of both

genders were selected in order to provide uniform results and minimize error that can occur due to variation in gender and weight. The animals were purchased from Zaria, Kaduna State and habituated at the Faculty of Pharmaceutical Sciences, Usmanu Danfodiyo University, Sokoto in a clean and well-ventilated environment at a temperature of 260C-280C. The experimental room was cleaned and disinfected regularly. The animals were housed and cared for in accordance with good laboratory practice (GLP) regulations. Ethical approval was obtained from the department of pharmacology, Faculty of Pharmaceutical Science, Usmanu Danfodiyo University, Sokoto.

Research Design

Grouping of Animals

Group 1: Negative control, non-diabetic (n=5)
Group 2: Positive control, diabetic without treatment (n=5)
Group 3: Diabetic treated with metformin 250mg/kg (n=5)
Group 4: Diabetic treated with 250mg/kg of extract (n=5)
Group 5: Diabetic treated with 500mg/kg of extract (n=5)

Induction of Diabetes

To induce Diabetes Mellitus in animals, the animals were weighed, and the basal Fasting Plasma Glucose of each animal was measured by bleeding the anesthetized animal on the tail and glucose level was estimated using a glucometer. The rats were then fasted for 12 hours prior to injection of alloxan dissolved in normal saline at a single dose of 150mg/kg body weight which was administered intraperitoneally as recommended by (Ajibola *et al.,* 2014). After that, the animals were monitored for 48 hours, and their fasting plasma glucose was measured to observe for any elevation in fasting blood sugar (FBS) using a glucometer. Only animals with FBGL above 126mg/dl (>7.0mmol/L) were used in the study (Lenzen, 2008).

Acute Toxicity

According to Lorkes (1983), an acute oral toxicity study was conducted in two stages, phases I and phase II (Chinedu *et al.,* 2013).

Phase I of Acute Toxicity Study

Group I, II, and III were created out of nine (9) Wistar rats, each including three (3) rats. The animals in groups I, II, and III were given a single intragastric gavage dose of 10 mg, 100 mg and 1000 mg of the extract per kg of body weight respectively, using an oral cannula. Following the extract's administration, observations were conducted to keep track of any harmful symptoms for the first four hours and then for the next twenty-four hours. For a maximum of 14 days, the rats were intensively observed for alterations in behavior and mortality (Duze *et al.,* 2012).

Phase II of Acute Toxicity Study

Groups I, II, and III, each consisting of one rat, were created from three (3) rats. Using an oral cannula, each rat was given a single intragastric gavage dose of 1600 mg, 2900 mg, and 5000 mg of extract per kg of body weight, respectively. Within the first four hours and then again for the next 24 hours following the extract's administration, observations and records of any harmful indicators were made. The rats were observed for up to 14 days in order to look for any changes in behavior and mortality (Duze *et al.,* 2012).

Sample Collection

After a 14 days period of feeding and treatment with *Tridax procumbens* extract, the animals were fasted for 12 hours over night and then anaesthetized in a glass jar containing wool soaked with chloroform. About five milliliters (5mL) of blood samples was collected from each animal through cardiac puncture where 2mls was dispensed into clean fluoride oxalate (for fasting plasma glucose) container and 3mls into lithium heparin (for fasting lipid profile) container. The blood samples collected in fluoride oxalate and lithium heparin containers were centrifuged at 4000 revolution per minutes for 10 minutes and the obtained plasma was transferred into a well labeled sterile cryovials, tightly caped and stored frozen at 20^{O}C until the time for biochemical analysis to evaluate the fasting plasma glucose and fasting lipid profile.

The rats were sacrificed and pancreas from each group was carefully removed, then transferred into specimen containers containing 10% formalin for proper fixation. The pancreas was transported to histopathology laboratory for histological examination.

The tissue sections after being fixed in 10% formalin were dehydrated in Ascending concentrations of alcohol: 70%, 95% and through Absolute concentration for ten minutes each. The sections were cleared in xylene and then infiltrated with wax. It was then embedded in molten paraffin wax and was cut to thin section of 3 µm thickness. The section was transferred into a warm water bath and was allowed to float on the surface and then picked up onto an albuminated slide. The slide was allowed to dry and the tissue sections were stained with Harris's hematoxylin for five minutes, rinsed in water and differentiated in 1% acid alcohol for ten seconds. The sections were blued in Scott's tap water for few minutes and then rinsed in water. The sections were counter-stained with eosin for three minutes and then rinsed in water. The sections were dehydrated in ascending concentrations of alcohol, through 70%, 90% and then absolute, for two minutes each. The sections were cleared in xylene and mounted in Distyrene Polystrene Xylene (DPX). The tissue sections were examined under light microscope to study histological features of the pancreas of the Wistar rats (Orchard and Nation, 2012).

Statistical Analysis

The data obtained were analyzed using Microsoft Office Excel 2013 and Statistical Package for Social Sciences (SPSS) version 27.0. Results were expressed as mean±SEM. Group comparisons was made using one-way analysis of variance (ANOVA), p value less than or equal to 0.05 ($p<0.05$) was considered as statistically significant.

Results

The results of phytochemical screening of methanolic extract of T. procumbens indicate the presence of alkaloids flavonoids, saponins, steroids and tannins. The result of acute oral toxicity showed that neither death nor abnormal behavior were recorded in the rats after 24 hours and 72 hours in both phase I and phase II. This indicated that the LD50 of the extract was greater than 5000 mg/kg. There is significant decrease ($p<0.05$) between the diabetic control group for triglyceride, total-cholesterol, LDL-cholesterol and atherogenic index when compared with Diabetic group treated with 500mg/kg of *T. procumbens* extract respectively except for HDL-cholesterol which significantly increases ($p<0.05$). There is no significant difference ($p<0.05$) between the diabetic control group for triglyceride and total cholesterol when compared to Diabetic group treated with 250mg/kg of *T. procumbens* extract. There is a significant increase($P<0.05$) in HDL-cholesterol level for diabetic control group when compared with that of Diabetic group treated with 250mg/kg of *T. procumbens* extract. There is also a significant decrease (P-value<0.05) in LDL-cholesterol level and atherogenic index for diabetic control group when compared with Diabetic group treated with 250mg/kg of T. procumbens extract. At the end of the experiment, there was a significant decrease ($p<0.05$) between the diabetic control group, Diabetic group treated with 250mg/kg of *T. procumbens* extract and Diabetic group treated with 500mg/kg of *T. procumbens* extract respectively.

Table 1: Lipid profile among the various Study Groups

GROUPS	N	TG (mg/dl)	TC (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	AI
I	5	63.13 ± 2.93^{a}	64.76 ± 3.75^{a}	37.52 ± 1.16^{a}	17.13 ± 2.89^{a}	0.23 ± 0.03^{a}
II	5	98.04 ± 2.34^{b}	106.19 ± 4.32^{bc}	32.10 ± 0.79^{b}	54.48 ± 4.37^{b}	0.52 ± 0.01^{b}
III	5	84.86 ± 2.80^{c}	83.23 ± 4.50^{ac}	37.40 ± 0.73^{a}	28.86 ± 3.93^{a}	0.35 ± 0.02^{c}
IV	5	92.32 ± 1.81^{b}	89.75 ± 7.92^{c}	36.35 ± 0.40^{a}	34.93 ± 7.95^{ab}	0.39 ± 0.04^{c}
V	5	83.00 ± 1.44^{c}	80.57 ± 3.50^{ac}	37.76 ± 0.58^{a}	26.21 ± 3.52^{a}	0.33 ± 0.02^{ac}
P-value		< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
F-value		30.78	9.21	7.90	8.86	14.55

Keys : Values are expressed as mean ± SEM, N = number of Wistar rat per group, TG = Triglyceride, TC =Total cholesterol, HDL-C = High density lipoprotein cholesterol, LDL-C = Low density cholesterol, AI = Atherogenic index, Group I = Normal control, Group II = Diabetic control, Group III = Diabetic group treated with metformin 250mg/kg, Group IV = Diabetic group treated with 250mg/kg of *T. procumbens* extract, Group V = Diabetic group treated with 500mg/kg of *T. procumbens* extract, p-value < 0.05 = significant, p-value < 0.05 not significant. (One-way ANOVA followed by turkey post-hoc test^{abc}) where different superscript indicates significant difference between the compared groups.

Table 2: Basal Fasting Glucose and Final Fasting Glucose among the Study Groups

GROUPS	N	B-FGLU (mg/dl)	F-FGLU (mg/dl)
I	5	90.72±3.67[a]	74.30±3.26[a]
II	5	221.85±91.54[a]	140.31±4.31[b]
III	5	177.13±67.98[a]	108.22±9.71[c]
IV	5	270.00±92.77[a]	111.40±2.82[c]
V	5	336.48±76.02[a]	109.7±3.34[ac]
P-value		>0.05	> 0.05
F-value		1.86	16.90

Keys: Values are expressed as mean ± SEM, N = number of Wistar rat per group, B-FGLU = Basal fasting glucose, F-FGLU = Final fasting glucose, Group I = Normal control, Group II = Diabetic control, Group III = Diabetic group treated with metformin 250mg/kg, Group IV = Diabetic group treated with 250mg/kg of *T. procumbens* extract, Group V = Diabetic group treated with 500mg/kg of *T. procumbens* extract, p-value > 0.05 = significant, p-value > 0.05 not significant, (One-way ANOVA followed by turkey post-hoc test[abc]) where different superscript indicates significant difference between the compared groups.

Histological Result of The Pancreas

Plates 1 shows a photomicrograph of the pancreatic cells in group I (Negative control, non-diabetic), group II (Positive control, diabetic without treatment), group III (Diabetic treated with metformin 250mg/kg), group IV (Diabetic treated with 250mg/kg of *T. procumbens*) and group V (Diabetic treated with 500mg/kg of *T. procumbens* extract) respectively.

SLIDE A: Photomicrograph of pancreas in group1 (normal control) showing lobules of pancreatic acini within which foci of regular pancreatic islet are seen (green arrow). (H&E: AX400)

SLIDE B: photomicrograph of pancreas in group II (Diabetic control) showing lobules of acini intrpersed by congested blood vessels. (H&E X100).

SLIDE C: photomicrograph of pancreas in group III (metfofmin control group) showing pancreatic acini interpersed by islet cells (yellow arrow). (H&E X200).

SLIDE D: photomicrograph of pancreas in group IV (250mg/dl) showing lobules of pancreatic acini separated by fibrous septae. No islet cells seen. (H&E X100).

SLIDE E: photomicrograph of pancreas in group V (500mg/dl) showing similar lobules of pancreatic acini and no islet cells seen (H&E X100).

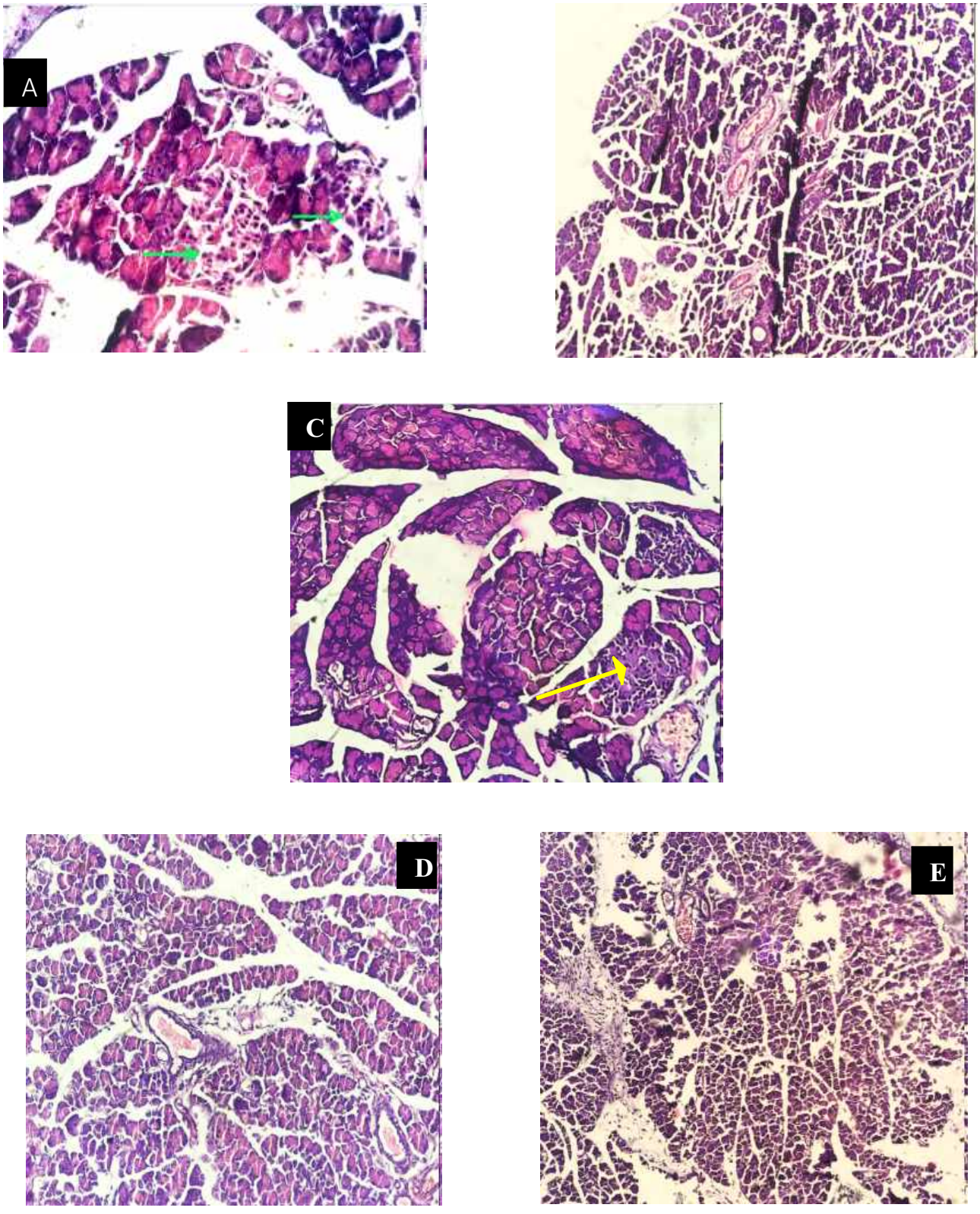

Plate 1: A Photomicrograph Showing Histol ogical Features of Pancreatic islet using green and yellow arrow

Discussion

Various traditional medicines and vegetables have been reported to be used in the treatment of diabetes mellitus (Kasole *et al.,* 2019). Moreover, the prevalence of herbal medicine use among patients with diabetes mellitus is high, with some studies indicating that more than 70% of individuals use herbal remedies for diabetes control (Lindberg *et al.,* 2020).

In this study, the presence of alkaloids, flavonoids, tannins, saponin, and steroids were detected. This agrees with the work of Nair *et al.* (2016), which established the presence of some certain phytochemical compounds in *T. procumbens* extract such as flavonoid, steroid, carbohydrate, proteins, tepernoids, saponin, glycosides, alkaloids, tannin. In addition to that, Al-Ishaq *et al.* (2019) reported that flavonoids show blood glucose lowering activities by enhancing GLUT-2 expression in pancreatic β-cells, enhancing insulin release, increasing expression and promoting translocation of GLUT-4 which can increase glucose uptake by the muscle, liver, and adipose tissue. Another research carried out by Kumar *et al.,* (2019) indicated that alkaloids are effective for pancreatic regeneration, insulin release and as well shows protective effect on oxidative tissue damage.

Acute toxicity is the ability of a substance to cause harmful effects shortly after a single dose or within a short period of time (usually within 24 to 48 hours). In this study the acute toxicity study was carried out before the commencement of the intervention with the methanolic extract as expressed by Lorke's method. The rats were observed for signs of toxicity of which in both phase I and phase II of the acute toxicity study, no mortality was recorded and absence of mortality in group loaded with highest dose of 5000mg/kg body weight is an indication that the median lethal dose (LD50) of methanolic extract of *T. procumbens* is greater than 5000mg/kg which is in agreement with similar study carried by Pareek *et al.* (2009) who reported that the (LD50) of 50% methanolic extract of *T. procumbens* is greater than 5000mg/kg.

Findings from this research work reported a statistically significant difference ($p<0.05$) between the final fasting plasma glucose level of the groups treated with 250mg/kg and 500mg/kg with that of diabetic control groups. The significant reduction in blood glucose level is in accordance with similar finding by Pareek et al. (2009) indicating the antidiabetic effect of *T. procumbens* which might be due to the presence of flavonoids, alkaloids and other phytochemical compounds.

From this study, there is a slight insignificant decrease ($p>0.05$) in triglyceride level in group treated with 250mg per kilogram body weight plant extract but a significant decreased ($p<0.05$) triglyceride level in groups administered with 500mg/kg extract and 250mg/kg body weight of metformin as compared with diabetic control group. This signifies a dose dependent variation, which in disagreement with similar experiment carried out by Pareek *et al*. (2009) who reported that administration of 250mg and 500mg per kilogram body weight of methanolic extract of *T. procumbens* significantly decrease triglyceride level.

In this study, a significant decrease in low-density lipoprotein cholesterol level was recorded ($p<0.05$) in group treated with 250mg and 500mg per kilogram body weight of *T. procumbens* extract when compared with the diabetic control group (Table 4.4). This is in agreement with related research conducted by Enwa *et al.* (2020) who reported a decreased LDL value in rats treated with methanolic extract of the plant.

Our finding also shows a significant increase in high-density lipoprotein cholesterol level ($p<0.05$) in groups treated with 250mg and 500mg per kilogram body weight of extract and as well group treated with 250mg per kilogram body weight of metformin respectively. High HDL exerts a protective effect by decreasing the rate of entry of cholesterol into the cell via LDL and increasing the rate of cholesterol release from the cell which is in line with similar studies carried out by Pareek *et al.* (2009) who observed that administration of 250mg and 500mg per kilogram body weight of *T. procumbens* extract significantly increase HDL level.

This research deduced a significant decrease ($p<0.05$) in atherogenic index of plasma in

groups treated with 250mg and 500mg per kilogram body weight of *T. procumbens* extract when compared to the diabetic control group (Table 2), indicating lower chances of developing heart disease and this coincides with related research carried out by Ikewuchi and Ikewuchi (2009).

An insignificant decrease in total cholesterol level was observed in this study ($p>0.05$) in group treated with 250mg per kilogram body weight of T. procumbens extract when compared to the diabetic control group and a significant decrease in group treated with 500mg per kilogram body weight (Table 4.4). This signifies a dose dependent variation, which contradicts similar experiment done by Pareek *et al.* (2009).

The body mass index between diabetic control and groups treated with 250mg and 500mg per kilogram body weight of *T. procumbens* methanolic extract showed no significant difference ($p>0.05$). This contradicts similar study conducted by Amagbegnon *et al.* (2021) and might be due to dietary composition, hormonal imbalance and stress.

Histopathological examination of pancreas tissues of negative control rats showed normal lobules of acinar with a regular pancreatic islets cell (slide A) while the diabetic control group shows lobules of acini interspersed by congested blood vessels (slide B). The degenerative alterations of the acini in current study were similar to previous studies which recorded that the diabetes induced by alloxan result in a considerable structural damage in tissues of pancreas as disturbance in acinar pattern structure, shrinkage of most acinar cells which is also in consistent with Hadi (2019) who reported that the size and number of pancreatic islets were decreased in diabetic rats in comparison to normal rats. The histopathological examination of pancreas in group III (metformin treatment group) shows acini interspersed by few islet cells (plate C) which may be due to inflammation that can change the blood vessel and surrounding leading to increased blood flow and congestion of blood vessel. The pancreatic examination of group treated with *T. procumbens* extract with dose 250mg/kg and 500mg/kg body weight shows lobules of pancreatic acini separated by fibrous septae with no islet cells (slide D and E) indicating that there is no regeneration of pancreatic β-cells, by the extract which is in disagreement with similar study by Jha and Chatterjee (2020) which states antidiabetic medicinal plants has the β-cells, regenerative effect.

Conclusion

From findings from this research, it was concluded that methanolic extract of *Tridax procumbens* plant has anti-hyperglycaemic effect which was dose dependent as it has shown a significant decrease in fasting plasma glucose level in both high and low dose without any physical toxic effect. Although, the histopathological examination showed no β-cells, regenerative effect which implied that the antidiabetic effect of *Tridax procumbens* extract was more of a different mechanism of action.

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