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Research Article

Glucose-lowering Effect and Anti-inflammatory Activity of Aqueous Leaf Extract of *Taraxacum officinale* in Wistar Rats.

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ABSTRACT

Background: The use of traditional medicine in treating and managing chronic diseases is currently a common practice. *Taraxacum officinale* (dandelion), commonly used as food, has been reported to have several pharmacological properties including blood glucose lowering effects in diabetes mellitus. In the present study, the hypoglycemic property of the leaves of *T. officinale* was investigated. Methods: The leaves of *T. officinale* were pulverized and extraction was done using distilled water. The extract was analysed for various classes of phytoconstituents. The antioxidant and anti-inflammatory effects were determined using 2, 2-diphenyl-1-picryhydrazyl (DPPH) and Carrageenan-induced foot edema respectively. The hypoglycemic effects of the extract were also studied in streptozotocin (STZ)-induced diabetic rats at three doses (10 mg/kg, 30 mg/kg and 60 mg/kg). Linear mixed model technique was used to analyze the multiple glucose measurements per rat. This model acknowledges the presence of dependency by introducing rat-specific random effect(s) which measures the individual rat variations either at baseline (random intercept) or at the different time point (random slope). Results: Saponins and polyphenols were found to be present in the extract. The linear mixed model estimated the overall trajectory of blood glucose levels. A random-intercept model was found to be sufficient to model the effect of treatment evolution. The results exhibited a dose-dependent decrease in the blood glucose levels of STZ-induced diabetic rats compared with the positive control (insulin treated group). Conclusion: The study has provided evidence that aqueous extract of *T. officinale* has hypoglycaemic property comparable to insulin over a period of time.

Keywords: Diabetes, *Taraxacum officinale*, insulin, hypoglycaemic, streptozotocin

INTRODUCTION

Many traditional health practitioners are endowed with a wealth of knowledge of medicinal plants used in the management of diabetes mellitus. This important traditional knowledge needs to be documented and validated. It is hoped that if this knowledge is tapped and investigated, potent hypoglycaemic agents may be discovered to manage the disease and improve the lives of sufferers at a reasonable cost. Plants have been sources of oral hypoglycaemic drugs. An example is galegine, which was isolated as an active hypoglycaemic agent from *Galega officinalis* (Fabaceae). The isolated galegine provided the template for the synthesis of metformin [1]. Also, the cyclopropamide amino acids, hypoglycine A and B isolated from *Blighia sapida* (Sapindaceae)[2], and the novel terpenoid-type quinones SP-18904 and SP-18905, isolated from *Pycnanthus angolensis* (Myristicaceae)[3], are some few examples of active hypoglycaemic constituents obtained from medicinal plants.

Taraxacum officinale, commonly known as dandelion is a member of the Asteraceae family. It is used as food; the leaves are used in salads and as tea, while the roots are sometimes used as a substitute for coffee[4]. The leaves and roots of dandelion have been shown to help in digestion (mostly as bitter digestive stimulants). The roots have demulcent action and prebiotic properties as well as hypoglycemic effects[5,6]. Dandelion contains an abundance of sesquiterpene lactones or bitter elements, principally taraxacin and taraxacerin[7]. Taraxacin and taraxacerin have been found in several pharmacological properties of dandelion. Phenylpropanoids in dandelion are believed to have modulating effects while sesquiterpene lactones have anticancer and anti-inflammatory effects[8]. Inflammation is a self-protective mechanism aimed at removing harmful stimuli, including damaged cells, irritants, or pathogens[9]. During an inflammatory process, the excessive release of reactive oxygen species (ROS) cause an imbalance in cellular functions. This leads to tissue damage resulting in chronic inflammatory states[10]. Chronic inflammatory

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Table 1: Results of the phytochemical screening of powdered *T. officinale*

Plant secondary metabolites	*T. officinale*
Saponins	+
Reducing sugars	-
Phenolics	+
Polyuronides	-
Cyanogenic glycosides	-
Alkaloids	-
Flavonoids	-
Triterpenes	-
Phytosterols	-

+ = present; - = absent

processes induce oxidative stress and reduce cellular antioxidant capacity[11]. The cellular side-effects of chronic inflammatory conditions are caused by excessive production of free radicals and depletion of antioxidants[12]. The role of antioxidants in chronic inflammatory conditions therefore is to complement the anti-inflammatory process and promote tissue repair[13].

Plants with varying chemical constituents possess pharmacological potentials which help in improving health care[14]. There is therefore the need to search for new effective but less expensive hypoglycaemic agents to replace some existing expensive antidiabetic agents which are also known to have adverse effects. Various cultures still manage diabetes mellitus with plant-based medicines, many of which have not been subjected to scientific scrutiny. Recent studies have shown that the combined extracts of *Portulaca oleracae* and *Taraxacum. officinale* may have blood sugar modulating activity in normoglycaemic and alloxan-treated hyperglycaemic rabbits[6]. However, the STZ-induced rat models have advantages over alloxan-induced ones. STZ-induced diabetic rats have the ability to sustain hyperglycaemia and development of well characterized diabetic complications with low incidence of ketosis and mortality[15]. Except for carcinogenicity[16], no safety studies seem available on this medicinal plant. Further research after both pre-clinical and clinical studies, suggested that *T. officinale* (dandelion) was safe to use[17]. It is in this direction that the hypoglycemic property of the leaves of *T. officinale* was investigated.

MATERIALS AND METHODS

Plant materials

Fresh leaves of *T. officinale* were obtained from the Arboretum of the Centre for Plant Medicine Research (CPMR) in the Eastern region of Ghana, and authenticated at the Plant Development Division of CPMR. Voucher specimen with number DPH/S-008 has been kept at the herbarium.The leaves were washed with distilled water, shade dried and pulverized.

Extraction

Pulverized dried leaves of *T. officinale* (300 g) were boiled in 3 liters of distilled water for 30 minutes and cooled. The resultant extract was decanted and filtered twice, pre-frozen and lyophilized into powder using a freeze dryer.

Table 2: IC_{50} of *T. officinale* and Butylated Hrdroxytoluene (BHT)

Extract/Standard	IC_{50} (mg/ml)
Taraxacum officinale	0.7065
Butylated Hrdroxytoluene	0.025

The dried powdery extract was weighed to determine the yield (8.3% w/w) and stored in a desiccator at room temperature.

Phytochemical Screening

A portion of the extract of the *T. officinale* leaves was screened phytochemically using standard methods as described by Harborne, 1973[18].

Antioxidant assay of T. officinale leaves

Scavenging of 2, 2-diphenyl-1-picryhydrazyl (DPPH) radical was used to evaluate the antioxidant effect of the extract. One (1) ml of each extract (0.15625, 0.3125, 0.625, 1.25, 2.5, 5 mg/ml) in methanol was added to 3 ml of methanolic DPPH solution (20mg/L) in a test tube. The reaction mixture was kept at 25^{O}C for 30 minutes. The process was repeated for Butylated hydroxytoluene (BHT*)* with concentrations (0.015625, 0.03125, 0.0625, 0.125, 0.25, 0.5 mg/ml). The absorbance of the residual DPPH was determined at 517nm in a spectrophotometer (Cecil CE 7200 spectrophotometer). The DPPH radical scavenging activity is calculated according to the following equation:

% DPPH radical scavenging activity = $1 - \frac{\text{Asample}}{\text{Acontrol}}$ x100;

where A_{sample} and $A_{control}$ are absorbance of sample and control respectively.

Animals

Adult Sprague Dowley male rats weighing 170-190 g and one (1) day post-hatch Cockerels (*Gallus gallus*) were housed under standard conditions of room temperature and fed with standard pelleted feed with tap water *ad libitum* in the Animal House of the Department of Pharmacology, CPMR. All the animals were treated in accordance with the National Institute of Health Guidelines for the care and use of laboratory animals. The research protocol was approved by the Ethics Committee of CPMR.

Toxicity Studies

After an over-night fast, an aqueous extract of *T. officinale* leaves suspended in distilled water was administered orally at doses of 2500 and 5000 mg/kg body weight to two groups of six animals respectively. The animals were observed over a 48- hour period for general behavior profile. Mortality in the groups was also recorded. Surviving animals were observed for a further period of 12 days for CNS defects in lachrymation, locomotion and respiration.

Induction of inflammation in chicks

The Carrageenan-induced foot edema model in chicks was used to evaluate the anti-inflammatory properties of the extract and compared to dexamethasone and diclofenac as reference drugs. Edema was induced by sub-plantar injection of 2% w/v Carrageenan into the right footpads of the chicks. The foot volume was measured before injection and at hourly intervals for 5 hours after injection by water displacement plethysmography as described by[19]. The

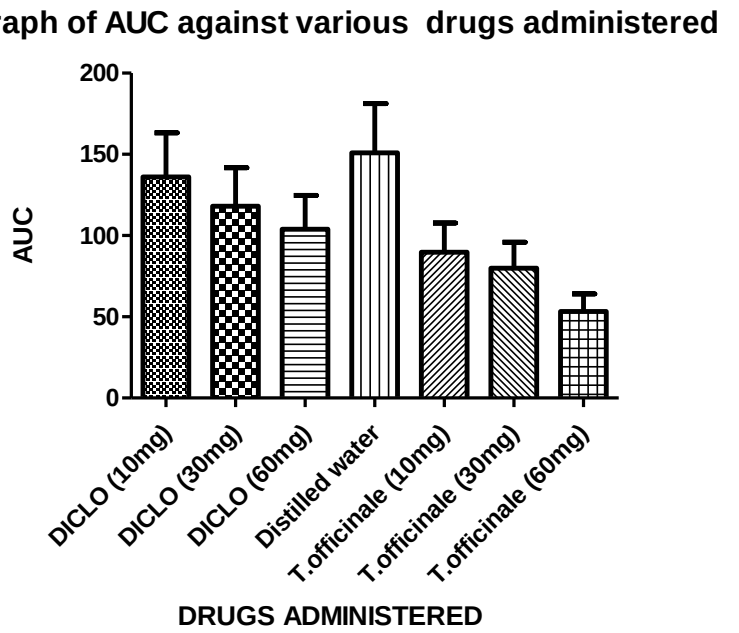

Figure 1: Anti-inflammation effect of *T. officinale.*

Table 3: Parameter estimates and standard errors for the linear mixed model with random intercept.

Variable	Parameters	Estimate	Standard Error	P-Values
	Intercept	23.96571	1.395153	<0.001
Dose	10mg	-6.73	1.973044	0.0006
	30mg	-8.41786	1.973044	<0.001
	60mg	-7.77429	1.973044	0.0001
	Insulin	-5.47714	1.973044	0.0055
Hours	Hours	0.84	0.174766	<0.001
Dose/Hour Interaction	10mg*Hours	-1.34143	0.247156	<0.001
	30mg*Hours	-2.19786	0.247156	<0.001
	60mg*Hours	-1.83714	0.247156	<0.001
	Insulin*Hours	-3.88571	0.247156	<0.001
Between rat variability at baseline	7.7481	2.7835		
Within rat variability	4.2760	2.0679		

edema component of inflammation was quantified by measuring the difference in foot volume before carrageenan injection and at the various time intervals. A sample size of 5 chicks per cage was used throughout the experiment.

Anti-inflammation effect of the aqueous extract of T. officinale leaves on the chicks

The chicks were randomly divided into six groups of five. The groups were labelled A, B, C, D, E and F. Groups A and B received the positive controls diclofenac (10, 30, and 60 mg/kg) respectively. Group C was given distilled water as the negative control. Groups D, E and F received the tested drug (*T. officinale* extracts) at 10, 30, and 60 mg/kg body weight respectively. The drugs were administered orally to the chicks. After treating the subjects with the various extracts, the foot volume of the chicks were measured once again using the water displacement plethysmography at an hourly interval for 5 hours.

Induction of diabetes in rats using streptozotocin (STZ)

Streptozotocin (0.588 g) was dissolved in freshly prepared 0.1M citrate buffer of pH-4.5. Diabetes was induced by injecting rats with a single dose of 60 mg/kg body weight of STZ intraperitoneally in rats [20]. Blood glucose levels were recorded before (baseline) and after a resting period of 48 hours to confirm a state of diabetes. Rats with blood glucose levels higher than 10 mmol/l were classified as diabetic animals and selected for the study.

Hypoglycaemic effect of the aqueous extract of Taraxacum officinale leaves on diabetic rats

The STZ induced diabetic rats were randomly divided into five groups of five animals each; Groups A, B, C, D and E. Groups A, B and C were given oral doses of 10, 30 and 60 mg/kg body weight of aqueous extract of *T. officinale* leaves respectively. Group D was given 1 unit/kg body weight of insulin, a standard antihypergylcaemic agent, to serve as positive control; Group E received 10 ml/kg body weight distilled water representing the negative controls.

Blood glucose level measurement

Blood glucose (BG) levels were initially measured hourly over a six hour period starting at 0 hour. The *T. officinale*

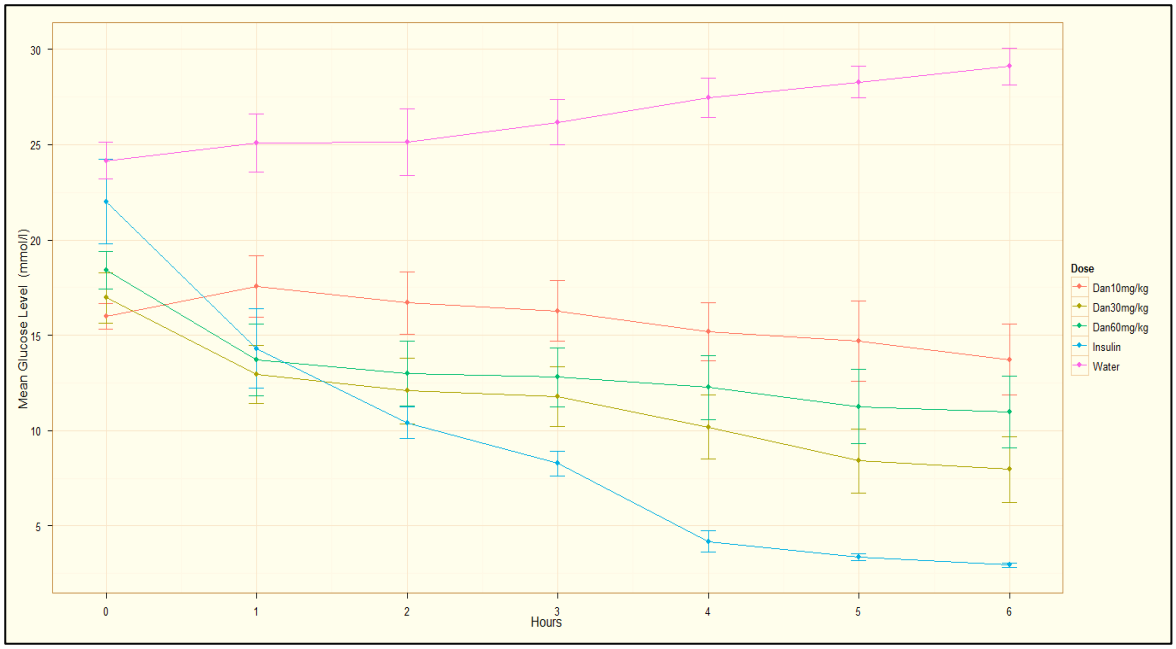

Figure 2: Hypoglycaemic effect of aqueous extract of *T. officinale* leaves on STZ-induced diabetic rats over a 6 hr period. All values are expressed as mean ± S.E.M. (N = 5); Dan = Aqueous extract of *Taraxacum officinale* leaves; INS = Insulin.

Table 4: Parameter estimates and standard errors for the linear mixed model with random intercept.

Variable	Parameters	Estimate	Standard Error	P-Values
	Intercept	24.628	2.030802	<0.001
Dose	10mg	-6.736	2.871988	0.019
	30mg	-8.508	2.871988	0.0031
	60mg	-6.176	2.871988	0.0315
	Insulin	-10.4	2.871988	0.0003
Hours	Days	0.148	0.087221	0.0897
Dose/Days Interaction	10mg*Days	-0.33	0.123349	0.0075
	30mg* Days	-0.30257	0.123349	0.0142
	60mg* Days	-0.50886	0.123349	<0.001
	Insulin* Days	-0.69886	0.123349	<0.001
Between rat variability at baseline	9.4389	3.0723		
Within rat variability	18.6383	4.3172		

extract was then administered to observe its effects on the glucose levels of diabetic rats. Blood samples were obtained from the tail vein of the rats and the blood glucose measured using Accu-Chek® Active glucometer (Roche Diagnostics GmbH, Mannheim Germany). The rats received standard diet and water every morning throughout the study period. At the end of the experiment, the rats were sacrificed and the organs (liver, pancreas, kidney) were taken and weighed to determine the organ to body ratio.

Statistical analysis

All the data provided in this study were represented as means ± S.E.M. Since this study involved multiple glucose measurements per rat, the linear mixed model was chosen as an appropriate statistical technique for the data analysis. This model acknowledged the presence of dependency by introducing rat-specific random effect(s) which measured the individual rat variations either at baseline (random intercept) or at the different time points (random slope). The model estimated the overall trajectory of glucose to see if it was increasing, decreasing or stable by including treatment-time interaction in the evaluation. After careful model building, a random-intercept model was found to be sufficient to model the effect of treatment evolution.

RESULTS

Phytochemical analysis

From Table 1, analyses of the aqueous extract of *T. officinale* showed the presence of two of the phytochemicals tested.

Acute Toxicity Studies

No deaths were recorded in 48 hours following the administration of a single oral dose of 5000 mg/kg body weight of the freeze dried extract of *T. officinale* leaves to six animals. This suggests that the oral LD_{50} is greater than 5000 mg/kg. Observation of animals over 12 days showed no adverse effects due to treatment with the extract. There were no physical signs of toxicity as evidenced by normal

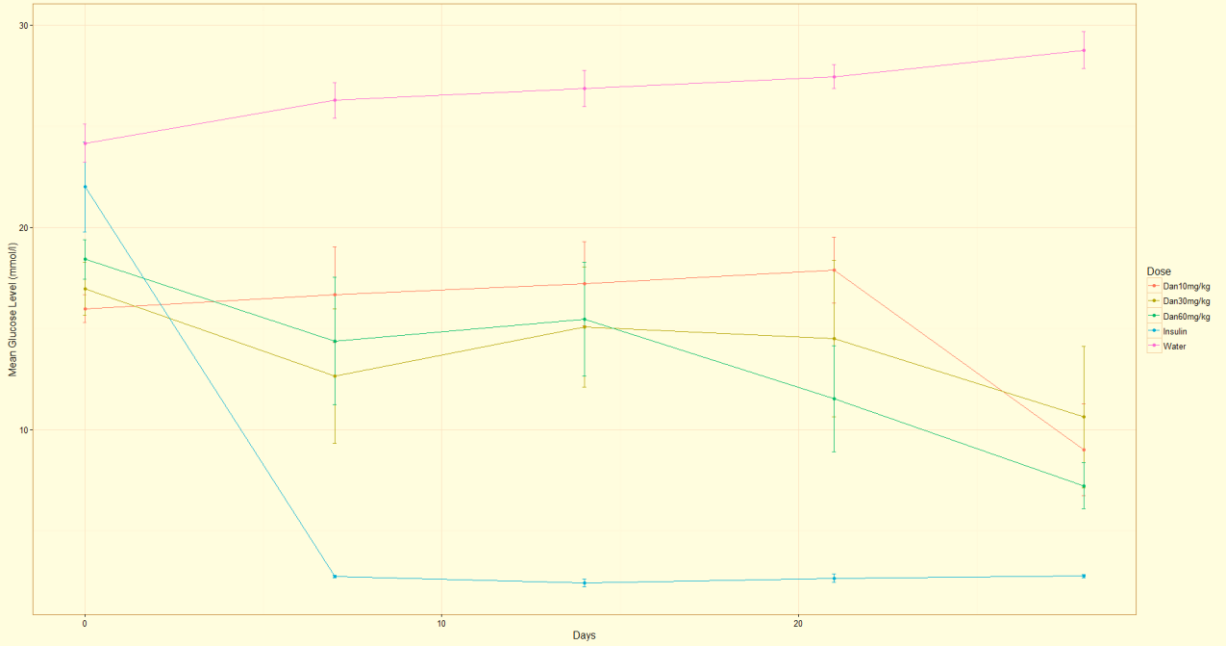

Figure 3: Hypoglycaemic effect of aqueous extract of *T. officinale* leaves on STZ-induced diabetic rats over a 28 day period. All values are expressed as mean ± S.E.M. (N = 5); Dan = Aqueous extract of *Taraxacum officinale* leaves; INS = Insulin.

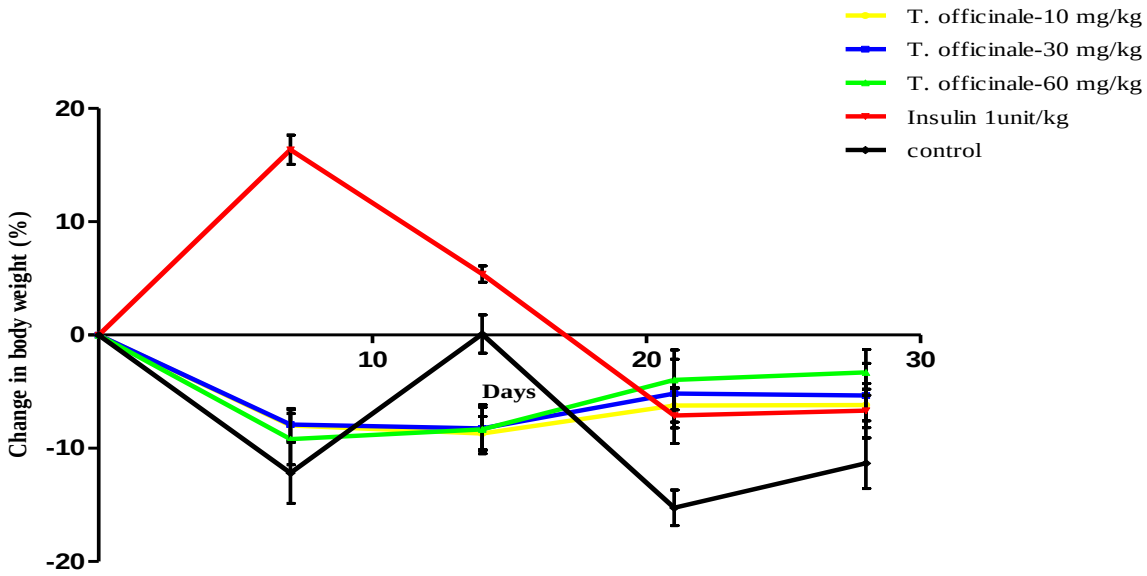

Figure 4: Effect of aqueous extract of *T. officinale* leaves on the body weight of STZ-induced diabetic rats over 28 day period. All values are expressed as mean ± S.E.M. (N = 5).

respiratory, locomotory and lachrymatory activities and the absence of pilo-erection.

Antioxidant effect of T. officinale

The concentration of sample required to scavenge 50% of DPPH is expressed as IC_{50} (Tab 2). The absorbance decreased with increasing free radical scavenging ability. However, in this assay, the extract showed a concentration dependent scavenging effect.

Anti-inflammation effect of T. officinale

The extract, caused significant ($P < 0.001$) dose-dependent inhibition of the carrageenan-induced inflammation in the seven day old chicks, the effect of which began 2 hours after carrageenan injection. Diclofenac (10-60 mg /kg) showed significant ($P < 0.001$) effect on the time course curve and dose dependently reduced the total edema (Fig 1). The area under the dose response curve (AUC) for the inhibition of foot edema is inversely correlated to the efficacy treatment hence the higher the anti-inflammatory activity, the lower the dose needed to inhibit the edema by 50%. This is expressed as IC_{50} (mg/kg) values. The leaf extract of *T. officinale* showed higher anti-inflammatory activity compared with Diclofenac.

Hypoglycaemic effect of the aqueous extract of T. officinale leaves

From Fig 2, *T. officinale* decreased the blood glucose levels of STZ induced diabetic rats compared to the untreated group over the 6 hr period. However, the reduction was dose independent, with 30 mg/kg having the

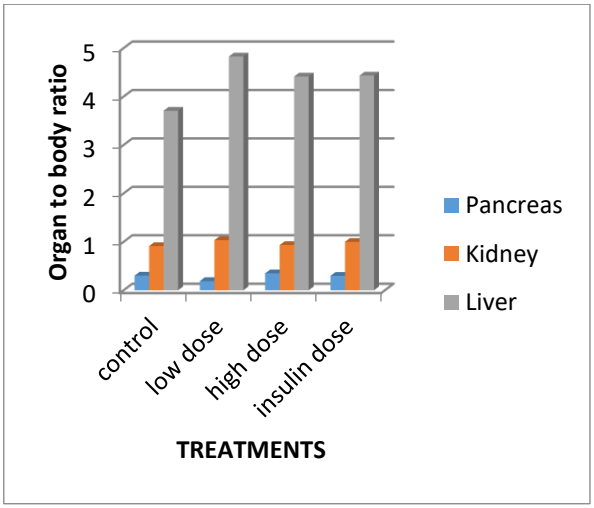

Figure 5: Hyperglycaemic group.

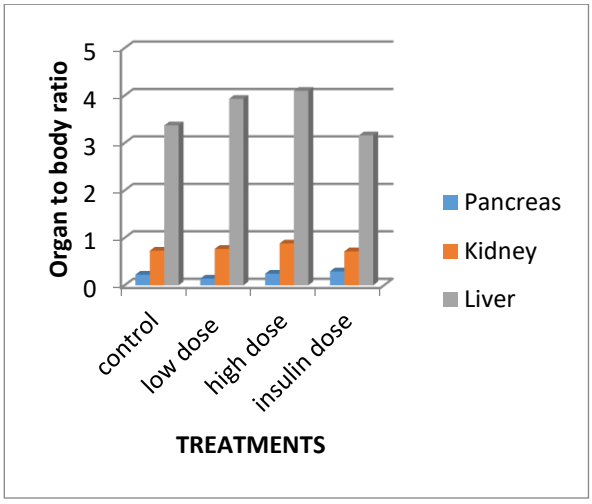

Figure 6: Normoglycaemic group.

best hypoglycemic effect among the three doses. Furthermore, the reduction in the blood glucose levels by *T. officinale* was less pronounced compared to the insulin treated group.

The results of the linear mixed model are presented in Table 3. From the results, it was observed that at baseline there was a significant difference in the glucose level between Control (water) and the other dose levels. The interaction between hours and the dose levels determines the trend in glucose levels. From the analysis, a significant difference in the glucose levels were observed between control and the rest of the dose arms. *T. officinale* at 10 mg/kg decreased the glucose level by 1.34 compared to that of Water. Similarly, *T. officinale* at 30 mg/kg, 60 mg/kg and Insulin decreased the glucose level by 2.19, 1.83 and 3.89 respectively relative to the glucose level of Water. Also, it is observed that, overall glucose decreased with increase in hours for *T. officinale* at 10 mg/kg, 30 mg/kg, 60 mg/kg, and Insulin but increased with time for Water (Fig 2).

Effect of T. officinale on body weight

Results in Fig 4 showed that there was a general trend of negative weight loss for all treated groups including the negative and positive controls. The aqueous extract of *T. officinale* did not appear to have any significant effect on the body weight of STZ- induced diabetic rats over the 28 day treatment period, unlike the controls (Tab 4).

Organ to body ratio

It was generally observed that the various treatments on both the diabetic and normoglycaemic rats had a significant effect on the liver with the low dose (10 mg/kg) treatment having the highest effect in the hyperglycaemic group and the high dose (60 mg/kg) treatment in the normoglycaemic group. Also, it was observed that the kidneys and pancreas from all the various groups showed fairly similar ratios in both major groups (Fig 5 and 6).

DISCUSSION

The results of this study showed a successful STZ-induction for the animal models. The animals were confirmed to be hyperglycaemic, having blood glucose of at least 10 mmol/L. Streptozotocin is known to induce this condition by destroying the *β*-cells of the pancreas, thus limiting the production of insulin, which is necessary for the absorption and hence metabolism of glucose[21].

It also causes alkylation of DNA leading to decrease in the functionality and size of the pancreas over time. It was observed from this experiment that there was an increase of the organ to body ratio of the liver, kidneys and pancreas. This may be due to the hypoglycaemic effect of *T. officinale* which causes inhibition of endogenous glucose production or activation of gluconeogenesis in the liver and muscular tissues[22].

Inflammation is associated with both secretory function of beta cell and insulin resistance[23]. Circulating inflammatory molecules can decrease beta cell functions directly by secretory dysfunction[24]. *In vivo* and *in vitro* studies have demonstrated that insulin acts as a messenger to instruct the body's cells to absorb glucose, in effect reducing blood glucose levels[25]. From the experiment, the extract was seen to inhibit the increase in foot volume significantly ($P<0.001$) from the second hour and thus, presumably, inhibited the synthesis and release of prostaglandins as well as kinins responsible for the inflammation[26]. The reduction in the foot volume was dose dependent for both extracts and standard drugs. The highest dose of the aqueous leaf extract (60 mg/kg) gave a slightly better reduction of carrageenan- induced paw thickness compared to the 10 mg/kg and 30 mg/kg doses of Diclofenac. This effect could be as a result of the sesquiterpene lactones and phenylpropanoids present in the leaf extract of the plant.

The antioxidant effects of many plants have been attributed to the presence of phenolic constituents such as flavonoids, phenolic acids, phenolic diterpenes and triterpenoids[27,28]. The presence of some of these plant secondary metabolites in the aqueous leaf extract as shown in the preliminary phytochemical screening may account for the antioxidant effect of the plants. From the phytochemical analysis, saponins and polyphenols were found to be present in the extract. A previous study showed that the presence of saponins in the extract produced maximum reduction of 73.1% and 76.03% glucose levels at day 1 and day 21 respectively[29]. One of the well-known properties of the

polyphenols, especially flavonoids, phenolic acids and tannins, on carbohydrate metabolism is inhibition of α-glucosidase and α-amylase, the key enzymes responsible for digestion of dietary carbohydrates to glucose[30,31] . Some polyphenols, including green tea catechins and epicatechins, chlorogenic acids, ferulic acids, caffeic and tannic acids, quercetin and naringenin, could interact with absorption of glucose from the intestine via inhibition of Na^+-dependent glucose transporters[32,33]. Some investigations have shown that polyphenolic compounds are also able to regulate postprandial glycemia and inhibit the development of glucose intolerance by a facilitated insulin response and attenuated secretion of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like polypeptide-1 (GLP-1)[34,35].

The results showed that aqueous extracts of *T. officinale* decreased the blood glucose levels of STZ induced diabetic rats compared to the untreated group over the 6 –hour and 28-day periods. This observation suggests that the *T. officinale* appears to have hypoglycaemic properties and the impact of this effect increased with time (days). Whereas the reduction in blood glucose by *T. officinale* was not as pronounced as that of the insulin treated group for the 6-hour period, it was comparable to the positive control (insulin treated group) in the 28 day period. However, the reduction of blood glucose levels was dose independent; with 30 mg/kg dose having the best hypoglycemic effect among the three doses and the higher dose producing minimal effect. This observation was similar to what had been reported for the bark extract of *Pterocarpus santalinus* [36]. This may be due to antagonism. At low doses, there would be less interference as a result of low concentrations of the extract having fewer antagonistic molecules[37].

The hypoglycaemic property of *T. officinale* could be attributed to a possible recovery of the *β*-cells which were previously destroyed after the STZ induction[38]. The phytoconstituents (especially, phenols) identified in the aqueous extract of *T. officinale* leaves may play a role in the recovery of the *β* – cells, which probably happened with time[39,40,41], indicating that the hypoglycemic effect of the extract remained active even when the pancreatic *β* – cells were destroyed. These active ingredients have been implicated in anti-diabetic pharmacological properties via various mechanisms such as the stimulation of insulin secretion from *β* - cells and/or inhibition of insulin degradative processes, reduction in insulin resistance, inhibition of hepatic gluconeogenesis and regeneration and/or repairing of the pancreatic *β* – cells[39.40].

Contrary to the weight gain associated with insulin use and its resultant risk of cardiovascular and metabolic outcomes[42,43], there appeared to be an insignificant weight variation with the diabetic rats which were treated with the extract. The absence of a significant effect of the extract on body weight presents the possibility of another agent joining insulin detemir, a novel basal insulin analogue with weight-sparing effect[44] as a possible insulin substitute. In view of the above findings, the study acknowledges the following limitations. First, this study was preliminary and focused on the acute toxicity of the extract. Extensive chronic toxicity studies are recommended.

CONCLUSION

The study has provided evidence to indicate that an aqueous extract of *T. officinale* has a hypoglycaemic property comparable to insulin over a 28-day period. However, this work could be explored further through well-designed clinical trials in order to produce alternative treatments to conventional diabetic therapies.

DECLARATIONS

Ethics approval and consent to participate

The research protocol used was reviewed and approved by the ethics committee of Centre for Plant Medicine Research Institute, Mampong Akuapim, Ghana.

Consent to publish

Not applicable

Availability of data and materials

Tables and figures are available as supporting files.

Competing interests

The authors declare they have no competing interests.

Funding

The research was self-funded

Authors' Contributions

Sarkodie JA contributed to the conception and design of the study, as well as the analysis of data and drafting of the manuscript; Debrah P contributed to the drafting and revision of the manuscript; Kitcher C contributed to the drafting and critical revision of the manuscript, Winston O, Akoto G and Hasford C contributed to the acquisition and analysis of data; Nyarko AK revised the manuscript and gave final approval for publication; Frimpong-Manso S, Oppong Bekoe E, Asiedu-Gyekye I and Banga KBN contributed to the revision and final approval of the manuscript. All authors have read and approved the final manuscript.

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Abbreviation List

DPPH - 2, 2-diphenyl-1-picryhydrazyl
STZ - Streptozotocin
ROS - Reactive Oxygen Species
CPMR - Centre for Plant Medicine Research
BHT - Butylated Hydroxytoluene
CNS - Central Nervous System
BG – Blood Glucose
LD50 – Lethal Dose at which 50% of the population is killed
IC50 – Concentration at which 50% of the population in inhibited
AUC – Area under Curve
DICLO – Diclofenac
DNA – Deoxyribonucleic Acid

GIP - Glucose-dependent Insulinotropic Polypeptide
GLP- 1 - Glucagon-like Polypeptide-1

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