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Anti-hyperglycaemic and Mode of Action of *Thaumatococcus danielli* (BENN.) BENTH Ethanol Leave Extract in Streptozotocin-induced Diabetic Rats

Folorunsho A. Ajayi[1], Olubukola. S. Olorunnisola[2*], Adewale. Adetutu[2], Folashade G. Olorunfemi[2], Abiodun O. Owoade[2], Peter Adegbola[2] and Olusegun K. Afolabi[2]

[1]Department of Physiology, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.
[2]Department of Biochemistry, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Thaumatococcus danielli (Benn.) Benth, a member of the Maranthaceae family has continued to be of immense benefit to the people in the tropics especially in Nigeria. The leaf is widely used among the "Yoruba's" as a wrapping leaf and for the management of diabetes mellitus.
Aim: This study, evaluated the anti-diabetic and possible mode of action(s) of ethanol leaves extract of *Thaumatococcus danielli* using *in vivo and in vitro* approach.
Methods: Diabetes was induced in Albino rats by administration of Streptozotocin (65 mg/kg/b.wt, i.p). The ethanol leave extract of *Thaumatococcus danielli* (at a dose of 250 mg/kg and 500 mg/kg body weight was administered at single dose per day to diabetes induced rats for a period of 14

**Corresponding author: E-mail: osolorunnisola@lautech.edu.ng;*

days. The possible mode of action of extract was assessed through *in vitro* inhibitory effect on alpha amylase, non-enzymatic glycosylation of haemoglobin and glucose uptake in yeast cell.

Results: The results showed that the plant extracts demonstrated dose and time dependent reduction in blood glucose. The extract at 250 mg/kg /b.wt and 500 mg/kg/b.wt caused a significant percentage reduction (35.00%/42.04% and 42.16%/60.43%) in blood glucose when compared with the group treated with (25 mg/kg/b.wt) of the standard drug (30.51/40.88%) and the diabetic control (10.46%/-13.67%) on day 7 and day 14 respectively. Although, the extract demonstrated significant ($p<0.05$) dose dependent inhibitory effect on alpha amylase with an IC_{50} of 837.97 µg/ml, its activity was significantly ($P<0.05$) lower than the standard Acarbose. Conversely, the extract showed stronger inhibition of non-enzymatic glycosylation of haemoglobin (87.51%) and enhance glucose uptake in yeast cells by 85.56% when compared with the standard drug Trolax and Metronidazole respectively.

Conclusion: The results of this study revealed that *Thaumatococcus danielli* (*Benth*) leaves contain anti-hyperglycaemic agent (s) and its possible mode of action is by promoting glucose uptake, inhibition of non-enzymatic glycosylation of haemoglobin and alpha amylase activity.

Keywords: Diabetes; Thaumatococcus danielli; alpha amylase; non-enzymatic glycosylation; glucose uptake.

1. INTRODUCTION

Diabetes mellitus is a major public health problem in the developed as well as developing countries [1]. The disease is characterized by chronic hyperglycaemia and glucosuria that result either from low levels of insulin secretion or resistance to insulin effects [2]. Diabetic mellitus is ranked seventh among diseases with high mortality in the world and the third when its fatal complications are taken into consideration [1]. According to WHO, 3% of the world population live with diabetes with an expected increase up to 6.3% by 2025 [3] due to population growth, stress, urbanization, substantial increase in purchasing power, lifestyle ease, metro life and increasing prevalence of obesity and physical inactivity [2]. Management of diabetes without any side effect is still a challenge to the medical community. The use of drugs is restricted by their pharmacokinetic properties, secondary failure rates, high cost and accompanying side effects [4]. Thus, it is necessary to search for cheaper, less toxic alternative drugs to overcome the problems of the existing therapy. Dependence on herbs as medicine in the treatment of disease is still much practiced by a large proportion of the rural populace because of its availability and affordability [5]. Herbal drugs constitute an important part of traditional medicine and literature shows that there are more than 400 plant species showing antidiabetic activity [6] among which is *Thaumatococcus danielli.*

Thaumatococcus danielli (Bennett) Benth.), also known as the sweet prayer plant or 'katemfe' grows throughout the hot, humid tropical rain forest and coastal zone of West Africa [7,8]. The plant is particularly found in southern parts of Ghana, Cote d'Ivoire and Nigeria. It is also known to exist in the Princes Islands, Angola, the Central African Republic, Uganda and Indonesia. 'Katemfe' is a rhizomatous, perennial and monocotyledonous herb, propagating itself by rhizomes [9].

All parts of the plant are useful and the stalk is locally used as food sweetener and in the production of Thaumatins [10]. The the leaves are used for thatching roofs and in wrapping foods such as unprocessed meat and kola nuts; semi processed foods such as fermented locust beans; processed foods such as cooked rice, beans, maize meal and pounded yam. The use of the leaves as a food wrapper/preservation material is no more restricted to the local populace resident in the villages and suburbs. It has gained widespread acceptance not only in the towns and cities of South-western Nigeria, but also in some parts of the United States and South Americas, where it is now acceptable for food packaging (wrapping), as not only exotic but also for flavour enhancing [11].

T. danielli is used in bakeries for sweetening bread and flavouring palm wine while in the food and confectionary industry of many countries, it is used as sweetener and flavour enhancer thus substituting synthetic sweeteners [12]. In Nigeria, this specie of plant is frequently used as wrapping leaf, however, very little is known about it medicinal properties especially its antidiabetic property.

The present study was design to evaluate the *in vivo* and *in vitro* antidiabetic potential of ethanolic leaf extract of *Thaumatococcus danielli*.

2. MATERIALS AND METHODS

2.1 Plant Collection and Identification

The leaves of *Thaumatococcus danielli* was collected with the aid of a local traditional herb dealer in the month of May 2015 from Masifa Area of Ogbomosho North, Oyo State, Nigeria. It was identified and authenticated by Prof. A.T.J Ogunkunle of the Department of Pure and Applied Biology, Ladoke Akintola University of Technology Ogbomosho, Oyo State, Nigeria. A voucher specimen with voucher number: (LHO 448) was prepared and the sample was deposited at the University Herbarium.

Fig. 1. *Thaumatococcus danielli*
(Source: Thaumatococcus danielli from its natural habitat in Ogbomoso environ)

2.2 Plant Preparation and Extraction

2.2.1 Preparation of plant extract

Fresh leaves of *Thaumatococcus danielli* were rinsed in tap water and air dried at room temperature (25-30ºC) for 2 weeks, grinded into fine powder with an electric Qlink blender (QBL-18L40). The powdered plants were stored in different waterproof bags before being used. 400 g of the blended plant was extracted with 99% ethanol at 70ºC using a Soxhlet extractor for 72 hours. The liquid ethanolic by-product of extraction was concentrated by fractional distillation. The solid sample obtained weighed 41.2 g. The dried ethanolic extract was then stored in an air-tight container and kept in a refrigerator at 4ºC.

2.2.2 Experimental animals

Twenty-five healthy adult male Wister albino rats weighing approximately 150-200 g were procured from Central Animal House, Faculty of Agriculture, Ladoke Akintola University of Technology Ogbomosho, Oyo State Nigeria, and provided with standard laboratory diet with water *ad libitum* procured from Sabo Market, Ogbomosho, Oyo State. Animals were housed under standard conditions of temperature (22±2ºC) and relative humidity (30-70%) with a 12:12 light: dark cycle and were allowed to acclimatize to the laboratory environment for a period of two weeks before the commencement of the experiment. The study was carried out after approval from Departmental Ethical Committee on Use and Care of Experimental Animals. The Animals were handle humanely in accordance with the guidelines of European Convention Protection for Vertebrate Animals and Other Scientific Purposes-ETS-123 [13].

2.2.3 Chemicals and reagents

Ethanol, Distilled water, Glucose, Streptozotocin,, Glibenclamide, Citrate buffer, Olive oil, Distilled water, ethanol, acetic acid, starch powder, glucose, yeast powder, metronidazole, sodium chloride, phosphate buffer, gentamycin, alpha amylase enzyme, acetate buffer, sodium hydroxide, iodine, potassium iodide and distilled DMSO. All the chemicals and reagents used for these studies were of analytical grade. Assay kits and reagents were purchased from Randox Laboratories Limited, United Kingdom. Match® glucometer with strips were purchased from Germany.

2.2.4 Animal grouping and extract administration

For the evaluation of anti-diabetic property of ethanolic leave extract of *Thamatococcus danielli* in Streptozotocin induced diabetic albino rat, the animals were divided into five groups each containing five animals:

Group 1: Normal rats receiving water *ad libitum* (Control)

Group 2: Streptozotocin induced diabetic rats (Streptozotocin -65 mg/kg/b.w., i.p)

Group 3: Diabetic rats treated with 250 mg/kg of ethanol leave extract of *Thaumatococcus danielli*

Group 4: Diabetic rat treated with 500 mg/kg body weight of ethanolic leave extract of Thaumatococcus *danielli.*

Group 5: Diabetic rat treated with 0.5 ml of Glibenclamide

2.2.5 Induction of diabetics and determination of blood glucose

The animals were made diabetic by single intra-peritoneal injection of 65 mg/kg/b.wt Streptozotocin in a sterile physiology saline. After 48 hr (without food, but water), blood sample were drawn from the tail vein and glucose levels were determined to confirm induction of diabetes using the Bayer counter ^{TM} test strips and blood glucose meter according to the instructions outline on the User Guide. All rats with blood glucose level (GBL) between the range of 200 - 300 mg/dL were considered diabetic [14] and were used for the study. In addition, 1 hr after the administration of Streptozotocin, the rats were also given pellets *ad libitum* and 5% dextrose saline in feeding bottle to overcome early hypoglycaemia [15]. The blood glucose levels of the animals were also determined before the administration of Streptozotocin by using the same procedures. The study was carried out after approval from Departmental Ethical Committee on Use and Care of Experimental Animals. The Animals were handle humanely in accordance with the guidelines of European Convention Protection for Vertebrate Animals and Other Scientific Purposes-ETS-123 [13].

2.3 *In vitro* Antidiabetic Assay

2.3.1 Alpha-amylase inhibition assay

Alpha amylase inhibitory activity of the extract was carried out according to the method described by Shekib et al. [16] with a few modifications. Starch solution (0.1% w/v) was prepared by stirring 0.1 g of potato starch in 100 ml of 16 mM of sodium acetate buffer and alpha amylase enzyme solution was prepared by mixing 27.5 mg of alpha amylase in 100 ml of distilled water. Sodium potassium tartarate solution and 3, 5 dinitro salicylic acid solution (96 mM) was missed to prepare the colorimetric reagent. 1ml of the control and plant compound were added to 1 ml starch solution and left to react with alpha-amylase solution under alkaline conditions at 25ºC for 3 minutes. The generation of maltose was quantified by the reduction of 3, 5 dinitro salicylic acid to 3- amino-5- nitro salicylic acid at 540 nm.

$$\text{Inhibition of alpha-amylase (\%)} = (\text{Abs}_{\text{sample}} - \text{Abs}_{\text{control}} / \text{Abs}_{\text{sample}}) \times 100$$

Where, Abs control is the absorbance of control reaction (containing all reagents except the test sample), and Abs sample is the absorbance of the test sample. All the experiments were carried out in triplicates.

2.3.2 Glucose uptake in yeast cells

The effect of the plant extract on glucose uptake in yeast cell was determined according to the method described by Ogundele et al. [17]. Briefly, commercial baker's yeast was washed by repeated centrifugation at 3000 rpm for 5 mins in distilled water until the supernatant fluids were clear and a 10% v/v suspension was prepared in distilled water. Different concentration of extracts (50, 100, 250, 500 and 750 µg/ml) was incubated with 1ml of glucose solution (2,5 and 10 mM) for 10 mins at 37ºC. 100 µl of yeast suspension was then added, the mixture vortexed and further incubated at 37ºC for 60 mins. After incubation, the tubes were centrifuged (2500 rpm; 5 mins) and glucose was estimated in the supernatant. The percentage increase in glucose uptake by yeast cells was calculated using the formula;

$$\text{Increase in glucose uptake (\%)} = (\text{Abs}_{\text{sample}} - \text{Abs}_{\text{control}} / \text{Abs}_{\text{sample}}) \times 100$$

Where, Abs control is the absorbance of control reaction (containing all reagents except the test sample), and Abs sample is the absorbance of the test sample. Al the experiments were carried out in triplicates.

2.3.3 Non-enzymatic glycosylation of haemoglobin assay

The effect of ethanolic leave extract of *T. danielli* on non-enzymatic glycosylation was investigated by estimating degree of non-enzymatic haemoglobin glycosylation colorimetrically at 520 nm. Solution of 1 ml glucose (2%), haemoglobin (0.06%) and 1 ml Gentamycin (0.02%) were prepared in 0.01 M phosphate buffer (pH 7.4). To the above mixture, 1 ml of different concentration of the plant extracts was added separately. The mixture was thereafter incubated in the dark for 72 hrs. Alpha-Tocopherol (Trolax) was used as standard [18].

All the tests were performed in triplicate

$$\text{\% Inhibition} = \frac{\text{Abs}_{\text{sample}} - \text{Abs}_{\text{control}}}{\text{Abs}_{\text{sample}}} \times 100$$

Where, Abs control is the absorbance of control reaction (containing all reagents except the test sample), and Abs sample is the absorbance of the test sample.

2.4 Statistical Analysis

Data were expressed as mean±SD and were statistically analysed using repeated measure analysis of variance with Dunnett's multiple comparison when compared against control and considered significant at $p<0.05$.

3. RESULTS

3.1 The Effect of Ethanolic Leaf Extract of *Thaumatococcus danielli* on Blood Glucose Level in Streptozotocin-induced Diabetic Rat

Table 1 showed that the administration of the extract and the standard (STD) at 250 mg/kg 500 mg/kg body weight and 25 mg/kg/b.wt respectively, caused a significant ($p<0.05$) dose and time dependent decrease in the blood glucose level with a percentage decrease of 35.00%/42.04% at 250 mg/kg/b.wt, 42.16%/60.43% at 500 mg/kg/b. wt and 30.51%/40.88 respectively when compared with the diabetic control group (-10.46%/-13.67) at day 7 and day 14. The activity of the extract was more effective than the standard drug at all the doses considered with the 500mg/kg body weight being most potent.

3.2 Effect of Extract of *T. danielli* and Acarbose on α-amylase Inhibitory Activity

Table 2 shows that ethanolic leave extract of *T. danielli* demonstrated significant dose dependent α-amylase inhibitory activity. Although, its activity is lower when compared to the standard drug at the same concentration. Fig. 2 shows that the IC50 of the plant extract is 837.97 µg/ml.

3.3 Effect of *T. danielli* Leave Extract and Metronidazole on Glucose Uptake in Yeast Cell

Figs. 3 and 4 shows that the ethanolic leave extract of *Thaumatococcus danielli* and the standard drug (metronidazole) caused a significant ($p<0.05$) dose dependent increase in % glucose uptake in yeast cell. The result also shows no significant change in percentage glucose uptake at all the glucose concentration (2 mM, 5 mM and 10 mM) considered. The highest % glucose uptake was observed at 750 µg/ml. Results also indicated that the extract had greater efficiency in increasing glucose uptake by yeast cells as compared to standard drug metronidazole after 72 hours (Fig. 4).

3.4 Inhibitory Effect of Extract of *T. danielli* and Trolax on Haemoglobin Glycosylation at 24, 48 and 72 hrs

The result shows that *T. danielli* displayed significant ($p<0.05$) inhibition of haemoglobin glycosylation at different physiological concentrations of the glucose over the period of 72 hrs in dose and time dependent manner. *T. danielli* exhibited higher inhibition of glycosylation as compared with the standard drug at 72 hours (Table 3).

4. DISCUSSION

Diabetes is a major health problem affecting major populations of the world [1]. Epidemiology studies and clinical trials strongly prove that hyperglycaemia is the major indicator of diabetes and principal cause of complications. Effective blood glucose control is the key to managing diabetes, preventing its complications and improving the quality of life in patients with diabetes. Thus, a sustained reduction in hyperglycaemia will decrease the risk of developing diabetic complications [19]. Streptozotocin is used as an agent to induce diabetes mellitus by selective cytotoxicity effect on pancreatic beta cells which consequently impair endogenous insulin release and as a result lead to increase blood glucose level [20]. The assessment of blood glucose is an important quantitative index in diabetes. In this study, the observed significant ($p<0.05$) dose and time dependent reduction in blood glucose of diabetic rats after 14 days of oral administration of ethanolic leave extract of *Thaumatococcus danielli* (Fig. 1) at 500 mg/kg and 250 mg/kg suggested that the plants contain antidiabetic agents. Other plant species in the same family reported with anti-hyperglycaemic activity include *Ravenala madagascariensis* Sonn., (Strelitziaceae) and *Cochlospermum planchonii* root extract respectively [21,22]. *T. danielli* exhibited higher anti-diabetic activity when compared with the standard Glibenclamide at both concentration used in this study (Table 1). It may be that the extracts caused the restoration of the pancreas therefore stimulating insulin

Table 1. Effect of ethanol leave extract of *Thaumatococcus danielli* fasting blood glucose level

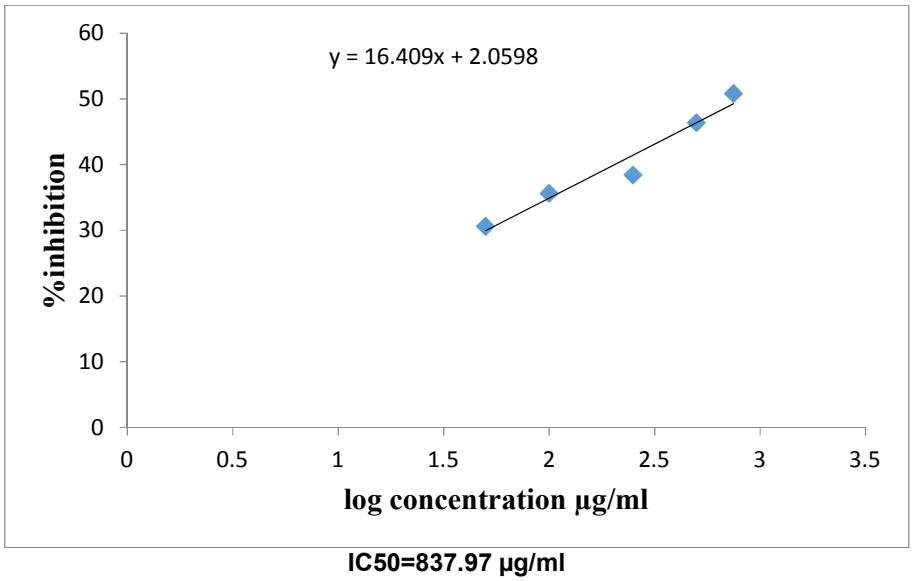
Experimental Group	Fasting blood glucose level (mg/dL)				
	BGT (0^{th} day)	BGAT (7^{th} day)	BGAT (14^{th} day)	% DFBG on the 7^{th} day	% DFBG on the 14^{th} day
Normal control	79.0 ±3.35**	81.22 ± 2.12	78.3 ± 1.54***	-2.81	0.02*
Diabetic control	260.0± 4.20	287.2± 3.5	301.2± 2.50	-10.46	-13.67
T. danielli (250 mg/kg.b.wt)	258.8± 2.40	168.2± 2.60	150.0±3.43**	35.00*	42.04*
T. danielli (500 mg/kg.b.wt)	262.8 ± 5.20	152.8±4.60	144.80±1.12**	42.16*	60.43*
Glibenclamide (600 µg/kg bw	208.4±11.06	144.0 ± 4.8	123.2±9.028**	30.51*	40.88*

*Values are expressed in Mean ± SD of 5 animals. BGT-Blood glucose before treatment, BGAT-Blood glucose after treatment. *P<0.05 compared with diabetic control group. % is percentage decrease in fasting blood glucose (DFBG). (- increase, + decrease)*

Table 2. Alpha-amylase inhibitory activity of ethanolic leave extract of *Thaumatococcus danielli*

Blank	Concµg/ml	STD-Acarbose		*T. danielli* extract	
		Abs	% inhibition	Abs	% inhibition
	50	0.55±0.05	56.10	0.341 ± 0.03	30.60
	100	0.64 ± 0.03	62.40	0.426 ± 0.02	35.62
(0.24 ± 0.02)	250	0.76 ± 0.02	68.47	0.492 ± 0.02	38.41
	500	0.98 ± 0.04	75.39	0.565 ± 0.05	46.31
	750	1.88 ± 0.02	87.22	0.616 ± 0.09	50.81

STD- Standard drug T. danielli extract, Abs- Absorbance, Conc- Concentration. Values are expressed as mean ± SD.



IC50=837.97 µg/ml

Fig. 2. IC50 value of alpha-amylase inhibition by ethanolic leave extract of *Thaumatococcus danielli*

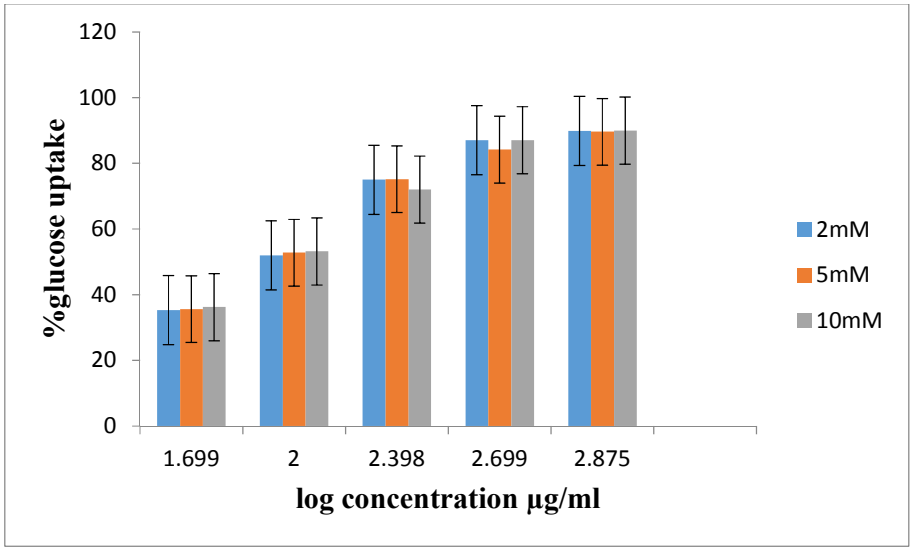


Fig. 3. Effect of ethanolic leave extract of *T. danielli* on glucose uptake by yeast cells

Table 3. Inhibitory (%) effect of ethanolic leave extract of *Thaumatococcus danielli* leaves and Trolaxon haemoglobin glycosylation at 24, 48 and 72 hrs

S/NO	PC (µg/ml)	24 hrs	48 hrs	Trolax at	
				72 hrs	72 hrs
1	20	76.13%	74.36%	84.50%	15.30%
2	40	85.45%	81.01%	86.22%	52.80%
3	60	86.20%	84.67%	87.39%	78.20%
4	80	87.89%	88.46%	87.41%	80.20%
5	100	89.09%	88.76%	87.51%	82.10%

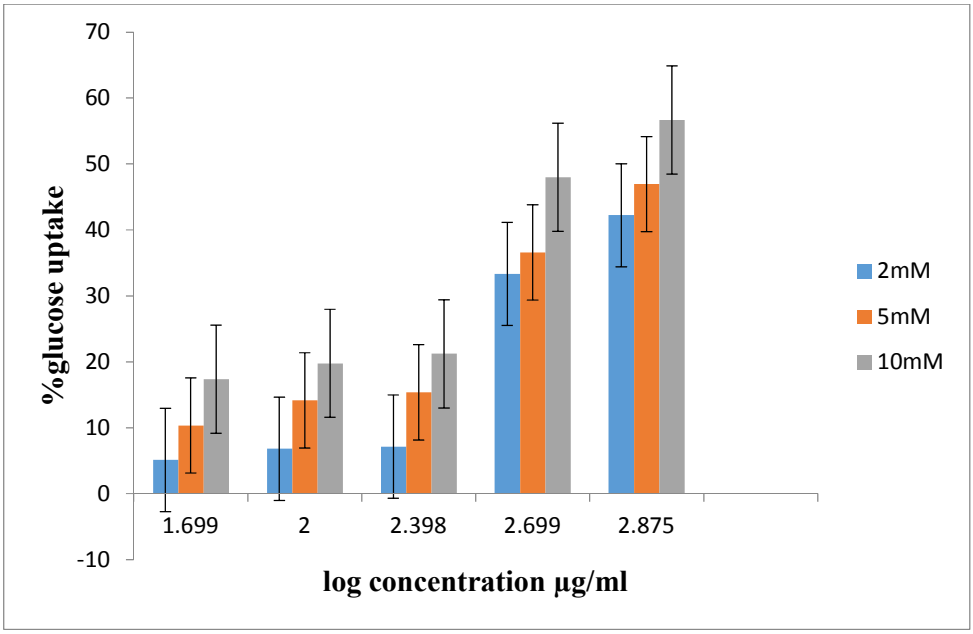


Fig. 4. Effect of metronidazole on glucose uptake by yeast cells

release. Glibenclamide stimulates insulin secretion from beta cells of islets of Langerhans and since the activity of the plant is significantly higher than Glibenclamide, we may suggest that the extract might have several mechanism(s) of anti-diabetic action. Our prediction was confirmed by the significant ($p<0.05$) dose dependent α-amylase inhibitory activity (IC50 of 837.97µg/ml) (Fig. 2) of the ethanolic extract of the plant (Table 2). Alpha amylase is an enzyme that hydrolyses alpha-bonds of alpha linked polysaccharide such as starch to yield high levels of glucose and maltose [23]. The result suggested that the plant might slow down the absorption of glucose in the guts leading to lower level of blood glucose. The ability of the plant (*T. daneilli)* to significantly inhibit pancreatic α-amylase might be due to the presence of phytochemicals (flavonoids and tannins) [24].

Another likely mechanism of the anti-diabetic effect demonstrated by the plant in this study could include its ability to increase glucose uptake in the peripheral tissue (fats and muscle cells). This was evident by the significant increase in glucose (2 mM, 5 mM and 10 mM) uptake across the cell membrane of extract treated yeast cell (Fig. 3). Glucose transport across yeast cell membrane occurs via facilitated diffusion down the concentration gradient. Hence, glucose transport occurs only if the intracellular glucose is efficiently reduced or utilized [23]. The effectiveness of glucose uptake causes a reduction in blood glucose level thereby prevents hyperglycemia. In this study, the rate of glucose uptake increased insignificantly in a dose dependent manner. The results obtained suggested that ethanolic leaf extract of *Thaumatococcus danielli* was capable of enhancing glucose uptake (utilization) thereby controlling the blood glucose level and preventing accumulation of glucose in the blood.

Glycosylated haemoglobin is an important clinical marker in diabetes remission. It helps to determine the degree of protein glycation during diabetes. Hyperglycemia leads to non-enzymatic reaction of glucose with proteins in vivo, chemically forming covalently attached glucose-adduct products and crosslinks between proteins. The excessive accumulation of rearranged late-glucose-adduct products, or advanced glycosylation endproducts (AGEs), has been implicated in complications of diabetes mellitus [25]. In the present study, the significant dose and time dependent inhibition of haemoglobin glycosylation by the leave extract of *Thaumatococcus danielli* (Table 3) suggested that the plant might protect against hyperglycaemic induced glycosylation thereby preventing the formation of monosaccharide senolize, α-ketoaldehydes, H_2O_2, free radical intermediates, elevated plasma peroxides and protein modifications which are found in diabetics complication [26]. The observed effect of *T. danielli* may be attributed to the bioactive

compounds (flavonoids, alkaloids phenols) present [26]. Presently, work is going on in our laboratory to identify and isolate the active compound(s) responsible for the observed pharmacological functions.

5. CONCLUSION

It is concluded that oral administration of ethanolic leaf extract of *Thaumatococcus danielli* could protect against hyperglycemia and its possible complication and the likely mechanisms of action(s) include inhibition of pancreatic α-amylase activity, enhancement of glucose uptake in the peripheral tissues and inhibition of formation of haemoglobin glycation. The results also showed that leave extract of *Thaumatococcus danielli* could be as adjunct to dietary therapy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was carried out after approval from Departmental Ethical Committee on Use and Care of Experimental Animals. The Animals were handle humanely in accordance with the guidelines of European Convention Protection for Vertebrate Animals and Other Scientific Purposes-ETS-123.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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