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Prolonged Effect of Niger Delta Honey on Blood Glucose and Haematological Parameters in Alloxan Induced Diabetic Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Author OO designed the study and performed statistical analysis. Arthur NC wrote the protocol and the first draft of the manuscript. Authors AEA and NC managed the literature searches. Authors OO, AEA and NC managed the analyses of the study. All authors read and approved the final manuscript

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ABSTRACT

Diabetes mellitus is a metabolic condition that develops when the body fails to produce enough insulin or when insulin fails to work properly, is a global health problem. This study was conducted to evaluate the metabolic effect of eight-week administration of Niger Delta honey on the blood glucose, haematological parameters, body weight and glycosylated haemoglobin in alloxan-induced diabetic rats. Six groups of 8 rats each were used. Group I served as control; Group II was given 10ml/kg/day of the honey solution; Group III served as diabetic control; Group IV diabetic rats received 10ml/kg/day of the honey solution. Group V diabetic rats were given a single daily dose of 0.6 mg/kg glibenclamide. Group VI were treated with both glibenclamide and honey concurrently. The present study showed that honey significantly (p<0.05) improved blood cells and indices, body weight but caused marked decrease in blood glucose levels as well as glycosylated haemoglobin in alloxan diabetic rats. Furthermore, honey caused a further reduction in blood glucose levels when used in combination with glibenclamide. In conclusion, the result of the present study suggests that honey might prevent alloxan-induced anaemia, immune-disturbances, thrombocytopenia, weight

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loss and hyperglycaemia. These effects are probably due to its additive mechanisms on the haematopoietic systems and on glucose metabolism. Therefore honey might be a cost-effective aspect of dietary management of diabetes mellitus and its complications. Additionally, honey and glibenclamide combined may offer additional beneficial effects in alloxan – induced diabetes by synergic mechanisms on glucose metabolism and by further improvement in the vascular integrity.

Keywords: Diabetes; honey; HbA1c; body weight; haematological; diabetic rats.

1. INTRODUCTION

Diabetes mellitus is a non-communicable disease defined as a metabolic disorder characterized by chronic hyperglycaemia resulting from lack of or resistance to insulin. It is a serious emergency which is considered to be one of the 6 major causes of death worldwide and requires constant care and attention. The recent prediction shows that in 2017, 8.8% of the adult population worldwide are living with diabetes and to rise to 9.9% by the year 2045 [1]. The prevalence rate projection of diabetes mellitus, estimated as 30.3 million people (9.4% US population), 23.1 million people are diagnosed and 7.2 million people (23.8%) undiagnosed [2]. The prevalence rate projection of undiagnosed diabetes population is growing most rapidly in low-and-middle– income countries, and Africa specifically, around 69.2% of all adults living with diabetes are estimated to be undiagnosed. Africa has the highest proportion of diabetes mellitus related mortality and the lowest health expenditure spent on diabetes [1].

In recent years, there has been a renewed interest and constant search globally in order to establish an efficient and appropriate complementary and alternative medicine associated with folklore practices over synthetic drugs for the treatment of diabetes mellitus. Pure honey as one of such promising medicine with natural origin has been acclaimed traditionally to have to benefit health-related effects, making it a perfect remedy from diabetes, heart disease, kidney disease, obesity to high blood pressure.

The use of honey as has been controversially discussed and not well accepted in the modern medicine [3-7]. Moreover, the sugar content of honey has led to uncertainty about associated risks of diabetes and of vascular complications of the disease. In the classification of glycaemic index, foods are classified as low (<55), middle (55-69), and high (>70); foods with low glycaemic index has been suggested to reduce blood glucose level and increase insulin secretion [8, 9]. Accordingly, the glycaemic index of honey varies from 32 to 87; and according to their botanical or geographical origins [8,10,11].

Evidence have that honey is a new effective medicine that possesses gastroprotective, hepatoprotective, reproductive, hypoglycaemic, antioxidant, antihypertensive, antibacterial, anti-fungal, antiviral, anti-inflammatory as well as wound healing properties that may be beneficial for combating multi-drug resistant bacteria as well as for preventing chronic inflammatory processes, such as atherosclerosis and diabetes mellitus [3-7,12-15].

Glibenclamide has been used as first-line drug in treatment of diabetes mellitus. Therefore, concomitant use of honey and glibenclamide in the management of hyperglycaemia may offer additional benefits in treatment of diabetes and the risk of attendant complications. Until now research information on the potential medicinal characteristics of Nigeria honey specifically from the Niger Delta region in diabetes is rather spare. The present study was aimed to determine the probable efficacy of long-term Niger Delta honey on blood components in normal, and with reversal of hyperglycaemia, as well as to show the effect of combination with glibenclamide on blood glucose levels in alloxan induced diabetic rats.

2. MATERIALS AND METHODS

2.1 Sample Collection

Pure, organic, raw or all-natural food or unprocessed honey (nicknamed Nature's Sweetener) was obtained from Divine honey bee farm in Delta state, Niger Delta region, Nigeria. The Institutional animal ethics committee approved the experimental protocol. All animal experiments were carried out according to the National Research Council guidelines for the care and use of laboratory animals.

2.2 Induction of Diabetes

Diabetes Mellitus was induced in overnight fasted rats via intraperitoneal administration of

200 mg/kg body weight of alloxan dissolved in normal saline. Two days after alloxan injection, development of diabetes was confirmed by measuring blood glucose levels in blood samples taken from tail vein and analyzed based on glucose oxidase-perioxidase principles [16] using digital glucometer (Accu-Chek Aviva, Germany) [17]. Rats with blood glucose concentrations of ≥ 12.0 mmol/L were considered to have developed experimental diabetes.

2.3 Experimental Animals Grouping and Treatment

Adult male Wistar rats weighing 200-250g were used in this study. The experimental rats were six groups of eight rats each. Using oral cannula, once each morning the rats were treated with either honey, glibenclamide (a known oral anti-diabetic drug; 0.6 mg/kg body weight) or both for eight weeks. Honey was diluted by adding distilled water and administered at a dose of 50% v/v. Each animal was administered honey solution at a dose of 10 ml/Kg body weight/day. The rats were housed in laboratory cages and were provided with standard feed and allowed access to water *ad libitum*.

Animals were treated for 8 weeks as follows

Group I: served as normal (non-diabetic) general control and didn't receive any honey or glibenclamide for the next 8 weeks.
Group II: (non-diabetic honey treated group): received honey 10 ml/kg body weight/day orally for 8 weeks.
Group III: served as positive (diabetic group) control and didn't receive any honey or glibenclamide for the next 8 weeks.
Group IV: (diabetic honey treated group): received honey 10 ml/kg body weight/day orally for 8 weeks.
Group V: (diabetic glibenclamide treated group): received glibenclamide 0.6 mg/kg body weight/day orally for 8 weeks
Group VI: (diabetic glibenclamide and honey treated groups): received honey 10 ml/kg body weight/day and glibenclamide 0.6 mg/kg body weight/day concurrently orally for 8 weeks.

2.4 Blood Collection and Analysis

At the end of the treatment period (8 weeks), the animals were anaesthetised and blood samples were collected using 5ml syringe via cardiac puncture and deposited in oxalate fluoride bottles for glycosylated haemoglobin (HbA1c) analysis or EDTA bottles for haematological analysis.

2.5 Haematological Analysis

An MC-6200 auto haematology analyser Shenzhen Maxcom Electronic Co., Ltd, China was used to analyse the various blood parameters

2.6 Measurement of Glycosylated Haemoglobin (HbA1c)

A rapid quantitative analysis using a fluorescence immunoassay (FIA) meter was used.

2.7 Statistical Analysis

The assays were carried out in triplicate, and the data were expressed as mean values and the standard deviation (mean ± SD). Statistical analysis was carried out using Scientific Package of Social Science software version 20.0 (SPSS, Inc. Chicago, IL) and Microsoft excel. Two different set of statistics, which is descriptive and analytical statistics was applied. The descriptive statistic was used to analyze mean and standard deviation (SD) whereby analytical statistics, one-way ANOVA was used to determine statistical significance among the groups. P value <0.05 were considered statistically significant.

3. RESULTS

Table 1 and Fig. 1 shows the observations of body weight, glycosylated haemoglobin (HbA1c) and blood glucose values of the rats after 8-week period of the experiment. In a time-dependent fashion (in days) the body weight continuously increased in generalcontrol (13.3%), honey treated non-diabetic (20.0%) and diabetic (17.2%) and decrease in diabetic control (3.7%), relative to the pre-treatment values. While the weight of the diabetic control (15.0%) was significantly ($p<0.05$) higher than that for the honey-treated non-diabetic (1.4%) and diabetic (1.8%), which were closely approximately to those observed in the general control (normal rats).

Table 1 illustrates that honey produced significant lowering in glycosylated haemoglobin

(HbA1c) in non-diabetic (3.5%) and diabetic (8.8%) while diabetic control group demonstrated increased (66.6%) compared with normo-glycaemic control group. Moreover, honey treated groups produced significant ($p<0.05$) reduction in HbA1c values (34.7%-37.9%) in comparison with diabetic control.

Table 1 and Fig. 1 also illustrated that the mean value of serum glucose concentrations in the diabetic control (20.5 ± 1.56 mmol/L or 24.24%) and the general non-diabetic control (6.50 ± 0.27 mmol/L or 26.71%) were significantly ($p<0.05$) raised while treatment demonstrated significant reduction in blood glucose in non-diabetic (4.75±0.25 mmol/L or 9.52%) or diabetic (16.50±1.90 mmol/L or 36.54%) versus pre-treatment values. Moreover, glibenclamide treatment resulted in a significant ($p<0.05$) reduction in glucose level (12.63±1.97 mmol/L or 35.23%) in diabetic rats. Furthermore combined honey and glibenclamide further caused a marked reduction in glucose concentrations (12.14±1.73 mmol/L or 38.58%) in diabetic rats relative to the initial values (Fig. 1). Significant reduction in blood glucose were evident in honey and glibenclamide alone and in the combined in the experimental diabetic rats by 19.51%, 38.38% and 40.83% respectively, in comparison with diabetic control. More so, combination of honey and glibenclamide produced significant reduction in blood glucose in diabetic rats by 3.95% compared with glibenclamide alone.

It is evident from Tables 2-3 that honey supplementation in diabetic resulted in significant ($p<0.05$) increase in red blood cell count (11.7%), packed cell volume (31.4%), haemoglobin concentration (31.4%), mean cell haemoglobin concentration (2.3%), mean cell volume (13.4%), white blood cell count (25.1%), granulocyte (4.8%), monocyte (47.2%), platelet count (14.3%), versus the general control (normal rats). Moreover honey significantly ($p<0.05$) increased red blood cell count in non-diabetic and diabetic rats by 99.6% and 103.9%; packed cell volume 102.8% and 104.3%; haemoglobin concentration 102.8% and 144.3%; white blood cell count 148.6% and 122.2%, mean cell haemoglobin concentration 48.5% and 30.4% but significantly decreased platelet count by 16.2% and 1.4%, mean platelet volume 28.5% and 4.4%, platelet distribution width 8.5% and 3.2%; and mean cell volume 17.4% and 5.4%, respectively relative to diabetic control.

Tables 2-3 also illustrated that honey treated diabetic produced decreased mean cell haemoglobin (4.92%), lymphocytes (9.8%) and platelet distribution width (0.47%). Meanwhile honey treated non-diabetic exhibited a significant increase in mean cell haemoglobin concentration (16.5%), mean cell volume (6.98%),white blood cell count (40%) granulocyte (9.07%) and lymphocyte (12%) than that for the honey-treated diabetic rat ($p<0.05$). A significant reduction ($p<0.05$) were evident in mean cell volume (1.04%), platelet count (2.89%), and platelet distribution width (5.89%), in honey treated non-diabetic, respectively with respect to general control. Overall, all honey treated groups demonstrated a significant lowering of platelet count (1.42% -16.22%), mean platelet volume

Table1. Effect of honey on blood glucose level, body weight and glycosylated haemoglobin

Treatments	Blood glucose (mmol/l)		Body weight(kg) (HbA1c)		Glycosylated haemoglobin
	Day 1	Day 56	Initial	Final	
General Control	5.13±0.23	6.50±0.27*	236.25±6.3	267.50±7.6*	3.41±0.04
Non-diabetic + honey	5.25±0.25	4.75±0.25	220.00±7.6	263.75±9.4*	3.53±0.08
Diabetic Control	16.50±1.80	20.50±1.56*	236.15±5.0	227.50±4.5*	5.68±0.5*
Diabetic + honey	26.00±0.38	16.50±1.90*	232.50±7.3	272.50±6.2*	3.71±0.06**
Diabetic+ Gliblenclamide	19.50±1.86	12.63±1.97*	=	=	=
Diabetic+honey+ Gliblenclamide	19.75±1.83	12.13±1.73*	=	=	=

*N = 8, * Significant change compared to initial ($p< 0.05$) and significant change compared to non-diabetic control ($p< 0.05$), **significant change compared to diabetic control ($p< 0.05$)*

Table 2. Honey effect on blood cells and indices

Treatments	Red blood cells			Erythrocyte indices		
	RBC ($x10^{12}$/L)	PCV (%)	Hb(g/dl)	MCHC (g/dl)	MCV(fl)	MCH(pg)
General Control	9.00±0.52	34.50±0.40	11.50±0.40	25.75±1.40	40.50±0.55	13.60±0.47
Non- diabetic+ honey	9.84±0.15*	42.90±0.08*	14.30±0.08*	30.00±0.40*	40.08±0.26	14.55±0.12
Diabetic Control	4.93±0.21*	21.15±0.10*	7.05±0.10*	20.20±0.26*	48.53±0.72*	9.90±0.21*
Diabetic+ honey	10.05±0.10**	45.33±0.18**	15.11±0.18**	26.34±0.78**	45.91±0.29**	12.93±0.14**

*N=8, *Significant changes compared to non-diabetic control (p<0.05); **Significant change compared to diabetic control (p<0.05)*

Table 3. Honey effect on white blood cells and platelets

Treatments	White blood cells				Platelets		
	WBC ($x10^9$/L)	Granulocyte (%)	Monocyte (%)	Lymphocytes (%)	Platelet count($x10^9$/L)	PDW(pg)	MPV(fl)
Non-diabetic Control	12.25±0.15	80.63±0.26	11.50±0.40	25.75±1.40	682.00±32.89	10.70±0.17	5.43±0.14
Non-diabetic + honey	17.15±0.28*	87.95±0.09*	14.30±0.08*	30.00±0.40*	662.25±1.32	10.07±0.21	5.27±0.21
Diabetic Control	6.90±0.10*	75.38±0.18*	7.05±0.10*	20.20±0.26*	790.50±2.23*	11.00±0.19*	7.37±0.09*
Diabetic+ Honey	15.33±1.18**	84.51±0.15**	15.11±0.18**	26.34±0.78**	779.25±2.14**	10.65±0.04**	7.05±0.08 **

*N=8, *Significant changes compared to non-diabetic control (p<0.05); **Significant change compared to diabetic control (p<0.05)*

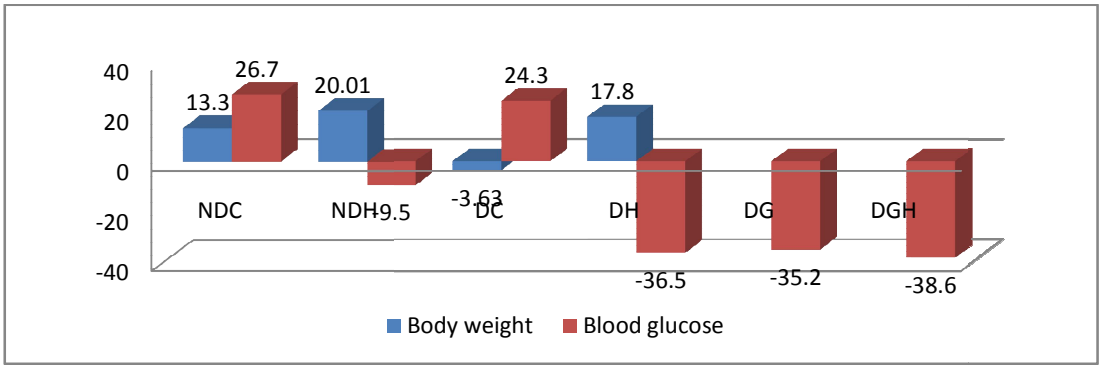

Fig. 1. Percent change in body weight with blood glucose level
(General control, GC; non-diabetic +honey, NDH; diabetic control, DC; diabetic + glibenclamide, DG; diabetic +glibenclamide +honey, DGH)

(4.37%-28.49%) and platelet distribution width (3.18%-8.45%) respectively with respect to diabetic control.

4. DISCUSSION

This study investigated the effects of eight-week supplementation of honey on some physiological parameters such as body weight, glycosylated haemoglobin (HbA1c), blood glucose, blood cells and indices, in normal and alloxan induced diabetic rats. Over the 8-week period of the study, we did not observe any anomaly in alloxan as regards induction of experimental diabetes in contrast to previous reports [18,19].

At the end of eight weeks, it was found that the physical inactive and sedentary non-diabetic control (normal rats) on daily chow for two-months, up-regulated blood glucose and even body weight in comparison with the pre-treatment values. These observations are in keeping with the hypothesis that physical inactive and sedentary lifestyle could be viewed as stressors in the pathogenesis of raised blood glucose levels (diabetes) and body weight gain (obesity) [17,20]. Accumulating evidence shows that regular physical activity and lifestyle modification with healthy dietary habits are beneficial in achieving and maintaining a normal healthy body weight, prevention and controlling the progression of major non-communicable diseases including diabetes.

In the present study, it was found that daily honey consumption for two-month by either non-diabetic or diabetic rats produced a mild increment in body weight (1.4%-1.9%) in comparison with general control (normal rats) collaborating with other studies [21-23]. This is an indication that honey improves diabetic body weight. In a seven-day study, Aliyu *et al*., found that the body weight of honey treated rats increased in a concentration dependent manner from 10% to 20% but started decreasing from 50% to 100% (v/v) [24]. On the other hand, insignificant differences in body weight in honey-fed rats [7] and honey-fed mice [14] have been reported for studies largely carried out in less than eight weeks. In clinical trials it was found that honey treatment for 30 days cause a mild reduction in body weight (1.3%) in subjects with normal values but does not increase body weight in overweight or obese subjects [25].

The mechanism in which honey uses to improve body weight is not yet clear. The observed increase in body weight has been attributed to the androgenic-anabolic characteristic of honey [24]. It has been suggested that its fructose content may have contributed [26], the antioxidant content has possible anti-catabolic properties, thus preventing excessive catabolism of proteins, leading to muscle recovery [27] or enhanced insulin yield due to possible regeneration of pancreatic beta cells may also explain weight protective effect of honey in diabetic rats [28].

Of particular interest was that 8-week honey consumption progressively and significantly ($p<0.05$) reduced glycosylated haemoglobin (HbA1c) levels in both diabetic and non-diabetic rats towards the reference range [29], collaborating that blood glucose control affects HbA1c [30] and long-term honey feeding can produce a significant decrease of HbA1c levels [7,12,21]. In a six week study, in contrast, a healthy non-diabetic rats fed with a honey-

containing diet did not show significant decrease in glycosylated haemoglobin [31]. Preponderance of HbA1c, a measure of the amount of glucose attached to haemoglobin, was observed for the diabetic control groups at the end of the two-month study. Clinical evidence support an increase in the HbA1c values at the end of 4 months in diabetic group who were not given honey, the HbA1c values decreased in the group that were given honey, and there was a significant statistical difference between the two groups [12]. On the other hand, in 8-week randomized clinical trial, honey consumption resulted to an increase in the HbA1c levels in diabetic patients [32].

The present study revealed that haemoglobin, red blood cell count and packed cell volume were significantly ($p<0.05$) raised after the two – month exposure of alloxan-induced diabetic and non-diabetic rats to honey in comparison to diabetic control or non-diabetic control. Besides, there was an increase in mean cell haemoglobin concentration and mean cell volume and decrease in mean cell haemoglobin in diabetic honey-fed rats while an increase in mean cell haemoglobin concentration and mean cell volume and decrease in mean cell haemoglobin in non-diabetic honey fed rats in comparison with referents. These collaborate that honey has ameliorative effect on alloxan induced anaemia and/or possess haematopoietic properties [33]. On the other hand, in a 7 day study, it was found that honey administration have no effect on haemoglobin and red blood cell counts but increased packed cell volume, mean corpuscular haemoglobin and white blood cell counts at 20% (v/v) as well as caused a decrease in mean cell volume and mean corpuscular haemoglobin concentration in a concentration-dependent manner [24].

Considering white blood cell parameters, there was statistically significant ($p<0.05$) increase in total leucocytes count, together with differential white blood cell counts - lymphocyte, granulocyte, monocyte, in honey diabetic and non-diabetic rats in comparison with referents, and supports the generalization that honey possesses immune-stimulant properties.

Our result revealed that honey consumption though promoted an increase in platelet count but no significant change occurred in the platelet count and platelet distribution width of honey fed diabetic groups compared to diabetic control. Our findings however, collaborates that honey possesses thrombopoietic properties. Collectively, our findings demonstrate evidence of possible ameliorating potential of long-term honey supplementation on red blood cell count, packed cell volume, haemoglobin concentration, white blood cell counts, platelet count in alloxan diabetic rats collaborating with various studies elsewhere which conclude that honey contain enhancing substances capable of improving haematological parameters, plausibly through their stimulating effects on the haematopoietic stem cell mechanisms.

While at the end of eight weeks, it was also found that daily honey consumption for two mouths resulted in a marked reduction in blood glucose level in either non-diabetic or alloxan induced diabetic rats. Similarly, it has been reported [23,34] that Nigeria honey elicited significant effectiveness in lowering blood glucose levels in alloxan-induced diabetic rats. On the other hand, it has been reported insignificant differences in fasting blood glucose in honey-fed rats [7] or in honey-fed mice [14]. Some studies also carried out in less than eight weeks, however, showed that there were no significant ($p>0.05$) differences across the honey-treated rats based on the glucose level [24]. In the present study, the prolonged period of 8 weeks administration of honey other than the 14- or 28 day period in some studies might have resulted in significant regeneration and healing of the previously alloxan damaged pancreatic beta cells. The observed glycaemic response of honey in diabetic rats might be attributed to the moderate doses of 10 ml/kg/day of 30% and 50% honey respectively used in our study. Notwithstanding, in the present study, the effect of Niger Delta honey orally compared with oral hypoglycaemic drug glibenclamide significantly reduced blood glucose concentrations in diabetic rats substantiating with the work by previous researchers [35,36]. Additionally, we also observed synergistic effect of natural honey by causing a further reduction in blood glucose levels when used in combination with oral hypoglycaemic drugs glibenclamide, than honey or glibenclamide alone in alloxan induced-diabetic rats which collaborates with the report of others [7]. Our findings are an indication that concomitant use of honey and glibenclamide may offer additional benefits in the treatment of diabetes and attenuate associated complications induced by alloxan.

Glibenclamide acts by stimulating the pancreatic beta cells to increase insulin output [36,37].

Although the cellular mechanisms underlying the mechanism of hypoglycaemic effect of honey is poorly understood, we propose that honey may potentiate the hypoglycaemic effect of glibenclamide by increasing the number of regenerated beta cells. Increased number of pancreatic beta cells together with the stimulatory effect of glibenclamide further increases insulin secretion and thus improved glycaemic response. It has been hypothesized that the fructose and oligosaccharides present in honey [7], a decrease in intrinsic antioxidant biomarker malondialdehyde (MDA) as well as honey induced hormone adiponectin [13] and antioxidant property of honey [5] might in some way contribute to the observed hypoglycaemic effect. Honey is a natural product, is hypothesized that synergistic effect, the presence of the bioactive phytoconstituents, and/or antioxidant properties or both, and potentiation action of several compounds, may provide the mechanistic links for hypoglycaemic modification of intrinsic oxidative stress mediating receptors; thereby improves glycaemic control associated with metabolic benefits [17]. Evidence also points to diminution in MDA oxidative stress-mediated lipid peroxidation mechanism for hypoglycaemic oxidative modifications [17]. Oxidative hyperglycaemia modification (oxidative stress) mechanistic link is associated with increased MDA [17]. Overall, our results of the animal experimentation presented in this study thus provided further support that Niger Delta honey consumption has a potential as an adjuvant along with anti-diabetic agent treatment. However, our future studies will investigate the composition of honey from Niger Delta origin to ascertain if it varies obviously from honey of other regions of Nigeria.

5. CONCLUSION

On the basis of above findings, it can be concluded that this study has demonstrated considerable evidence that long-term honey supplementation can exert haematopoietic, thrombopoietic, immune-stimulatory, hypo-glycaemic actions and improves body weight and glycosylated haemoglobin in alloxan diabetic rats. These potential benefits support the accumulating evidence that dietary honey has an effective therapeutic value to prevent metabolic derangements and reduction of deleterious effects of diabetes mellitus. Besides its health benefits, honey will further reduce the cost of management of diabetes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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