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Evaluation of the Effects of the Extracts of Ginger and Aloe Vera on Wistar Rats Model of Type 2 Diabetes Induced With Dexamethasone and High Fat Diet

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ABSTRACT: To investigate the antidiabetic and antihyperlipidemic activities of ginger and aloe vera extracts formulation in dexamethasone induced diabetic wistar rats administered oral doses (100, 200 and 500 mg/kg body weight), eighty four wistar albino rats were used in this study, being divided into fourteen groups of six rats each and fed with high fat diet, inducted with dexamethasone, and treated with Glimepiride, Metformin, Cinnamon, Ginger, and Aloe vera in various doses with the exception of the normal and negative controls. Each sample of blood serum and plasma was analyzed using Randox kits to test for various biochemical and hematological parameters. Compared with the normal control, the mean values of the parameters were significantly different ($p<0.05$) from each other with few exceptions. The groups treated with Glimepiride, Metformin, and Cinnamon showed improvement. The various doses of Ginger, Aloe vera, and their mixture, showed improvement with an increase in the level as the dose increased. Conclusively, the assessment of insulin resistance studied using the models proved that insulin resistance can be managed when appropriate lifestyle is adopted. These findings support the antihyperglycemic and antihyperlipidemic properties of Glimepiride, Metformin, Cinnamon, Ginger, and Aloe vera in various doses and thus help in preventing future complications of diabetes.

KEYWORD: Ginger, Aloe vera, Type 2 diabetes, Dexamethasone, high fat diet, synergetic, Insulin resistance.

I. INTRODUCTION

The lack of perfect models for type-2 diabetes, coupled with financial restrictions on obtaining and maintaining animals, and social restrictions on extensive use of animals in experimentation, indicate that a more practical approach would involve a series of in vitro prescreens before testing a potential new hypoglycaemic agent in animals. Many in vitro techniques have been developed to elucidate the varied mechanisms of action of hypoglycaemic agents discovered by in vivo bioassays. Three aspects of the hypoglycaemic response are commonly studied in vitro: insulin release from the pancreatic islets, peripheral insulin binding and glucose uptake, and effects on hepatic enzymes [1].

In this study, we shall discuss a number of experimental animal models used in diabetes research. It is important to emphasize that diverse experimental animal models are essential for developing new anti-diabetic agents and for fully investigating promising agents before human clinical trials. It is expected that more therapeutic alternatives will become available with future advances in diabetes research.

Diabetes is a lifestyle non-communicable disease of mankind considered as one of the most significant global health problems that afflict both young and old in all parts of the world irrespective of their gender (International Diabetes Federation)[2]. The disease is a metabolic condition caused by the body's inability to produce or make use of insulin, and it drastically decreases the quality of human life. Nigeria has the highest number of people with diabetes in Africa with 3,921,500 cases reported on a prevalence rate of 4.99% [3]. Type 2 diabetes (T2D) accounts for 95% of all cases reported (IDF, 2013; American Diabetes Association [4].

The causes of T2D are multi-factorial which includes both genetic and environmental elements that affect the β-cell function and insulin

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sensitivity [5-6]. Africa is blessed with enormous biodiversity of resources yet plagued with several diseases [7].

The HOMA-IR was developed in 1985 and has been widely used for IR quantification. However, insulin measurement is still not readily available in many routine laboratories and entails standardization issues [8]. Insulin resistance (IR) involves decreased cell sensitivity to insulin and is a central characteristic of metabolic syndrome (MS) [9]. IR predisposes to several metabolic disorders including hyperglycemia, high blood pressure, and dyslipidemia, all of them strongly associated with diabetes, atherosclerosis, and cardiovascular disease. The evaluation of IR requires sophisticated methods which are not available for use in daily clinical practice [10].

Simental-Mendia and his associates [11] and Guerrero-Romero and his associates [12] have proposed and validated a new formula to evaluate IR from the levels of serum triglycerides (TAG) and fasting glucose (FG), which is known as 'Triglyceride/Glucose Index' (TGI), this formula is a potential diagnostic tool when other standard methods are not available. Since the measurement of fasting insulin is cumbersome with no standard assay available, an insulin-free equation for estimating insulin resistance was sought and developed. In 2010, the product of the fasting levels of triglycerides and glucose (TyG), the so-called triglycerides and glucose index (TyG index), was suggested as a useful surrogate measure for insulin resistance in healthy adults [12].

Uncorrected high insulin will usually, over time result in insulin resistance. Development and increase in insulin resistance, shows that a person is heading for diabetes; when insulin can act no more, the glucose level then rises rapidly, and diabetes is the consequent result of these metabolic changes [13]. Investigation of insulin homeostasis has become, therefore, very important in DM and this is what is being advocated in developing countries such as Nigeria.

1.1 Aim and Objectives of the Study

Aim: The aim of this study is to evaluate the effects of the extracts of ginger and aloe vera on wistarrats model of type 2 diabetes induced with dexamethasone and high fat diet through a comparative study of their physiological indices.

Objectives: The objectives of the study include to:

I. Use renal profile of the rats as a tool for the assessment of insulin resistance on wistar rats model of type 2 diabetes
II. Evaluate the triglyceride and High density lipoprotein index of wistar rats induced with dexamethasone and high fat diet to measure insulin resistance in experimental rats
III. To compare the hematological parameters of rats induced with dexamethasone and high fat diet
IV. Compare the effectiveness of natural plants extract (ginger and aloe vera) source with and without two anti-insulin resistant drugs (Glimepiride and Metformin) and one anti-insulin resistant herb (Cinnamon) after inducement of insulin resistance by dexamethasone and high fat diet (25% lard, 7% egg, and 15% sucrose), all known for their effectiveness in the assessment of insulin resistance, and management of diabetes.

1.2 Significance of the Study

Over the years, ginger and aloe vera have been used as spice and drink respectively, which have generated lots of interest throughout human existence as a medicinal panacea. This study would be particularly beneficial in our society where the essence of aloe vera as drink and ginger as food supplement is undermined and their cultivations is considered not essential [14].

1.3 Study Area

The study was carried out in Choba, University of Port Harcourt (Uniport) campuses, and University of Port Harcourt Teaching Hospital (UPTH), all in Obio/Akpor Local Government Area of Rivers State, Nigeria. The study area is located in the Niger Delta region, bordering the Atlantic Ocean. The area lies approximately in latitudes 6°54´N and longitudes 4°53´E

Choba

Plate 1.1 Map of the Study Area (Google)

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II. MATERIALS AND METHODS

The extracts used were those of aloe vera, ginger, and cinnamon.

2.1 Collection of Test materials

The test materials (Aloe vera and ginger) were purchased from Mile 3 Diobu and Choba markets in Port Harcourt City and Obio/Akpor Local Government Areas respectively of Rivers State, Nigeria. The aloe vera sample was identified by Dr. ChimezieEkeke of the Department of Plant Science and Biotechnology, University of Port Harcourt and deposited in the Departmental herbarium with the voucher number UPH/P/184.

2.2 Preparation of Extracts:

2.2.1 Preparation of Ginger extract

Ginger rhizomes were washed with clean sterile distilled water and allowed to air-dry for one hour, then the outer covering of the ginger was manually peeled off and the ginger washed again and extracted. Aqueous ginger extract was prepared according to methods previously reported by [15] in which one hundred gram (100 g) of fresh, washed ginger cloves was macerated in a sterile, ceramic mortar. The homogenate was then filtered off with a sterile, muslin cloth and used.

The plant material (ginger) was finely ground to powder with a blender. 100g of the ground ginger was mixed with one liter of sterile deionized water and kept in a water bath at 60ºC for five hours, then filtered through sterile filter paper "Whatman, UK". The filtrate was exposed at 40 ºC to a hot air oven for evaporation of water. The filtrate was then kept in a refrigerator at 4 ºC until use [16].

2.2.2 Preparation of Aloe vera extract

Aloe veracrude extract was prepared by washing the leaves with tap water and thereafter weighed. Care was taken not to tear the green rind that could contaminate the fillet with leaf exudates. A traditional hand filleting method of processing Aloeleaves was used. In this method, the lower leaf base, the tapering point at the leaf top and the short spines located along the leaf margins were removed by sharp blades. The blade was then introduced into the mucilage layer below the green rind avoiding the vascular bundles, and the top rind was removed. The epidermis of the leaves was peeled off, and the parenchymatous tissue was collected. The colourless, solid mucilaginous gel was cut into pieces. The gel was lyophilized and ground. The lyophilized gel powder was then packed into soxhlet apparatus and extracted with 90% ethanol at 90° C for four (4) hours. The ethanol containing the extract was filtered and concentrated using rotary evaporator and was stored at 90°C.

2.3 Experimental Animals

A total of eighty four (84) male Wistar albino rats (Rattusnorvegicusdomesticus) were used for the study. The population of interest with regards to this study cuts across all age, sex, race, social and cultural background. The Wistar albino rats were purchased from the animal house of the Department of Biochemistry, University of Port Harcourt, Rivers State. They were weighed and housed in standard cages. The weight of the Wistar albino rats ranged from one hundred and fifty to two hundred gram (150-200g). Habituation conditions were 25–32°C and relative humidity of 45±5% with twelve (12) hours light and dark cycle. The animals were allowed to feed with standard diet and water ad libitium, and to acclimatize with the new housing condition within fourteen (14) days. The experiment was based on approved guidelines for the use of laboratory animals.

2.3.1 Experimental Animal Design

The following approach was employed in grouping the animals; the animals were grouped into two major groups: control Group A, and test Groups B, C, and D.

Group A: The control group consisted of six (6) rats each, and was subdivided into:

(a) Normal control: This sub-group was treated with just distilled water aside the general feed and serve as normal control.

(b) Negative control: This sub-group was treated with diet and with dexamethasone to induce insulin resistance which could result in type 2 diabetes but not treated.

Group B: This test group was divided into 4 sub-groups which consisted of 6 rats each.

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Table 3.1 Test Group B

S/N	TREATMENT	INDUCTION DEXAMETHASONE AND HIGH FAT DIET			
GROUP		B1	B2	B3	B4
1	ANTI-INSULIN RESISTANT DRUG (GLIMEPIRIDE 0.032mg/kg)	YES			
2	100mg/kg ginger extract		YES		
3	100mg/kg aloe vera extract			YES	
4	100mg/kg ginger and aloe vera extract (50:50)				YES

Group C: This test group was divided into 4 sub-groups which consisted of 6 rats each.

Table 3.2 Test Group C

S/N	TREATMENT	INDUCTION DEXAMETHASONE AND HIGH FAT DIET			
GROUP		B1	B2	B3	B4
1	ANTI-INSULIN RESISTANT DRUG (METFORMIN 8mg/kg)	YES			
2	300mg/kg ginger extract		YES		
3	300mg/kg aloe vera extract			YES	
4	300mg/kg ginger and aloe vera extract (50:50)				YES

Group D: This test group was divided into 4 sub-groups which consisted of 6 rats each.

Table 3.3 Test Group D

S/N	TREATMENT	INDUCTION DEXAMETHASONE AND HIGH FAT DIET			
GROUP		B1	B2	B3	B4
1	ANTI-INSULIN RESISTANT HERB (CINNAMON 500mg/kg)	YES			
2	500mg/kg ginger extract		YES		
3	500mg/kg aloe vera extract			YES	
4	500 ginger and aloe vera extract (50:50)				YES

2.4 Blood Sample Collection

Whole blood sample collection was by cardiac puncture and the samples were collected into EDTA and heparinized bottles respectively. The heparinized blood samples which were allowed to stand for 30 minutes to clot, centrifuged at 3,000 rpm for 10min for proper separation, separated into plain bottles and labeled accordingly. This was stored frozen, until when needed for biochemical and haematological analysis.

2.5 ANALYSIS

2.5.1Biochemical Analysis

The Renal profile was analysed. Also, Lipid Profile, ile, and Blood Glucose were analysed using Randox Kits (RANDOX, USA).

2.5.2 Haematological Analysis

Full blood count (FBC) comprising the Red Blood Cell (RBC) count and its components alongside Platelet levels, and the White Blood Cell (WBC) count and its components were analysed.

Full Blood Count

It covers red blood cell (RBC) count and its components alongside platelet (PLT) count, and white blood cell (WBC) count alongside its components.Model – mindray bc-6800 auto haematology analyzerWhole blood samples: K_2 EDTA (1.5 – 2.2mg/ml) anticoagulated collection tubes were cleaned to collect venous blood

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samples. The samples were mixed according to the laboratory's protocol. A clean uncapped centrifugal tube was presented to the sample probe and it was ensured that the probe went deep into the bottom of the tube to avoid spills, hangings and bubbles. The aspirate key was pressed to start dispensing the diluent. The centrifugal tube was removed when the buzzer sounded.

2.6 Statistical analysis

All data were subjected to statistical analyses. Statistical analysis was performed using SPSS version 21 (IBM, U.S.A). The data was analyzed using one-way analysis of variance (ANOVA) and significant differences were determined using post Hoc Duncan multiple comparison test ($p<0.05$). The results were considered significant at 95% confidence level. The values were represented as mean ± standard Error Mean (SEM)

III. RESULTS

3.1Renal profile of the rats

Table 3.1 below reveals the renal profile values for the animal subjects. The results showed a significant difference ($p\leq0.05$) in the electrolytes for the test groups relative to the control groups. The negative control group (untreated) showed no improvement while the test groups treated with the standard drugs and herb showed improvement. The doses of the plants extract also showed improvement with an increase in the level of improvement as the dose increased.

The results also showed a significant difference ($p\leq0.05$) in the level of Urea and Creatinine for the test groups relative to the control groups. The negative control group (untreated) showed no improvement while the test groups treated with standard drugs and herb (Glimepiride, Metformin, and Cinnamon) showed marked improvement. The 100mg/kg, 300mg/kg, and 500mg/kg doses of the plants extract (Ginger, Aloe Vera, and a mixture of both in equal proportions) also showed marked improvement with an increase in the level of improvement as the dose increased.

Table 3.1 Renal profile of rats from the different groups

GROUP	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	H_2CO_3 (mmol/l)	Urea (mmol/l)	Creatinine (mmol/l)
NORMAL CONTROL	139.50± 1.12^{b,c,d,e}	3.90± 0.09^{c,d,e}	97.33± 0.71^{b,c,d,e}	25.67± 0.88^{b,c,d,e}	3.22± 0.26^{b,c,d,e}	60.83± 1.83^{b,c,d,e}
NEGATIVE CONTROL	132.50± 1.85^{a,c,d,e}	5.21± 0.12^{a,c,d,e}	87.25± 1.55^{a,c,d,e}	18.50± 0.65^{a,c,d,e}	7.73± 0.51^{a,c,d,e}	89.00± 3.24^{a,c,d,e}
GLIMEPIRIDE	135.75± 1.11^{b,d,e}	4.23± 0.09^{a,b,d,e}	93.25± 0.85^{a,b,d,e}	21.50± 0.65^{a,b,d,e}	4.50± 0.21^{a,b,d,e}	70.75± 2.06^{a,b,d,e}
METFORMIN	137.25± 1.11^{a,b,c,e}	4.33± 0.13^{a,b,c,e}	95.75± 1.31^{a,b,c,e}	23.25± 0.75^{a,b,c,e}	4.38± 0.26^{a,b,c,e}	68.25± 2.50^{a,b,c,e}
CINNAMON	136.00± 0.41^{a,b,d}	4.53± 0.15^{a,b,c,d}	94.75± 0.85^{a,b,c,d}	22.75± 1.03^{a,b,c,d}	5.25± 0.19^{a,b,c,d}	71.00± 2.12^{b,c,d}
100mg/kg GINGER	135.75± 0.85^{a,b,d,}	4.70± 0.11^{a,c,d,e}	90.25± 0.63^{a,b,c,d,e}	20.50± 0.65^{a,b,c,d,e}	6.28± 0.26^{a,b,c,e}	78.25± 1.44^{a,b,c,d,e}
100mg/kg ALOE VERA	134.75± 0.85^{a,b,d}	4.80± 0.10^{a,b,c,d,e}	92.00± 0.91^{a,b,c,d,e}	21.75± 0.41^{a,b,c,d,e}	6.14± 0.28^{a,b,c,d,e}	76.90± 1.55^{a,b,c,d,e}
100mg/kg GINGER + ALOE VERA	135.50± 0.87^{a,b,d}	4.73± 0.17^{a,b,c,d,e}	92.75± 0.65^{a,b,c,d,e}	21.75± 0.48^{a,b,c,d,e}	6.06± 0.20^{a,b,c,d,e}	76.60± 2.40^{a,b,c,d,e}
300mg/kg GINGER	136.25± 0.63^{a,b,d}	4.63± 0.11^{a,b,c,d,e}	93.00± 0.71^{a,b,c,e}	22.25± 0.63^{a,b,c,d,e}	6.00± 0.18^{a,b,c,d,e}	76.95± 1.25^{a,b,c,d,e}
300mg/kg ALOE VERA	135.75± 1.11^{a,b,d}	4.78± 0.11^{a,b,c,d,e}	94.00± 1.29^{a,b,c,d,e}	21.00± 0.85^{a,b,c,d,e}	5.93± 0.27^{a,b,c,d,e}	75.80± 2.20^{a,b,c,d,e}
300mg/kg GINGER + ALOE VERA	136.80± 0.73^{a,b,d}	4.70± 0.07^{a,b,c,d,e}	95.50± 0.58^{a,b,c,d,e}	22.20± 0.49^{a,b,c,d,e}	5.80± 0.20^{a,b,c,d,e}	73.00± 1.81^{a,b,c,d,e}

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500mg/kg GINGER	136.25± 0.63^{a,b,c,d,e}	4.55± 0.11^{a,b,c,d,e}	93.00± 0.71^{a,b,c,d,e}	23.25± 0.63^{a,b,c,d,e}	5.90± 0.18^{a,b,c,d,e}	72.50± 1.25^{a,b,c,d,e}
500mg/kg ALOE VERA	136.60± 0.75^{a,b,c,d,e}	4.56± 0.09^{a,b,c,d,e}	94.20± 0.66^{a,b,c,d,e}	22.60± 0.51^{a,b,c,d,e}	5.68± 0.19^{a,b,c,d,e}	73.00± 1.77^{a,b,c,d,e}
500mg/kg GINGER + ALOE VERA	137.00± 1.29^{a,b,c,d,e}	4.40± 0.09^{a,b,c,d,e}	95.20± 0.85^{a,b,c,d,e}	23.75± 0.85^{a,b,c,d,e}	5.50± 0.37^{a,b,c,d,e}	72.50± 2.40^{a,b,c,d,e}

Data are expressed as Mean ± Standard error of mean (SEM), n=84. Values found in a column with common superscript letter a, are significantly different ($p \leq 0.05$) when compared to the normal control. Values with the superscript b, are significantly different ($p \leq 0.05$) relative to the negative control. Values with the superscript c, are significantly different ($p \leq 0.05$) compared to the Glimepiride group. Values with the superscript d, are significantly different ($p \leq 0.05$) compared to the Metformin group while values with the superscript e, are significantly different ($p \leq 0.05$) compared to the Cinnamon group.

Where:

Na^+ - Sodium ion, K^+ - Potassium ion

Cl^- - Chloride ion, H_2CO_3 - Bicarbonate

3.2 Biochemical indices of the rats

Figure 3.2 below reveals the Glucose levels for the animal subjects. The results showed a significant difference ($p \leq 0.05$) in the level of Glucose for the test groups relative to the control groups. The negative control group (untreated) showed no improvement while the test groups treated with standard drugs and herb (Glimepiride, Metformin, and Cinnamon) showed marked improvement. The 100mg/kg, 300mg/kg, and 500mg/kg doses of the plants extract (Ginger, Aloe Vera, and a mixture of both in equal proportions) also showed marked improvement with an increase in the level of improvement as the dose increased.

HOMA-IR, TYG and TG-HDL indices, and Insulin (INS) for the animal subjects are also shown in figure 3.2below. There was a significant difference ($p \leq 0.05$) in the biochemical Indexes for the test groups relative to the control groups. Insulin for the Normal control group was 0.88±0.34 mIU/L, while that for the Negative control (Induced but not treated) was 11.65±0.51 mIU/L. The HOMA-IR Index for the Normal control was 0.19±0.07, while that for the Negative control was 6.67±0.14. Both Insulin and HOMA-IR for the Negative control were significantly different from the Normal control indicating a significant increase in insulin resistance as is found in Type 2 Diabetes.

The TYG index and TG-HDL index of the Negative control were also statistically different from that of the Normal control;3.75±0.02 and 4.54±0.02 for TYG index, and 1.03±0.06 and 3.80±0.43 for TG-HDL index, respectively for the Normal control and Negative control groups. The test groups treated with standard drugs and herb (Glimepiride, Metformin, and Cinnamon) showed improvement in the Indexes. The 100mg/kg, 300mg/kg, and 500mg/kg doses of the plants extract (Ginger, Aloe Vera, and a mixture of both in equal proportions) also showed improvement with an increase in the level of improvement as the dose increased.

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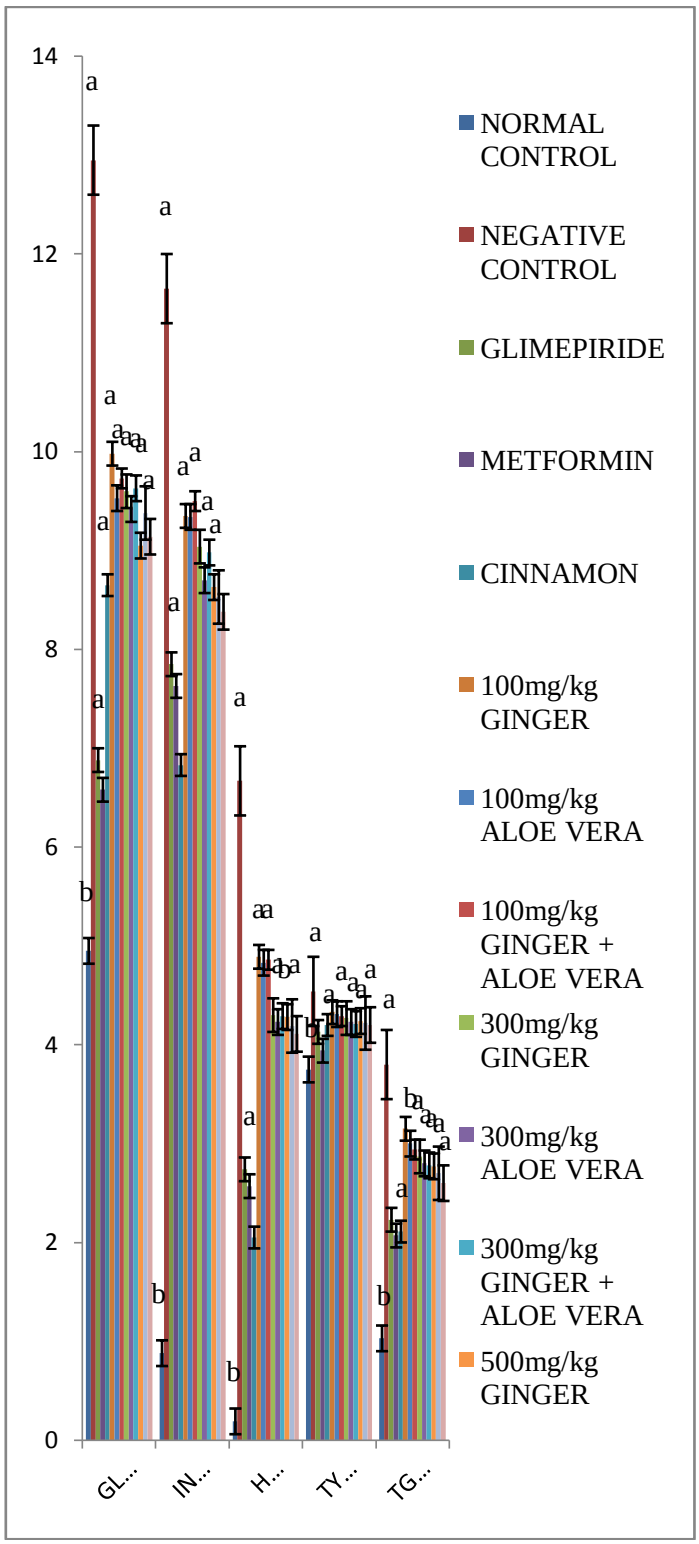

Figure 3.2 Biochemical indices of rats from the different groups

Data are expressed as Mean ± Standard error of mean (SEM), n=84. Values found in a column with common superscript letter a, are significantly different ($p \leq 0.05$) when compared to the normal control. Values with the superscript b, are significantly different ($p \leq 0.05$) relative to the negative control.

Where:

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HOMA-IR – Homeostatic model assessment of insulin resistance
TYG – Triglyceride-Glucose
TG-HDL – Triglyceride-High density lipoprotein

3.3 Some Haematological Profile of the rats

Table 3.3 below reveals some haemato logical parameters for animal subjects. The results showed that red blood cell (RBC) count, packed cell volume (PCV), and haemoglobin (Hb) count were significantly higher ($p \leq 0.05$) in the negative control and test groups relative to the normal control group. Platelet (PLT) count on the other hand was statistically higher in the negative control and test groups than the normal control group. The test groups treated with standard drugs and herb (Glimepiride, Metformin, and Cinnamon) showed improvement. The 100mg/kg, 300mg/kg, and 500mg/kg doses of the plants extract (Ginger, Aloe Vera, and a mixture of both in equal proportions) also showed progressive improvement with increase in the dose of extract. PLT count levels decreased as the dose of extract increased.

Table 3.3 Some Haematological profile of rats from different groups

GROUP	RBC (mL)	PCV (%)	Hb (g/dL)	PLT (mL)
NORMAL CONTROL	3.83 ± 0.14^{b}	$35.07\pm1.08^{b,c}$	11.27 ± 0.39^{b}	141.50 ± 6.00^{b}
NEGATIVE CONTROL	4.22 ± 0.12^{a}	$37.20\pm1.08^{a,}$	12.28 ± 0.37^{a}	175.25 ± 9.62^{d}
GLIMEPIRIDE	4.15 ± 0.17^{a}	$36.65\pm2.02^{a,b}$	11.90 ± 0.68^{a}	$155.25\pm3.30^{a,b,d}$
METFORMIN	4.10 ± 0.13^{a}	35.95 ± 0.60^{b}	$11.75\pm0.52^{b,c}$	153.75 ± 4.78^{a}
CINNAMON	$4.05\pm0.16^{a,b}$	36.80 ± 1.30^{a}	11.65 ± 0.41^{b}	158.50 ± 4.33^{c}
100mg/kg GINGER	4.18 ± 0.13^{a}	$37.75\pm1.38^{b,e}$	12.08 ± 0.44^{a}	$163.80\pm4.16^{a,c,e}$
100mg/kg ALOE VERA	4.14 ± 0.07^{a}	$36.20\pm0.71^{a,b}$	12.14 ± 0.22^{a}	$164.60\pm3.20^{b,c,e}$
100mg/kg GINGER + ALOE VERA	4.13 ± 0.07^{a}	$36.09\pm0.71^{a,b}$	12.04 ± 0.22^{a}	168.60 ± 4.49^{a}
300mg/kg GINGER	$3.96\pm0.09^{a,b}$	$36.09\pm0.29^{a,b}$	12.00 ± 0.44^{a}	$162.00\pm7.59^{b,c,d}$
300mg/kg ALOE VERA	3.90 ± 0.25^{b}	$36.75\pm0.03^{a,b}$	11.88 ± 0.35^{b}	$163.25\pm4.91^{a,c,d,e}$
300mg/kg GINGER + ALOE VERA	$3.90\pm0.15^{b,c,d}$	35.90 ± 2.04^{b}	11.58 ± 0.68^{b}	$164.25\pm5.02^{a,b,c}$
500mg/kg GINGER	$3.85\pm0.10^{b,c,d}$	35.40 ± 2.20^{b}	11.63 ± 0.72^{b}	$161.25\pm3.20^{b,c,d}$
500mg/kg ALOE VERA	$3.88\pm0.25^{a,e}$	36.00 ± 2.48^{b}	11.53 ± 0.83^{b}	$160.75\pm4.64^{b,d}$
500mg/kg GINGER + ALOE VERA	$3.87\pm0.29^{b,c,d,e}$	35.50 ± 1.04^{b}	11.43 ± 0.37^{b}	$162.25\pm7.55^{c,d}$

Data are expressed as Mean ± Standard error of mean (SEM), n=84. Values with the superscripts a, b, c, d, e are significantly different ($p \leq 0.05$) compared to the normal control, negative control, Glimepiride, Metformin, and Cinnamon groups respectively.
Where:
RBC – Red blood cell
PCV – Packed cell volume
Hb – Haemoglobin
PLT - Platelet

IV. DISCUSSION

Due to the complexity in determining an individual prone to insulin resistance, it becomes also difficult to interpret the animal model of insulin resistance as an inference to what is obtainable in humans. According to [17], the usefulness of rat model of non-insulin dependent diabetes mellitus (NIDDM) is nevertheless questionable, and they never can consider a clear experimental model of hypertension. There are a number of factors which can contribute to becoming obese such as eating a high calorie diet (high fat diet), not getting enough physical exercise, genetics, medical conditions and being on medications. Loss of body weight has been shown to improve blood glucose levels [18], and has allowed people with type 2 diabetes to come off or avoid going onto insulin resistance. Cinnamon has been known to increase insulin sensitivity while Glimepiride and Metformin have been known to decrease insulin resistance and the risk of type 2 diabetes [19].

Type 2 diabetes affects the homeostasis acid-base regulation. High glucose concentration results in an osmotic force that draws water to the extracellular space. This dilutes extracellular sodium and results in lower blood sodium level [20]. In our result, a decrease in blood sodium level was observed as we moved from normal, to pre-diabetic and diabetic subjects, though the decrease were not statistically significant at $p<0.05$. Potassium levels are also altered in diabetes. High plasma glucose concentrations result in potassium efflux to the extracellular space, causing hyperkalemia [20]. This was observed in this study. Diabetic ketoacidosis is a clinically significant assay-based disturbance in diabetes. It occurs due to an increase in the rate of hepatic ketoacid generation. Bicarbonate (H_2CO_3) degrades to carbon (IV) oxide and water, and anion gap

acidosis results. This is observed in the significantly lower Bicarbonate levels in the pre-diabetic and diabetic groups. The chloride values also follow the same trend. The same pattern of electrolyte imbalance is seen in the rat subjects as shown in figure 4.7 for the animal models. In general, diabetic subjects are at increased risk of assay-based disturbance and electrolyte disturbances. The increased risk is due to the diseased state of diabetes itself and the associated disruptions in glucose homeostasis, drugs used to treat diabetes, and the organ damage associated with diabetes [20]. The urea and creatinine levels of the pre-diabetic and diabetic groups were higher than that of the non-diabetics. This was also same animal groups where there was an observed increase in urea and creatinine in the diabetic animals. This is in agreement with other studies which reported that hyperglycaemia is one of the major causes of progressive renal diseases [21]. Approximately 20% to 30% of diabetics will develop abnormal kidney function, represented by a reduced glomerular filtration rate and a rise in serum urea and creatinine. Administration of Glimepiride and Metformin ameliorated the condition. Cinnamon also had a similar effect as the standard drugs. There was also an improvement with the extracts of Ginger and Aloe Vera in different concentrations though to a lesser degree. In this study, we found that insulin resistance was increased significantly in the pre-diabetic and diabetic groups as depicted by the HOMA-IR index, in the test animals. This is expected and in line with other studies as it is known that insulin resistance is a major risk factor and predicts Type 2 diabetes [22]. The hall-mark of Type 2 diabetes is an abnormally high glucose that is unresponsive or only slightly responsive to insulin regulation. It is known that, TyG index shows a positive correlation with HOMA-IR [23]. In this work, TYG index also followed the same pattern, being significantly increased in the pre-diabetic and diabetic in the test animals but was not as predictive as the HOMA-IR index. TG-HDL was also increased in the pre-diabetic and diabetic in the test animals. However, it did not follow a linear pattern as HOMA-IR and TYG index as the TG-HDL index was higher in the pre-diabetic than the diabetic group. This may reflect life style changes as subjects that were already known diabetics may already be taking intervention measures to ameliorate the diabetic condition. Treatment with the standard drugs Glimepiride and Metformin led to improvement in all indices. The herb, Cinnamon faired very well as the standard drugs in improving the indices. Treatment with the extracts of Ginger and Aloe Vera and their mixture also led to improvements in the indices albeit to a less degree.

Analysis of the haematological parameters in the animal test groups in this study showed that there were alterations in the haematological indices in the diabetic state. Diabetes is a metabolic disease that is characterized by hyperglycaemia, dyslipidemia, hypertension, and impaired hematological indices. Several hematological changes affecting the red blood cells (RBCs), white blood cells (WBCs), and the coagulation factors are shown to be directly associated with DM [24]. Other hematological abnormalities reported in the DM rats include RBCs, WBCs, and platelet dysfunction. [25]. The animal test models followed generally, the same pattern, with RBC, PCV and Hb all being significantly higher in the negative control group relative to the Normal control group. It was stated that this might be partly explained by the increased HbA1c in the diabetic state [26]. In this study, HbA1c of the diabetic patients were also higher than that of the controls. Platelet count and WBC count and its components were also found to be elevated in the diabetic animal models relative to the normal control group. This is in agreement with findings reported by several previous studies and might be the indirect features of insulin resistance syndrome, since it is associated with increased WBC and RBC counts, and increased levels of Hb [24]. Increase in WBC indices in the diabetic group compared with the control group might also be the result of the increased oxidative stress triggered by the high levels of hyperglycemia in the diabetic patients. In contrast to this study, some other study have actually reported a decrease in RBC count, Hb and PCV levels [27]. This might be expected in diabetes of long duration as chronic hyperglycaemia and glycation of red blood cell membrane proteins will lead to accelerated aging of RBCs. Diabetics with long term complications such as Diabetic Nephropathy will also have reduced kidney function and reduced production of erythropoietin and ultimately decreased RBC count. Treatment of the animal test groups with the standard drugs and herbs led to a reduction in insulin resistance as measured by the HOMA-IR and the TYG and TG-HDL index. This also resulted in an improvement in the adverse effects of the disease condition as shown by the improvement in the HbA1c levels, Lipid profiles, Renal Profiles, and the Haematological parameters. Treatment with the plant extracts also led to mild improvements in these indices.

V. CONCLUSIONS

Based on our findings, the assessment of insulin resistance studied using the animal model proved that insulin resistance can be managed when appropriate lifestyle is adopted. This can be deduced from the result obtained by administration of varying doses of Ginger, Aloe Vera, and mixture of both plant extracts to the animal test subjects. This increased the insulin sensitivity and ameliorated the effect of insulin resistance as seen by the return of some of the diabetic markers assayed. Recognition and monitoring of insulin resistance in the normal and diabetic patient will likely lead to a more successful preventive approach and a better therapeutic intervention measure and management of the diabetic patient.

RECOMMENDATIONS

It is recommended that this research should be further carried out using larger animal samples. Also, further research should be carried out on this plant extracts and their effects not only as it relates to diabetes but also their involvement in some of the intermediary metabolic pathways.

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