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Research Article

Formulation and Evaluation of Tablets Containing Extracts of Three Medicinal Plants for Anti-Diabetic Activity

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ABSTRACT

The aim of this work was to evaluate the hypoglycaemic activity of herbal tablets containing the combined hydro-alcoholic extracts of the leaves of *Vernonia amygdalina* Del., *Ocimum gratissimum* Linn and *Telfairia occidentalis* Linn in experimental animals. The leaves of these three plants were collected, identified, dried and the constituents extracted by maceration. The phytochemical constituents of the extracts were identified by suitable and appropriate techniques. Herbal tablets containing the combined extracts were formulated and prepared by wet granulation method. The physical properties of the tablets evaluated included weight uniformity, disintegration time, thickness, diameter, hardness and friability. The hypoglycaemic activity of the extracts and herbal tablets was demonstrated in experimental animals using metformin tablet as the model drug. Results showed that the extracts contain flavonoids, alkaloids, tannins and terpenes in various degrees. All the batches of tablets met pharmacopoeial and regulatory requirements for weight uniformity, friability and disintegration time. The hardness of the tablets was adequate for tablets prepared by wet granulation method. Treatment of alloxan-induced diabetic rats with the extracts or herbal tablets containing the extracts caused reductions in the glycaemic levels of the diabetic rats within 8 h. In conclusion, the reductions in the glycaemic levels exhibited by the combined extracts or herbal tablets containing the combined extracts are comparable with the results obtained with metformin tablet ($p < 0.05$).

Keywords: *Vernonia amygdalina, Ocimum gratissimum, Telfairia occidentalis,* tablets, hypoglycaemic activity

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CONTENTS

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycaemia, in which the fasting plasma glucose is greater than 7.0 mmol/L, or plasma glucose greater than 11.1 mmol/L, 2 h after a meal[1,2]. This condition is caused by insulin deficiency, often combined with insulin resistance. Glucose transportation into the cells from the systemic circulation is facilitated by insulin hormone. The absence of this hormone causes the accumulation of sugar in the blood[3]. The symptoms of hyperglycaemia include polyuria, polydipsia, polyphagia, urinary tract infections among others[4]. These could lead to complications such as retinopathy, nephropathy, and cardiovascular disease. According to the World Health Organization, at least 171 million people worldwide suffer from diabetes mellitus[5]. The disease presently has no cure, but could be managed and controlled. The goals of treatment are to minimize or eliminate symptoms and prevent the development of complications.

Drugs used in the treatment of diabetes mellitus include insulin, sulfonylureas (glibenclamide, glimepiride, glipizide); biguanides (metformin); meglitinide derivatives; alpha-glucosidase inhibitors; thiazolidinediones among others[6]. The challenge of availability and affordability of these orthodox remedies in developing countries led to search for suitable herbal alternatives.

It has been reported that more than 1,200 plants have been used in traditional medicine for the management of diabetes mellitus because of their hypoglycemic activity[7]. Most of these plants contain antioxidants, flavonoids, tannins and other phytochemicals capable of stimulating and regenerating pancreatic beta cells. They increase insulin secretion and enhance glucose uptake by tissues. Combinations of these herbal remedies are usually employed in the management of the disease[8]. The need to formulate and produce these into suitable dosage forms has become necessary.

Tablets are drug delivery systems that provide accurate and convenient means of administering unit dose of medicaments into the body. They are easy to carry, easy to swallow and are attractive in appearance. Unpleasant odour or taste of the drug could be masked. They shield medicaments from atmospheric conditions of moisture, light or air, thereby prolonging their physicochemical and microbiological stability. They are easy to administer and could deliver the intended dose of drug with a high degree of accuracy[9].

The use of extracts from the leaves of *Vernonia amygdalina* Del., *Ocimum gratissimum* Linn and *Telfairia occidentalis* Linn in the management of diabetes mellitus has been reported[8,10,11]. But there is no report of the use of tablet formulations of these plants in the management of diabetes mellitus. The aim of this work was to evaluate the hypoglycaemic activity of herbal tablets containing the combined hydro-alcoholic extracts of the leaves of *Vernonia amygdalina* Del., *Ocimum gratissimum* Linn, and *Telfairia occidentalis* Linn in experimental animals.

2. Materials and Methods

Vernonia amygdalina Del*., Ocimum gratissimum* Linn. and *Telfairia occidentalis* Hook leaves were harvested from a farm in Jos, Nigeria in March 2021; 80% ethanol (Sigma-Aldrich®, Germany), Dragendorff reagent, Mayer's reagent, glacial acetic acid, ferric chloride, Molisch reagent, concentrated sulphuric acid, dilute ammonia solution and chloroform (Merck, Germany), lactose, maize starch, magnesium stearate and talc (May and Baker Ltd., England).

Plant Collection and Identification

Fresh leaves of *Vernonia amygdalina, Ocimum gratissimum* and *Telfairia occidentalis* were obtained from Jos, Nigeria, and authenticated by the authorities of the Federal College of Forestry, Jos where voucher of the samples was kept at the College herbarium. The authentication numbers of the fresh leaves of *Vernonia amygdalina, Ocimum gratissimum* and *Telfairia occidentalis* are FHJ181, FHJ298, and FHJ1123 respectively.

Preparation of Extracts

The method reported by Oparah *et al*.[12] was adopted. The plant materials were washed severally with distilled water, dried under sunlight for 7 days and milled. A 1.0 kg quantity was macerated in 500 ml of distilled water contained in an air-tight container with constant stirring for 3 days. The contents were filtered and the filtrate was evaporated to dryness in an evaporating bath at 40°C for 2 weeks and weighed. The percentage yield was determined according to the formula:

$$\% \text{ Yield} = \frac{w_1}{w_0} \times 100 \quad \ldots\ldots\ldots\ldots\ldots 1$$

Where w_1 is the weight of extract; w_0 is the weight of dried leaves.

Phytochemical Screening of Extracts

The method reported by Ejikeme et al.[13], Trease and Evans[14], Harbone[15], was used for the phytochemical screening of the extracts. The extract was tested for alkaloids, glycosides, saponins, carbohydrates, flavonoids, and terpenoids.

Formulation of Granules

Batches of herbal granules containing extract (1.2 % w/w), lactose (82.8% w/w), maize starch (10% w/w), acacia (5% w/w), magnesium stearate and talc (each 0.5% w/w) were prepared. Each extract and lactose were mixed thoroughly in a tumbling mixer. This was wet-massed in a mixer/granulator with an aqueous solution of acacia to a damp, coherent mass. The wet mass was screened through

a 1.7 mm mesh sieve and dried in a drying cabinet (Gallen Kamp, England) at 60^{o}C for 1 h. The dried granules were screened through 1.0 mm mesh sieve.

Preparation of Tablets

Tablets containing *Vernonia amygdalina, Ocimum gratissimum*, *Telfairia occidentalis* and the combined extracts respectively, were prepared. The batch size was 500 tablets. In each case, the dry granules were mixed with maize starch, magnesium stearate and talc in a tumbling mixer and compressed into tablets in a single-punch tabletting machine (Eagle Scientific Machines, Nottingham). The machine was fitted with a 12 mm flat-faced punch and die sets. The target tablet weight was 500 mg. The same compression pressure was used irrespective of the tablet batch. The tablets were evaluated 24 h after preparation.

Tablet Evaluation

The British Pharmacopoeia[24] method was employed in the evaluation of tablets.

Weight uniformity

Twenty tablets selected at random from each batch were weighed individually and collectively. The average weight was determined. Each batch passes the test if not more than two tablets deviate from the average weight by 5%. Results are presented as mean $\pm$ SD.

Hardness

The hardness of five tablets selected at random from each batch was determined using tablet hardness tester (Erweka, TBH 28, Germany). The average hardness was recorded.

Thickness and Diameter

The thickness and diameter of twenty tablets selected at random from each batch were determined using Vernier calliper. The mean and standard deviation values were recorded.

Friability

The friability of the tablets was determined in a friabilator (Eagle Scientific Ltd, England). Ten tablets from each batch were weighed initially (W_i). The tablets were rotated in the friabilator at 25 rpm for 4 min and weighed (W_f). The percentage friability was calculated as follows:

$$\% \text{ Friability} = \frac{Wi - Wf}{Wi} \times 100 \ldots\ldots\ldots 2$$

Disintegration time

The disintegration time of six tablets selected at random from each batch was determined in distilled water at 37°C in a disintegration apparatus (Eagle Scientific Machines, Nottingham). The mean disintegration time was recorded.

Glycaemic Activity

The method reported by Momoh and Mohammed[16] was adapted to investigate the glycaemic activity of the extracts and herbal tablets. Wistar strain albino rats of both sexes weighing between 120 to 150 g were used. The animals were housed in standard environmental conditions with 12 h light-dark cycle. They were fasted for 12 h, but were allowed free access to water before the commencement of the experiments. The weights of the animals were determined.

Induction of experimental diabetes

Diabetes was induced by intraperitoneal injection of alloxan monohydrate dissolved in normal saline in a dose of 200 mg/kg body weight of the rats. After 48 h, 2 drops of blood were collected from the tail vein of the rats. The glucose content of the blood was immediately determined using a glucometer machine, Accu-Chek® (Roche, Switzerland). Animals with glucose levels greater than or equal to 126 mg/dl were used for subsequent study. The rats (36) were grouped into A – F and A_1 – F_1, representing extract-treated and herbal tablet-treated groups respectively. Each group consisted of three (3) rats. The rats in Group A were administered a single dose of 12 mg/kg body weight of *Telfairia occidentalis* extract mixed with normal saline using gastric intubation. The same procedure was used to administer *Vernonia amygdalina* and *Ocimum gratissimum* extracts to rats in groups B and C respectively. Rats in groups D, E and F received similar doses of the combined extracts (1:1:1), normal saline and metformin respectively. The same procedure was used for rats in groups A_1 – F_1 except that tablets containing the extracts were administered in place of the extracts. Metformin served as a positive control while normal saline served as a negative control.

Blood collection and glucose analysis

Blood samples (2 drops) were collected from the tail vein of the rats under mild ether anaesthesia, and the glucose level was immediately measured at 0, 1, 2, 4, 6 and 8 h after oral administration using Accu-Chek® (Roche, Switzerland). The percentage glycaemic change in the experimental animals was calculated as a function of time using the formula:

Glycaemic change (%) = $\frac{C_1 - C_2}{C_1} \times 100$ …… 3

Where C_1 and C_2 are the initial and final glucose concentrations in the rats respectively. The blood glucose levels produced by the extracts and herbal tablets were plotted against time.

Statistical Analysis

The results were expressed as mean ± standard deviation of blood glucose levels. Data were analyzed using Student's t-test and one-way analysis of variance (ANOVA) at 5% level of significance.

3. Results and Discussion

The yields of the extracts obtained from *Ocimum gratissimum*, *Telfairia occidentalis* and *Vernonia amygdalina* are 5.27, 9.78 and 10.26% respectively. The yield values obtained for the extracts are low compared to those obtained by previous workers who used maceration process and methanol and water mixture. Recent studies have shown that microwave-assisted extraction (MAE) and Soxhlet extraction generally produce higher yield of extracts than maceration[17]. The extract yield is directly

related to the economic viability of the extraction process and the usefulness of the extract in large-scale production. The higher the percentage yield, the more viable is the extraction process. All the extracts are soluble in water, producing clear solutions. Table 1 shows the phytochemical constituents present in the extracts. Flavonoids, alkaloids, tannins, cardiac glycosides and terpenes are present in all the extracts in abundance. Steroids are present in *Vernonia amygdalina* in abundance compared to *Ocimum gratissimum* or *Telfairia occidentalis* in which it is present in appreciable and trace amounts respectively. Carbohydrates are present in trace amounts in all three extracts, while saponins are present in only *Vernonia amygdalina*. These results agree with previous reports[18,19,20].

Alkaloids and flavonoids are present in all the extracts in relative abundance. Alkaloids are abundant in the leaf extracts of *Ocimum gratissimum* and *Vernonia amygdalina*, but present in appreciable quantity in *Telfairia occidentalis.* Flavonoids are abundant in the leaf extracts of *Ocimum gratissimum* and *Telfairia occidentalis*, but present in appreciable quantity in *Vernonia amygdalina* extract. *Ocimum gratissimum* extract exhibited relatively high glycaemic control compared to the other extracts. This may be due to the presence of flavonoids and alkaloids in reasonable proportions compared to the other extracts. Previous studies have shown that the hypoglycaemic activity of these plant extracts is due to the presence of flavonoids, alkaloids and phenolic compounds present in plant extracts[14], particularly the flavonoids[21]. There seems to be a relationship between glycaemic control of the extracts and the proportion of flavonoids and alkaloids present. The combined extracts demonstrated higher glycaemic control than the individual extract at equivalent dose. This may be attributed to the relatively high content of these phytochemical constituents in the combined extract compared to the single extract. Previous studies also reported similar discovery[22,23].

The physical properties of the herbal tablets are shown in Table 2. The mean weight of tablets containing *Vernonia amygdalina* extract is 507 mg. The corresponding values for tablets containing *Ocimum gratissimum*, *Telfairia occidentalis* or the combined extract are 515, 507 and 556 mg respectively. All tablet batches met pharmacopoeial[19] requirement for tablet weight uniformity. The hardness of tablets ranged from 5.0 kgF for tablets containing *Vernonia amygdalina* or *Telfairia occidentalis* extract to 6.0 kgF for those made with the combined extracts. Tablets containing *Vernonia amygdalina* or *Ocimum gratissimum* extract exhibited high friability values, while those made with *Telfairia occidentalis* or the combined extracts exhibited low values. The disintegration times of the herbal tablets ranged from 14.58 min for tablets containing *Vernonia amygdalina* extract to 20.58 min for those made with the combined extracts.

The mean weights of each batch of tablets are greater than 350 mg. For batches of tablets to pass the weight uniformity test, not more than two of the individual tablet weights should deviate from the average weight beyond ± 5%, and no tablet should differ from the average tablet weight by more than twice that percentage[24]. All batches of herbal tablets passed pharmacopoeial uniformity of weight test[24]. This may be attributed to even distribution of the powder in the die cavity, good flow properties of the granules and uniform compression force used in the tablet compression.

All the batches of herbal tablets possessed adequate mechanical strength. The hardness values are within 4-7 KgF considered to be satisfactory for tablets prepared by wet granulation method. High hardness and low friability values are requirements for compressed tablets. Although the values of friability obtained for tablets containing *Ocimum gratissimum* or *Vernonia amygdalina* extracts are outside the range allowed for tablets prepared by wet granulation method, those made with *Telfairia occidentalis* or the combined extracts are within 0.1-1.0%. A maximum weight loss of not more than 1% generally is considered acceptable for most products[25]. The binder type and concentration, the granulation and compression processes seem to be adequate. Tablet crushing strength and friability are related to the mechanical strength of tablets. Both parameters give an idea of the resistance to chipping, abrasion or breakage of the tablets during storage, transportation and handling. Tablet hardness is important since it influences the disintegration time and dissolution rate of tablets.

The disintegration times of the herbal tablets ranged from 14.58 min for tablets containing *Vernonia amygdalina* extract to 20.58 min for those made with the combined extracts. The British Pharmacopoeia recommends a disintegration time of 15 min or less for immediate release tablets[24], while United States Pharmacopoeia recommends 30 min[26]. All the batches of herbal tablets passed the USP disintegration time test, while only tablets made with *Vernonia amygdalina* passed the BP disintegration time test. Disintegration of tablets usually precedes dissolution of the active constituents. The disintegration of tablets is dependent on parameters such as the temperature of the immersion fluid, the nature and amount of binder used, the force of compression and the concentration of the disintegrant used[27]. The soft and sticky nature of *Ocimum gratissimum* and *Telfairia occidentalis* extracts respectively may have influenced the long disintegration times obtained for tablets containing these extracts.

Table 1: Phytochemical constituents

Tablet	*Ocimum gratissimum*	*Vernonia amygdalina*	*Telfairia occidentalis*
Flavonoids	+++	++	+++
Alkaloids	+++	+++	++
Tannins	+++	++	+++
Cardiac glycosides	+++	+++	++
Terpenes	++	+++	++
Steroids	++	+++	+
Carbohydrates	+	+	+
Saponins	-	+	-
Anthraquinones	-	-	-

Key: + trace; ++ present in appreciable quantities; +++ present in abundance.

Table 2: Physical properties of herbal tablets

Batch	Mean tablet weight (mg)	Friability (%)	Mean hardness (KgF)	Mean thickness (cm)	Mean diameter (cm)	Disintegration time (min)
A	507	1.90	5.00	0.33	1.30	14.58
B	515	2.00	5.40	0.31	1.41	16.64
C	507	0.70	5.00	0.32	1.34	19.63
D	556	0.60	6.00	0.32	1.33	20.58

KEY: A: *Vernonia amygdalina* extract. B: *Ocimum gratissimum* extract. C: *Telfairia occidentalis* extract. D: Combined extract

Figure 1 shows the influence of extracts on the glycaemic levels in rats. Of the three (3) extracts, *Ocimum gratissimum* demonstrated the highest hypoglycaemic activity while *Vernonia amygdalina* extract demonstrated the least. Metformin possessed the highest hypoglycaemic activity. There was no observable decrease in blood sugar level upon the administration of normal saline used as negative control. The drugs could be ranked in their order of increasing glycaemic control as metformin > combined extract > *Ocimum gratissimum* > *Telfairia occidentalis* > *Vernonia amygdalina* extracts.

Figure 2 shows the influence of the formulated herbal tablets on the glycaemic levels in rats. A similar trend of glycaemic activity was also obtained in the herbal tablets containing the extracts. Amongst the three (3) herbal tablets, those containing *Ocimum gratissimum* extract demonstrated the highest hypoglycaemic activity, while those containing *Vernonia amygdalina* extract demonstrated the least. Tablets containing the combined extract demonstrated higher hypoglycaemic activity than those containing single extract at equivalent dose. The tablets could be ranked in their order of increasing glycaemic control as metformin > tablets containing combined extract > tablets containing *Ocimum gratissimum* > tablets containing *Telfairia occidentalis* > tablets containing *Vernonia amygdalina* extracts.

Figure 3 shows the influence of the combined extracts and herbal tablets containing the combined extracts on blood glucose levels in rats. The glycaemic level exhibited by the combined extracts is lower than that exhibited by the herbal tablets containing the combined extracts, which is equally lower than the level possessed by metformin. Ranking in order of increasing glycaemic control is metformin > herbal tablets containing the combined extracts > the combined extracts.

Figures 4 – 6 show the influence of herbal tablet formulations on glycaemic control. Herbal tablets exhibited higher glycaemic control than the corresponding leaf extract in all cases. The differences are statistically significant ($p < 0.05$). This suggests that each herbal tablet delivered the constituents of the respective extract in a wholesome manner.

The glycaemic control exhibited by each extract was replicated in the herbal tablets containing the extract. This suggests that the herbal tablets delivered the extracts in a wholesome manner. The combined extract demonstrated hypoglycaemic activity higher than the individual extracts at equivalent dose, but lower than that of Metformin. Similar results were obtained by previous workers[22,23,28]. Herbal tablets exhibited higher glycaemic control than the

corresponding leaf extract in all cases. The differences are statistically significant ($p < 0.05$). This suggests that each herbal tablet delivered the constituents of the respective extract in a wholesome manner.

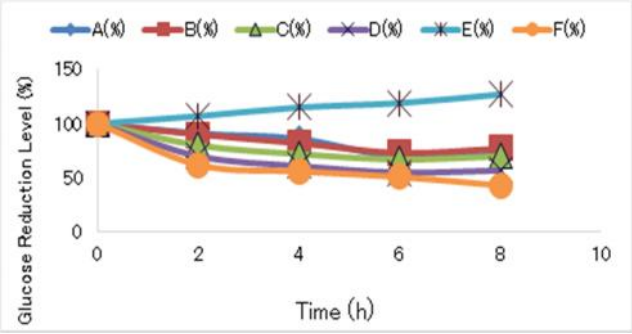

Fig. 1**:** The influence of the extracts on blood glucose levels in rats. A: *Telfairia occidentalis* extract; B: *Vernonia amygdalina* extract; C: *Ocimum gratissimum* extract; D: Combined extract; E: Normal saline F: Metformin

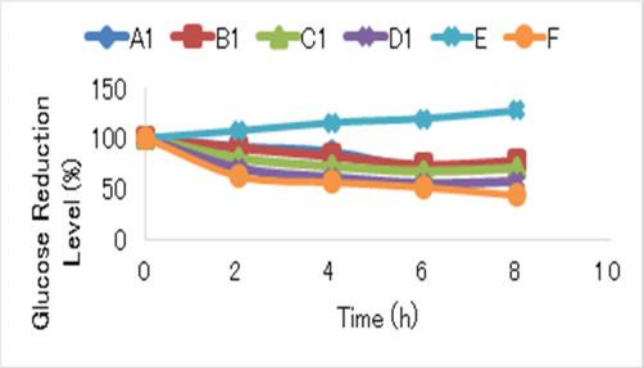

Fig. 2**:** The influence of the herbal tablets on the blood glucose levels in rats. A_1: Tablets containing *Telfairia occidentalis* extract; B_1: Tablets containing *Vernonia amygdalina* extract; C_1: Tablets containing *Ocimum gratissimum* extract D_1: Tablets containing the three extracts; E: Normal saline; F: Metformin

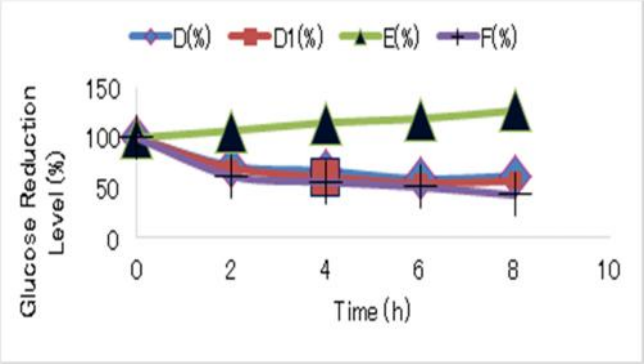

Fig. 3: The influence of the combined extracts and herbal tablet containing the combined extracts on blood glucose levels in rats. D: The combined extracts, D_1: Tablet containing the combined extracts; E: Normal saline F: metformin.

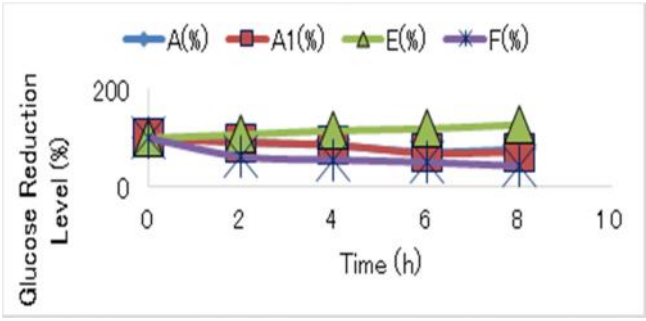

Fig. 4: The influence of *Telfairia occidentalis* extract and tablets containing the extract on blood glucose levels in rats. A: *Telfairia occidentalis* extract, A_1: Tablets containing *Telfairia occidentalis* extract, E: Normal saline and F: Metformin.

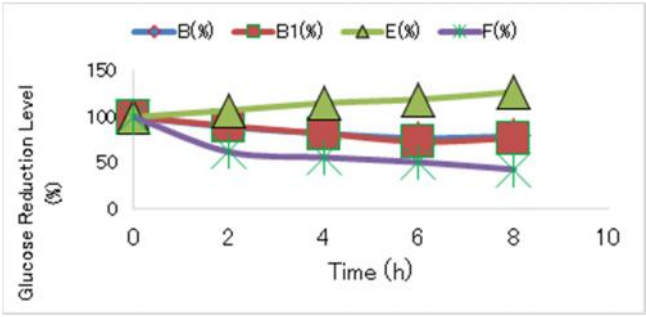

Fig. 5: The influence of *Vernonia amygdalina* extract and tablets containing *Vernonia amygdalina* extract on blood glucose levels in rats. B: *Vernonia amygdalina* extract, B_1: Tablets containing *Vernonia amygdalina* extract, E: Normal saline and F: Metformin.

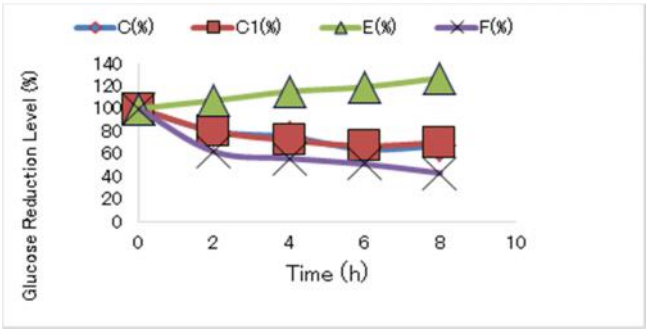

Fig. 6: The influence of *Ocimum gratissimum* extract and tablets containing *Ocimum gratissimum* extract on blood glucose levels in rats. C: *Ocimum gratissimum* extract, C_1: Tablets containing *Ocimum gratissimum* extract, E: Normal saline and F: Metformin

4. Conclusion

Aqueous-ethanolic extracts from the leaves of *Vernonia amygdalina*, *Ocimum gratissimum* and *Telfairia occidentalis* demonstrated hypoglycaemic activity in male and female Wistar albino rats. The hypoglycaemic activity of the combined extract was significantly higher than those of the individual extracts ($p < 0.05$). There was no significant difference between the hypoglycaemic activity of the combined extract or herbal tablets containing the

combined extract with metformin used as reference standard ($p < 0.05$). The herbal tablets delivered the constituents of the extracts to the experimental animals in a wholesome manner.

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