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Synergistic Blood Sugar Lowering Effect of the Combined Leaf Extract of Vernonia amygdalina (Del), Telfairia occidentalis and Ocimum gratissimum in Alloxan Induced Diabetic Rats

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ABSTRACT
Background: The incidence of diabetes mellitus is reportedly on the rise, especially in developing countries, and it is estimated that these countries will witness a 69% increase between 2010 and 2030. A high cost of medical care of diabetes is forcing an increasing number of people into the use of herbal alternatives for cure. In particular, polyherbal strategies of diabetic management are being canvassed as offering better prospects for maximal therapeutic effect and minimum adverse effects. We therefore assessed the effect of a cocktail of *Vernonia amygdalina*, *Telfairia occidentalis* and *Ocimum gratissimum* on blood sugar in diabetic rats. **Materials and Methods:** Eighty (80) male adult wistar rats weighing 80-150g were divided into four equal groups (A, B, C and D) and rendered diabetic by intraperitoneal administration of alloxan 150 mg/kg (Sigma St. Louis, MO, USA). Each group of diabetic rats was further divided into four sub-groups of five rats each and treated with *Vernonia amygdalina, Telfairia occidentalis, Ocimum gratissimum* and a combination of all three extracts respectively. Sub-groups 1, 2 and 3 were administered 10 mg/kg, 50 mg/kg and 500 mg/kg of the corresponding extract, while sub-group 4 rats of every group received distilled water and served as control. All administrations were given intraperitoneally and 12 hour post-treatment blood glucose levels determination undertaken. **Results:** The leave extracts of *Vernonia amygdalina, Telfairia occidentalis* and *Ocimum gratisimum* each possessed significant blood sugar lowering activity in diabetic rats, for all dosage levels. In combination, they produced a synergistic blood sugar lowering effect relative to each constituting part.**Conclusion:** *Vernonia amygdalina, Telfairia occidentalis* and *Ocimum gratissimum* are each effective in causing hypoglyceamia singly and in combination. Their synergistic interplay may hold the potential for a more cost-effective approach to human diabetic management in resource constrained settings as Nigeria.
Keywords: *Vernonia amygdalina, Telfairia occidentalis, Ocimum gratissum,* diabetes mellitus, polyherbalism, synergistic effect.

Introduction

Diabetes mellitus is a chronic metabolic disorder, arising from deficit insulin production or defective secretion and/or utilization of synthesized insulin. The former condition is frequently referred to as Type-1 diabetes, while the latter is also known as Type-2 diabetes. Irrespective of the type, diabetes mellitus is typically characterized by elevated blood glucose levels. In pathological terms however, Type-1 diabetes is associated with T-cell mediated autoimmune destruction of pancreatic beta cells, where as in Type-2 diabetes, which is often associated with obesity and sedentary life styles, there is gradual development of resistance to insulin (Zimmet *et al*., 2001) . The incidence of diabetes mellitus is reported to be on the rise, especially in developing countries (including Nigeria), and it is estimated that between 2010 and 2030, developing countries will witness a 69% increase in the diabetic prevalence in adult populations, compared to a 20% increase for developed countries (Shaw *et al.,*2010). This scale of disease burden attributable to diabetes has qualified it as a major threat to human wellbeing in the 21st century (Zimmet *et al*., 2001).

Insulin is the mainstay of treatment of Type-1 and some Type-2 diabetes who fail to attain adequate blood glucose levels with oral hypoglycemic agents. Clinically useful drugs currently available for the treatment of diabetes can be classified into three broad groups: Those that increase endogenous insulin secretion, such as sulphonylureas (e.g glibenclamide, glindes, insulin analogs, glucagon-like peptide 1 agonists and dipeptidyl peptidase-IV inhibitors). This class of drugs acts on the sulfonylurea receptors of the pancreas to enhance insulin secretion. Second is the group of drugs that improve insulin sensitivity of cells, and consist of the thiazolidinediones, which act as agonists on peroxisome proliferator-activated receptor gamma (PPARγ). Also included in this group are the biguanides, with metformin as a typical example. Group three hypoglyceamic agents comprise of α-glucosidase inhibitors, such as acarbose, and act by reducing both the digestion of polysaccharides and their bioavailability (Mooradian, 2000; Sheehan, 2003).

The efficacy of currently available pharmaceutical agents notwithstanding, satisfactory control of blood glucose in diabetics remains a daunting challenge for physicians and other practitioners. This situation has been linked to the progressively declining cell-mass and function of the pancreatic β-cells (Wallace and Mathews, 2000). In addition, these drugs exhibit limited tolerability and in some cases, significant side effects (Moller,

2001; Rotenstein *et al*., 2012). Quite often in clinical practice, it is the case that a combination of two or more hypoglycemic agents is required to better control blood sugar levels, and the incidences of diabetic complications, complex side effects and drug induced hypoglycemic emergencies occur commonly (Gill *et al.,*2009; Ogbera *et al.,*2007; Yusuf *et al.,*2008). These situations further increase the overall number of medications that patients have to consume in a day and their frequencies, with predictive implications for costs to patients and high non-compliance rate to medications among diabetics (Enwere *et al.,* 2006). It also enhances the potential for recourse to herbal medicines, as more affordable and more acceptable alternatives (Yusuff *et al.,* 2008).

A large percentage of people around the world (particularly Africa and Asia) depend on herbal medicines for health care (WHO, 2008). This shift has been attributed to their accessibility, affordability and culturally acceptable characteristics, amidst rising incidence of chronic non-communicable diseases and soaring health care costs (WHO, 2013). In the light of rising importance of herbal medicine in global health care systems, WHO has recently updated its Traditional Medicine Strategy (WHO, 2013). The ten year strategic plan (2014-2023), focuses on supportive engagement with member states to harness potential contributions of their traditional medical systems towards people's wellness, and promoting safety and effectiveness of traditional medicine practice through regulation, research and integration of traditional systems into mainstream health systems, where appropriate.

In Nigeria, a number of plants are used by traditional therapists in the management of diabetes mellitus (Etuk and Mohammed, 2009; Gbolade, 2009). Frequently, many herbal diabetic recipes contain a combination of different plant sources put together for therapeutic purposes. This practice (Polyherbalism) is an evolving pharmacological principle, with inherent advantage of producing maximum efficacy and minimum side effects (Ebong *et al*., 2008). Polyherbalism is particularly appropriate in therapeutic management of diabetes given that the patho-physiological lesions in diabetes are multiple, the use of more than a single therapeutic agent is often required to reverse all or majority of the diverse dimensions of the disease process. Therefore, with their plethora of ingredients and multimodal mechanisms of actions, polyherbal therapies are considered the preferred therapeutic approaches to diabetic management (Tiwari and Rao, 2002; Atangwho et al., 2009; Ebong et al., 2008). Several studies have shown that traditional medicines may in fact provide better hyperglycaemic control than current conventional drugs (Rates, 2001; Roja and Rao, 2000).

Despite the attractive nature of polyherbalism, most studies to verify herbal diabetic therapeutic efficacy claims have continued to focus on individual plants. Very few studies have focused on polyherbalism (Adebajo *et al*., 2013; Ejike *et al*., 2013). The present study therefore, intends to extend this frontier by investigating the blood glucose lowering effect of a combination of the three extracts (*Vernonia amygdalina, Telfairia occidentalis* and *Ocimum gratissimum*) in alloxan induced diabetic rats.

Vernonia amygdalina (Del)*,* popularly known as bitter leaf, is a shrub of 2 – 5 m tall, of the family *Asteraceae.* It is known variously in different parts of Nigeria: Ewuro in Yoruba, Onugbu in Igbo, Chusa-diki in Hausa, Tyuna in Tiv and Etidot among the Ibibios (Egedigwe, 2010). The shrub grows under a wide range of ecological zones in Africa. The leaves of *Vernonia amygdalina* are used as vegetable for soup making, as well as treatment of fever. Phytochemicals analysis has revealed the presence of phytates, oxalates, tannins, flavinoids and sapponins (Akah *et al*., 1992; Igile *et al*., 1994). The extracts of *Vernonia amygdalina* have been found to exhibit anti-diabetic, antimalarial, antihelminthic and antibiotic properties in animal studies (Farombi, 2003).

Telfairia occidentalis is a perennial plant and its fruits are amongst the largest known (Bosa and Mgbeogwu, 1963). It is very popular due to the high nutritional value of its leaves and seeds (Johnson and Johnson, 1976). Phytochemical analysis has revealed the presence of flavinoids, tannins, saponins and phenolic compounds (Adeniyi *et al*., 2010). The seed oil is suitable for the manufacture of soap, vegetable oils, paints and varnishe (Burkhill, 1985). The plant is reported to be effective in the treatment of an array of disease conditions such as anemia, convulsion, atherosclerosis, hypertensive disorders, hypercholesterolemia, liver pathologies and a range of inflammatory conditions (Iwu, 1983). Eseyin *et al*., (2000; 2005), has demonstrated the hypoglycemic activity of the leaves and seeds of *Telfairia occidentalis*.

Ocimum gratissimum is a shrub plant of the Lamiaceae family, which grows in Nigeria and most parts of the West African region (Sofawora, 1982). Some local names of the shrub in Nigeria are Daidoya (Hausa), Nchuawu (Igbo) and Efinrin (Yoruba). The leaves of *Ocimum gratissimum* are used for a number of therapies in traditional medical practice, including bacterial infections, fevers and diarrhoeas. It is also used nutritionally as a food spice. Further, the antidiabetic efficacy of the leave extract has been reported (Aguiyi *et al.,* 2000; Egesie *et al*., 2006).

Materials and Methods

Plant material:

The leaves of *Vernonia amygdalina, Telfairia occidentalis and Ocimum gratissimum* were obtained in Jos between the months of November and December, 2010, by the consultant herbalist of the Department of

Pharmacology, University of Jos, Dr. Azija. They were identified by Mr. I. A. Kareem of College of Forestry, Jos. Voucher specimens were prepared and deposited at the Herbarium of the Department of Pharmacognosy, University of Jos.

Preparation of extract

Fresh leaves of the three plants were washed, air dried and pounded in a mortar and pestle. 50g of the powdered leaves of each plant was weighed and mounted in a soxhlet extractor containing mixture of ethanol (80%) and water in premeasured quantities. The set-up was maintained at 60-67^{0}C and extraction process undertaken for 42 hours on each sample. The extracts obtained were dried on a hot plate and refrigerated at 4^{0}C until needed for use.

Animals

Eighty (80) male adult wistar rats weighing 80-150g were obtained from the Animal House of University of Jos. The rats were fed with grower's mash and water *ad libitum*, under standard laboratory conditions of temperature (28 ± 2^{0}C), relative humidity (50 ± 5%) and 12 hour light/ darkness cycle. They were allowed to acclimatize for 72hrs and then separated into four groups (A, B, C and D) consisting of 20 rats each for the study.

Induction of diabetes and blood glucose estimation

The rats were starved for a 24-hour period and a fasting blood sugar level determined thereafter, using dextrostix glucose testing strip and read off a glucometer (Glucometer GX model, Ames Incorporated Germany). Next, a diabetic state was induced by intraperitoneal injection of 150mg/kg of Alloxan (Sigma St. Louis, MO, USA), and post-administration (48 hrs) blood glucose levels measured. Only rats with blood glucose levels of greater than three-fold basal levels (160mg) were used in the study. Then, each diabetic group (A, B, C and D) was further divided into four sub-groups of five rats each (A1, A2, A3 and A4; B1, B2, B3 and B4; C1, C2, C3 and C4; D1, D2, D3 and D4). Groups A, B, C and D rats were treated with *Vernonia amygdalina, Telfairia occidentalis, Ocimum gratissimum* and a combination of all three extracts respectively, with sub-groups 1, 2 and 3 administered 10 mg/kg, 50 mg/kg and 500 mg/kg of the corresponding extract. Sub-group 4 of every group received distilled water and served as control. All administrations were given intraperitoneally. 12 hours afterwards, blood was again collected from the tail vein of the rats and blood glucose levels estimated as above.

Results

The administration of alloxan, followed by graded doses of the three extracts caused a significant fall in blood sugar level in the treated rats relative to control rats. This means that the extracts of *Vernonia amygdalina, Telfairia occidentalis* and *Ocimum gratissimum* are effective in causing hypogluceamia individually. These effects are shown in Tables 1, 2 and 3 below. In a similar way, the combination of all three extract also caused substantial fall in blood glucose in treated rats compared to their control counterparts. Relative to the individual extracts, the combination produced a synergistic effect, which occurred in the 10-50 mg dose range. These are depicted in Table 4.

Discussion

The findings of this study have further confirmed the hypoglycemic effects of *V. amygdalina, T. occidentalis* and *O. gratssumum,* and provide empirical support for their use in herbal practice to treat diabetes mellitus. The findings further agree with earlier reports of Akah and Okafor (1992) on the hypoglyceamic activity of *V. amygdalina* in diabetic rats and Esseyin *et al*., (2000) on *T. occidentalis*. The findings also agree with Egesie *et al*., (2006) who have demonstrated the blood glucose lowering activity of *O. gratissimum*. We have also revealed that the combination of *Vernonia amygdalina, Telfairia occidentalis* and *Ocimum gratisimum* leaves possess blood sugar lowering effect and a combination of these three extracts produced a greater effect than the constituents administered individually. This finding is in line with Ejike and colleagues (2013) who also achieved synergism in blood lowering effect using a mixture of the decoctions of leaves of *Gongronema latifolium, Ocimum gratissimum* and *Vernonia amygdalina* in experimental rats.

In general terms, herbal medicines often comprise of a complex mixture of diverse phytochemicals such as tannins, alkaloids, sapponins and polyphenols as well as dietary fibre which interact in a synergistic way to produce the desired blood sugar lowering therapeutic effect (Adebajo *et al.,* 2013; Tiwari and Rao, 2002). However, more specific studies undertaken to better understand the mechanism of action of plants used in the management of diabetes have yielded a range of explanations. Some plants are known to inhibit α-amylase or α-glucosidase, while others have been shown to have agonist effect on the PPARγ receptor, responsible for enhanced glucose uptake and metabolism by tissues. Still other plants enhance the release of insulin from the pancreas, improve glucose uptake by liver and skeletal cells, or aid the expression of GLUT4 mediator of glucose transport into adipose and muscle cells. Specifically, *Vernonia amygdalina* is known to increase GLUT4 receptor expression, while *Telfairia occidentalis* inhibit α-amylase and α-glucosidase enzymes. Some bioactive constituents responsible for all or some of the beneficial effects of plants used in herbal treatment of diabetes include alkaloids, terpenes, flavinoids and hydroxylated compounds. *Ocimum gratissimum* contains flavinoids,

which are associated with antioxidant properties, particularly its free radical scavenging activity. This property is known to shield islet cells from oxidative damage and aid regeneration of pancreatic β-cells. Furthermore, they may prevent formation of advanced glycated end products (AGEs) associated with diabetic complications as artherosclerosis, neuropathies, nephropathies, retinopathies and erectile dysfunctions (Rahimi *et al*., 2005). Therefore, *Ocimum gratissimum* may play the important role of preventing diabetic complications.

Conclusion

The study has shown that *Vernonia amygdalina, Telfairia occidentalis* and *Ocimum gratisimum* leaves possess blood sugar lowering effect and a combination of these three extracts produced a greater hypoglyceamic effect than the constituents singly administered. It is possible that the component extracts acted through differential molecular mechanisms to achieve the synergistic effect observed. This synergistic interplay may hold the potential for a more cost-effective approach to human diabetic management in resource constrained settings such as Nigeria. The significance of this effect however needs further exploration.

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IJU designed and undertook the experiment, analyzed data and wrote the manuscript. EOE acquired experimental animals and helped experimental processes, while JCA and FKO both reviewed the design and proof read the final manuscript'

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Table 1: Effect of ethanolic extract of *Vernonia amygdalina L.* in *alloxan-induced diabetic rats*

Group	Dose of extract administered (mg/kg)	Fasting blood sugar level (mg/dl)	Blood sugar level after alloxan (mg/dl)	Blood sugar level after extract (mg/dl)
A	10	54.3±1.2	248±1.0	73±1.1*
B	50	53±0.3	327±0.1	96±1.0*
C	500	57±1.6	352±0.7	100±1.2*
D (Control)	-	46.8±1.2	263±1.0	246±1.3

Values are mean ±SEM
*Statistically significant compared to control at 5% significant level (P≤0.05)

Table 2: Effect of ethanolic extract of *Telfairia occidentalis* in alloxan-induced diabetic rats

Group	Dose of extract administered (mg/kg)	Fasting blood sugar level (mg/dl)	Blood sugar level after alloxan (mg/dl)	Blood sugar level after extract (mg/dl)
A	10	50.1±1.1	202±1.5	87±1.2*
B	50	41±1.2	222±1.3	86±1.4*
C	500	54±1.0	223±2.0	98±1.7*
D (Control)	-	46.8±1.3	243±1.7	215±1.2

Values are mean ±SEM
*Statistically significant compared to control at 5% significant level (P≤0.05)

Table 3: Effect of ethanolic extract of *Ocimum gratissimum* in alloxan-induced diabetic rats

Group	Dose of extract administered (mg/kg)	Fasting blood sugar level (mg/dl)	Blood sugar level after alloxan (mg/dl)	Blood sugar level after extract (mg/dl)
A	10	57.3±1.0	224±1.3	76±1.1*
B	50	48±1.3	232±1.6	83±1.5*
C	500	54±1.4	206±1.0	91±1.3*
D (Control)	-	47.8±1.2	216±1.5	201±1.2

Values are mean ±SEM
*Statistically significant compared to control at 5% significant level (P≤0.05)

Table 4: Effect of combination of ethanolic extracts of *Vernonia amygdalina, Telfairia occidentalis* and *Ocimum gratissimum* in alloxan-induced diabetic rats

Group	Dose of extract administered (mg/kg)	Fasting blood sugar level (mg/dl)	Blood sugar level after alloxan (mg/dl)	Blood sugar level after extract (mg/dl)
A	10	67±1.1	351±1.4	85±1.3*
B	50	59±1.3	290±1.9	70±1.1*
C	500	49±0.9	310±1.2	98±0.7*
D (Control)	-	58±1.2	317±1.6	277±1.4

Values are mean ±SEM
*Statistically significant compared to control at 5% significant level (P≤0.05)
The combination of the three extracts (VTG) produced a greater blood sugar lowering effect in diabetic rats than each of its components, indicating a synergistic effect of its constituents. This can be seen in figure 1, below.

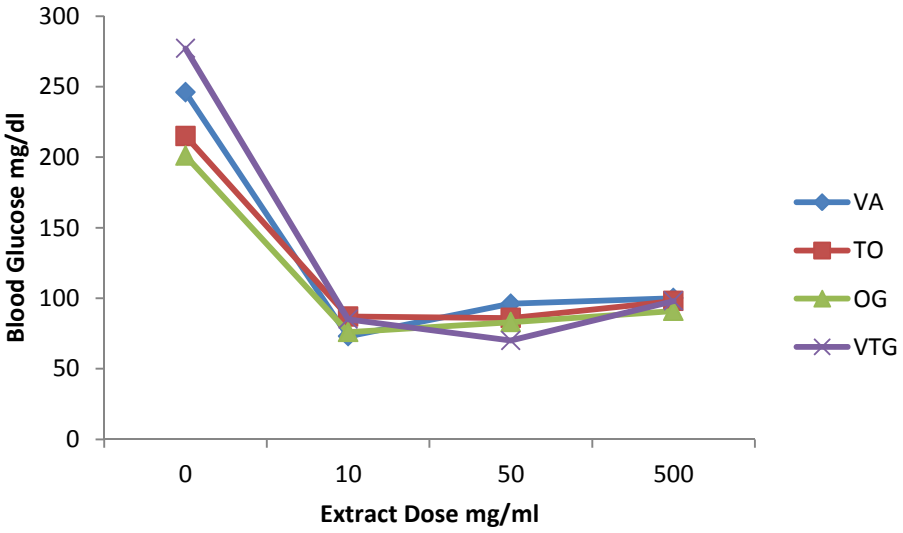

Figure 1: Blood sugar levels in response to graded doses of extracts
VA= *Vernonia Amygdalina;* TO= *Telfairia Occidentalis;* OG= *Ocimum gratissimum;* VTO= *Vernonia Amygdalina, Telfairia Occidentalis* and *Ocimum Gratissimum*