

## **Comparative Antidiabetic Potentials of Leaf Extracts of *Salacia lehmbachii*, *Tetracarpidium conophorum*, *Artocarpus heterophyllus* and Glibenclamide in Alloxan Induced Diabetic Rats**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author EGA designed the study and wrote the protocol. Author OOJ managed the animals, collected all data, performed the statistical analysis and wrote the first draft of the manuscript. Authors OCU and OAE did the literature search and also wrote part of the manuscript. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Diabetes mellitus is a global public health disorder that threatens the economies of all nations, particularly developing countries. In this study the comparative effects of the antidiabetic potentials of Glibenclamide and three well known plants used by our locals in the management and prevention of diabetes was elucidated. DM was induced by intraperitoneal injection of alloxan at a dose of 100 Mg/Kg bodyweight. The rats were randomly divided into six groups (n=5). Group 1 is the normal control, fed with normal saline orally daily for 3 weeks. Group 2 is diabetic control given normal saline orally for 3 weeks. Group 3 is diabetic rats treated with leaf extracts of *T. conophorum* at concentrations of 50 mg/kg body weight orally for 3 weeks. Group 4 is diabetic rats

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treated with leaf extracts of *S. lehmbachii* at concentrations of 50 mg/kg body weight orally for 3 weeks. Group 5 is diabetic rats treated with leaf extracts of *A. heterophyllus* at concentrations of 50 mg/kg body weight orally for 3 weeks and Group 6 is diabetic rats treated with Glibenclamide. The results revealed that on day 21, the difference between the rats treated with the leaf extracts were highly significant ( $P < 0.05$ ) in relation to reversal of hyperglycemia when compared with the positive control group, although the reduction level of *T. conophorum* was better when compared with *S. lehmbachii*, *A. heterophyllus* and Glibenclamide ( $T.c < S.l < Gl < A.h = 88.1 \text{ Mg/dl} < 91.1 \text{ Mg/dl} < 91.3 \text{ Mg/dl} < 123.2 \text{ Mg/dl}$ ). This may have occurred due to the regeneration of the damaged  $\beta$ -Pancreatic Islets cells by the plant extracts which contain phytochemicals that constitutes a protective factor against cardiovascular diseases by helping to increase the viability of the beta cells and reduction of muscle wasting and loss of tissue proteins in these rats exposed to alloxan or other oxidative stress. It is therefore highly encouraged to carry out more pharmacological and clinical studies on these plants which will help in production of a novel herbal drugs which will be affordable and readily available for the management of this ailment.

**Keywords:** *Tetracarpidium conophorum*; *Salacia lehmbachii*; *Artocarpus heterophyllus*; Glibenclamide; diabetes mellitus; phytochemistry; rats.

## 1. INTRODUCTION

The role of traditional medicine in solving health problems is gaining recognition the world over [1], and this is attributed to the great number of people in the developing countries who depends on traditional medicine for their health care needs [1,2]. Even individual countries have encouraged the use of plants and plant products for the prevention and cure of diabetes mellitus as alternative medicine [3], and therefore it calls for research into indigenous plant medicines to be encouraged to improve health care of the citizens of those communities.

Diabetes mellitus is one of the leading causes of death in developed and developing countries today. It is a metabolic disorder of multiple aetiologies, characterized by chronic hyperglycaemia, absolute or relative lack of insulin and late complications due to disturbances of carbohydrate, fat and protein metabolism [4,5]. Diabetes mellitus is a global public health disorder that threatens the economies of all nations, particularly developing countries. This is fuelled by rapid urbanization, nutritional transition and upward sedentary lifestyles with the epidemic rising in parallel with the worldwide increase in obesity. Diabetes mellitus remains a burden world over despite the availability but unaffordable numerous antidiabetic drugs causing a rise in its prevalence with associated deaths and deformities associated with it [5]. There has been an increase in the cases of diabetes across the world due to an increase in the population, aging, increasing prevalence of obesity and physical inability [6,7].

*Salacia lehmbachii* is a little woody plant of the family of celestraceae with height of about 3M [8], with leaves of simple, opposite, ovate-oblong, acuminate with yellowish and shining flowers on the auxiliary tubercles [8]. The fruits are globose orange with a unique large seed at the centre, with two to four seeds almost at the periphery of the pulp [8,9]. *S. lehmbachii* can be found in the tropical rain forest of the South-Eastern Nigeria and Cameroon [6,8]. Its root-bark water extract has been reported to possess anti-inflammatory and analgesic properties [8,10,11], anti-abortifacient activity [8,12], antidiuretic property [13,11], and anti-cholinergic property [8,14] and nil hepatic toxicity [8] in wistar rats. Its root decoction has also been used in South-Eastern Nigeria to treat and cure fever from malaria and gastro-intestinal infections [8].

*Tetracarpidium conophorum* is a climbing shrub cultivated in Southern Nigeria and Western Cameroon for its leaf, root, fruit and nut [15,16]. It was reported by [17,18] that *T. conophorum* possesses antimicrobial and antifungal properties, [19] reported on its antidepressant property while [20] and [21,22] reported on its antibacterial and antidiabetic properties.

*Artocarpus heterophyllus* belong to the mulberry family (Moraceae) and genus Artocarpus and it is known by other names such as Jackfruit in English, Karthal and Panas in Hindus, Kanthal in Bengal and Palaa in Tamil but popularly known as Jak [23]. It is an evergreen, latex producing plant with erect tree that grows up to 80 feet in height. The fruits are of dietary use and are important sources of carbohydrate, protein, fat, vitamin and minerals. It is the natural fruit of

Bangladesh and is extremely important by the natives. The fruit skin is extremely rough and thick with spines, the bark, roots, leaves and fruits are attributed with diverse medicinal properties and used in various traditional and folk systems of medicine to treat a range of ailments [24].

## 2. MATERIALS AND METHODS

### 2.1 Plant Materials

The leaf samples of the plants to be investigated were harvested from Ikot Nakanda village in Akpabuyo, Cross River State, Nigeria during the months of October – December 2015. The plants leaves were authenticated by a Taxonomist in Botany Department of the University of Calabar, Calabar, Cross River State, Nigeria as *Tetracarpidium conophorum*, *Salacia lehmbachii* and *Artocarpus heterophyllus* and was deposited at the herbarium for reference with voucher specimen number 688-2A.

### 2.2 Chemicals and Drugs

All chemicals used were purchased from sigma chemical, Merch chemical supplies, SD fine and Himedia. All other chemicals used were obtained commercially and were of analytical grade.

### 2.3 Preparation of Extracts

The leaves were washed with tap water then rinsed in distilled water and shade dried at room temperature for two weeks. The dried samples were crushed into powder by the use of electric blender and the extraction of the active ingredient from the leaf powder was carried out using specific method [25,26]. 25 g of the powdered leaves were extracted by Soxhlet apparatus using 250 ml of ethanol and n-hexane in a separate flask. The extraction lasted for six hours. The extracts obtained was concentrated by evaporation using water bath at 100°C and then stored at 4°C in cold room.

### 2.4 Experimental Animals

Adult male wistar rats were used for this study and were obtained from the Department of Pharmacology animal house of the University of Calabar, Nigeria and were kept in wired cages for two weeks prior to this experiment. They were fed *ad libitum* and allowed free access to drinking water during the whole period of the experiment. The animals were divided into 6 groups of 5

animals each. Group 1 is the normal control, fed with normal saline orally daily for 3 weeks. Group 2 is diabetic control given normal saline orally for 3 weeks. Group 3 is diabetic rats treated with leaf extracts of *T. conophorum* at concentrations of 50 mg/kg body weight orally for 3 weeks. Group 4 is diabetic rats treated with leaf extracts of *S. lehmbachii* at concentrations of 50mg/kg body weight orally for 3 weeks. Group 5 is diabetic rats treated with leaf extracts of *A. heterophyllus* at concentrations of 50 mg/kg body weight orally for 3 weeks and Group 6 is diabetic rats treated with Glibenclamide (250 Mg/Kg body weight).

### 2.5 Induction of Experimental Diabetes

Diabetes mellitus was induced by intra peritoneal injection of alloxan at a dose of 100 mg/kg body weight to overnight fasted rats [26]. Rats with plasma glucose levels above 250 mg/dl were considered as severe diabetic and were used in the experiment [16].

### 2.6 Measurement of Blood Glucose Levels

Blood was drawn from the tail vein after a soft massage and measured using an automated glucose analyzer (fine test Auto-coding™ Premium, Infopia, Korea) as described by [27].

### 2.7 Determination of Total Phenolic Content

This was determined by Folin – Ciocalteu reagent [28,26] 10ml of the samples were taken into a test tube and made up to the volume of 1ml with distilled water. Then 0.5ml of Folin – Ciocalteu Phenol reagent (1:1 with water) and 2.5ml of sodium carbonate solution (20%) were added sequentially in each tube in triplicate manner. Soon after vortexing the reaction mixture, then the test tubes were placed in dark for 40 minutes and the absorbance was recorded at 725nm against a reagent blank.

### 2.8 Determination of Total Flavonoid Content

Flavonoid content was determined using aluminum chloride colorimetric method with some modifications [29,26]. The sample solution (0.5 ml) was mixed with 1.5ml of 95% ethanol, 0.1 ml of 10% aluminium chloride hexahydrate, 0.1 ml of 1M potassium acetate, and 2.8 ml of distilled water. After incubation at room temperature for 40 minutes, the absorbance of

the reaction mixture was measured at 415nm. The same amount (0.1 MI) of distilled water was substituted for the amount of 10% aluminum chloride as the blank. All test were performed in independent triplicates, the total flavonoid content was expressed in milligram per gram extract of quercetin Equivalent.

The remaining Phytochemical analysis was done using the methods of [30,31,32,33], although with slight modifications.

## 2.9 Statistical Analysis

The results obtained were expressed as Mean  $\pm$  Standard Error of Mean (SEM). Significant difference between the control and experimental values were assessed using student's t-test and the results were considered significant at values less than 0.05 (P=0.05). Graphical representations were designed using Microsoft Excel (2007).

## 3. RESULTS AND DISCUSSION

Herbal medicine is gaining popularity in various parts of the world and the plants whose parts are used for the treatment have been found to possess antimalaria, anticancer, antiobesity, antidiabetic, antimicrobial, antifungal properties and the properties are helpful in the formulation of drugs and potentially offer significant nutritional and dietary benefits [34]. These characteristics occurs due to some bioactive metabolites embedded in these plants. DM is a global public health crisis that threatens the economies of all nations of the world, mostly the developing nations [35]. This is fuelled by the rapid urbanization, nutritional transition and increasing sedentary lifestyles with the epidemic growing in parallel with the worldwide rise in obesity [34,35].

**Table 1. Phytochemical analysis of *A. heterophyllus* leaf extracts**

Phytoconstituents	Inference
Flavonoids	+++
Anthocyanins	+
Tannins	++
Saponins	+
Phytosterols	++
Glycosides	+
Alkaloids	++
Triterpenoids	++
Phenols	+
Dihydromorins	+

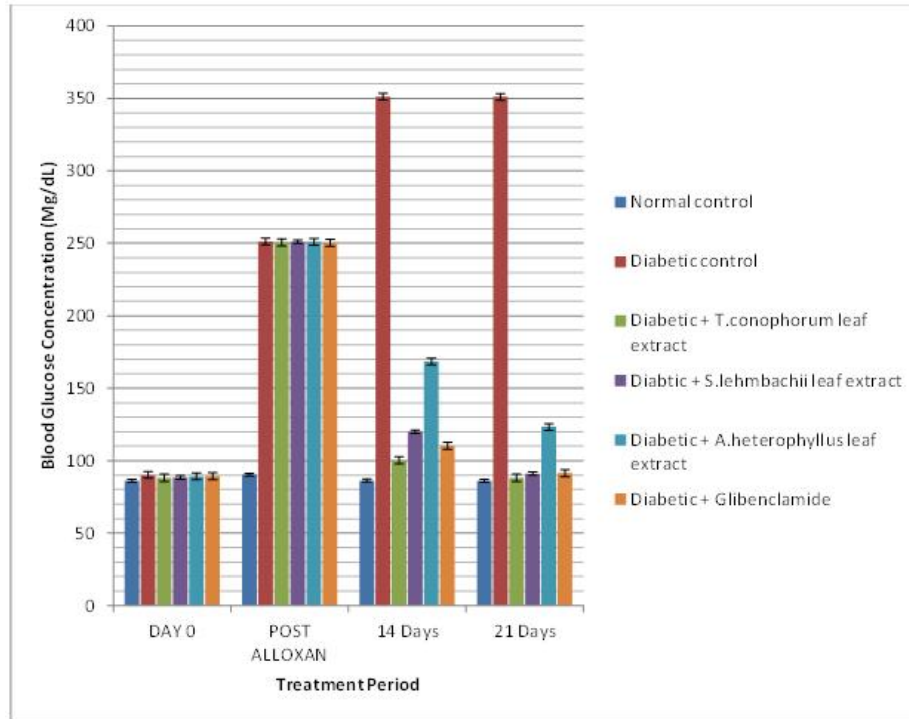
**Table 2. Phytochemical analysis of *T. conophorum* leaf extracts**

Phytoconstituents	Inference
Tannins	+++
Alkaloids	+++
Phenols	+
Saponins	+++
Oxalates	++
Flavonoids	++
Garlic acid	+

**Table 3. Phytochemical analysis of *S. lehmbachii* leaf extracts**

Phytoconstituents	Inference
Salacinol	+++
Kotalanol	++
Tannins	++
Salasol	+
Salaterpene	+
Glycosides	+
Lehmbachol	+
Mangiferin	++
Polyphenol	+

Hyperglycemia is a metabolic complication of both clinical and experimental diabetes [35,36]. From these work, the treatment of the diabetic rats with the extracts of the plants resulted in a significant fall (P<0.05) compared to the diabetic controls. The reduction may be due to the inhibitory effect of the active principles on enzymes of cholesterol biosynthesis [35,37,38], or due to enhanced activity of the enzymes involved in bile acid synthesis and its excretion [39] or may even be due to the regeneration of the damaged  $\beta$  cells or could be due to interference with lipocytes breakdown that causes increased sensitivity of insulin receptors [16]. All these actions may have occurred due to the phytochemicals including salacinol and kotalanol polyphenols found in *S. lehmbachii*, flavonoids, sterols found in *A. heterophyllus*, which help the plant to possess phytoestrogenic and antioxidant properties and alkaloid, tannins, saponins, flavonoids and others found in *T. conophorum* which help it to boost its pharmacological properties. From these results it can be inferred that the antidiabetic potential of *T. conophorum* was better on the third week when compared to *A. heterophyllus*, Glibenclamide and *S. lehmbachii* ( $T.c < S.l < Gl < A.h = 88.1 \text{ Mg/dl} < 91.1 \text{ Mg/dl} < 91.3 \text{ Mg/dl} < 123.2 \text{ Mg/dl}$ ). This high potentiative nature of *T. conophorum* may be as a result of the phytochemicals – Alkaloids, saponins, tannins,



**Fig. 1. Comparative antidiabetic effects of *T. conophorum*, *S. lehmbachii*, *A. heterophyllus* and Glibenclamide in alloxan induced diabetic rats**

Results show Mean  $\pm$  SEM of five values.  $P < 0.05$  vs control and treated groups

oxalates, phenols and garlic acid embedded in this plant. The Phytochemicals found in these three plants can be exploited in the production of cheap and readily available herbal drugs which will aid in the treatment and prevention of diabetes considering the cost implication involved in its management the world over.

#### 4. CONCLUSION

The isolations and characterization of the active ingredients in the plants fractions followed by further pharmacological and clinical studies would aid in the production of novel herbal drugs for the treatment and prevention of diabetes which will be affordable and readily available as an alternative therapies to the conventional medications.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

All the authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have

therefore been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

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#### COMPETING INTERESTS

All authors have declared that no competing interests exist.

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