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ASSESSMENT OF HYPERGLYCEMIC POTENTIALS OF KHAYA ANTHOTHECA STEM-BARK EXTRACTS ON ALLOXAN-INDUCED DIABETIC RATS

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Abstract

Introduction: Medicinal plants have been the basis of treatment of various diseases in African traditional medicine as well as other forms of treatment from diverse cultures of the world. Khaya anthotheca is a member of the family Meliaceae, a native to Africa. It is a medicinal plant widely used for several therapeutic purposes. Herein, phytochemical study, hyperglycaemic investigations was carried out on the methanol extract of Khaya anthotheca Stem-bark. Materials and Methods: However, 35 rats were distributed into seven groups to evaluate the anti-diabetic activity of K. anthotheca stem-bark methanol extract at the dosage range of 50-400 mg/kg/b.wt. The analysis was done using the software-SPSS one-way ANOVA at a significance level $p<0.05$. Results: The result of the anti-diabetic study reveals that extract elicited substantial ($p<0.05$) inhibition of hyperglycaemic. The plant Khaya anthotheca stem-bark methanol extract displayed profound ($p<0.05$) anti-hyperglycaemic action at the dosage of 200 mg/kg/b.wt, 300 mg/kg/b.wt. and 500

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mg/kg/b.wt. against induced diabetic rats. Conclusion: This study therefore suggests the use of Khaya anthotheca as a hypoglycaemic agent and for treatment of diabetic. Further studies are needed to discover the bioactive constituent of the plant responsible for this anti-diabetic activity.

Keywords: Assessment, Hyperglycaemic, East African, Khaya Anthotheca, Stem-Bark, Alloxan-Induced, Diabetic Rats

INTRODUCTION

Medicinal plants have been the basis of treatment of various diseases in African traditional medicine as well as other forms of treatment from diverse cultures of the world. This calls for caution in the use of medicinal plants of which the use is presently on the increase due to easy availability, affordability, accessibility, and promising efficacy comparable to the often-high cost and adverse effects of standard synthetic drug agents. This chapter highlights some safe medicinal plants with good toxicological profile in laboratory animals and/or cell culture experiment that are qualified for clinical trials in humans. Several medicinal plants were evaluated for their good toxicological profile using online research. After much screening, only those medicinal plants without serious toxic effects in animals and cell culture experiments were chosen and precisely discussed (Hao, 2020).

Several compounds derived from traditional medicinal plants have found way into modern medicinal practice through extensive research and drug development, there are number of plants with potential medicinal value that are still largely unexplored.

East African (Khaya Anthotheca) is a deciduous tree which is very well known for its wood quality, while its medicinal properties are just beginning to be realized. Paulownia wood is light and flexible, but does not crack or deform easily and is known for its physical strength, texture (light to medium clay-sandy), grain, and color (Zhu et al., 1986). The wood has considerable moisture resistance and flame-retardant properties (Li and Oda, 2007). Moreover, as a short rotation fast growing tree, Paulownia has already attracted attention as a potential bioenergy crop that can help in both carbon sequestration and in producing transportation fuel (Basu et al., 2015; Vaughn et al., 2015).

The plant plant, which is used in African traditional medicine for treatment of diseases helmenthiasis, malaria, gonorrhea, abdominal pain and migraine (Toyang et al.,2012, Amri

and KIsangau, 2012). The Khaya genus is also used for the treatment of convulsion, fever, cough, stomach ache, rheumatism and dermatomycosis (Ojokuku et al., 2010).

However, diabetes is a chronic disease that occurs when the pancreas cannot produce enough insulin, or when the body is unable to effectively use the insulin it produces. On the other hand, the deficiency of insulin secretion and the shortage of beta cells in the pancreas will lead to high sugar levels in the blood. High blood sugar or hyperglycemia is one of the common effects of uncontrolled diabetes and leads to severe damage to many organs, especially nerves and blood vessels Such as retinopathy, heart disease, liver, and renal failure. (Akinnuga et al., 2011; Sebbagh et al.,2009 and Reid, 2006, Reid 2018). High blood sugar in the long term promotes generic oxidative stress, retinopathy, foot damage, hearing impairment, and skin conditions (bacterial and fungal infections). (El-Serag et al.,2008, Al-Hayaly, et al., 2020)

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from defect in insulin secretion and insulin inaction (Kangralkar et al., 2010; Adoum et.al., 2012). It is a disease with worldwide significance and increasing prevalence because of its impact on health, quality of life and life expectancy of patients as well as health care system (Subbiah et al., 2006). This disease affects millions of people worldwide and the number of patients increasing by the day with a population projected to be about 592 million or more by the year 2035 (Guariguata et al., 2013).

Pharmacological Activity of Khaya Anthotheca

Antifungal Activity

The major focus of integrated pest management is to effectively manage and control pests without causing harm to humans, animals and the environment. In recent times, bioactive natural compounds, particularly secondary metabolites with antifungal activities that are nontoxic to humans, highly biodegradable and with very low persistence in the environment are considered alternatives to conventional pesticides in pest management and control (Abdelgaleil et al., 2005).

Several plants with fungitoxic activities against pathogens have been reported in the literature. Using radial growth approach, Abdelgaleil et al. (2005) investigated in vitro antifungal activity of isolated limonoids from the diethyl ether of the stem bark of K. ivorensis against a plant pathogen fungus (Botrytis cinerea Pers.). The results revealed that the 10 limonoids (methyl angolensate, methyl 6-hydroxyangolensate, 3-deacetylkhivorin,

3,7-dideacetylkhivorin, 1,3,7-trideacetylkhivorin, 7- deacetylgedunin, 7-deacetoxy-7-oxogedunin, swietenine, 3-O-detigloyl 3-O-acetylswietenine and 3-O-acetylswietenolide) isolated from the stem bark of K. ivorensis exhibited antifungal activities at the test concentrations. It was reported that the highest fungal growth inhibition was demonstrated in methyl angolensate (62.8% at 1000 mg/L and 73.3% at 1500 mg/ L) and 1,3,7-trideacetylkhivorin (64% at 1000 mg/L and 68.6% at 1500 mg/L).

Nephroprotective Activity

In a study by Zemo et al. (2021) on assessing the putative neuroprotective properties of the plant in ovariectomized rats, treatment with K. anthotheca decoction reduced MDA and increased GSH levels in brain homogenates ($p< 0.01$). As estradiol valerate, the decoction, prevented neurodegeneration observed in cortices and hippocampi of untreated ovariectomized animals. The result suggested that K. anthotheca is endowed with neuroprotective effects and warrant further studies, including other models of neurodegeneration and dementia

Hepatoprotective Activity

In humans, the liver is considered a major detoxification site and therefore, it is a principal drug exposure target in the body (Kumari and Kakkar, 2012). Liver injuries induced by drugs and liver cirrhosis have been reported to be the ninth main cause of mortality in western and developing countries. Efficient and less-harmful treatments of liver injury, especially with the use of natural compounds, are of interest in the pharmaceuticals (Kouam et al., 2017).

The hepatoprotective activity and molecular mechanisms of action of limonoids from the stem bark of K. grandifoliola were evaluated against acetaminophen (APAP)-induced hepatotoxicity in normal human liver L-02 cells line (Kouam et al., 2017). The results of the study showed that three isolated limonoids, namely 17-epi-methyl-6hydroxylangolensate, deacetoxy7R-hydroxygedunin and 7- deacetoxy-7-oxogedunin demonstrated protective activity against APAP-induced hepatotoxicity as the limonoids improved the cellular antioxidant defense system as well as modified the major processes involved in APAP cell-death mechanism. The increased expression of mitogen-activated protein kinase phosphatase (Mkp)- 1 and the nuclear translocation of nuclear factor erythroid 2-related factor-2 (Nrf2) were identified as the molecular mechanism of action of protection of the isolated limonoids against APAP- induced hepatotoxicity.

Anti-inflammatory Activity

Inflammation is an activated defense response in the body to living tissue injuries caused by a damaged immune system, microbial infections and other physical agents (Ghasemian et al., 2016). Although the basic purpose of inflammatory activation is to contain and get rid of the harmful agents, and eliminate defective tissue parts in order to heal the system, organ and tissue affected, the mediators responsible for these processes in the acute inflammation phase may not progress well, thereby resulting to chronic inflammation (Oguntibeju, 2018). Chronic inflammation has been implicated in the development of several diseases such as arthritis, atherosclerosis and obesity-associated diabetes (Zhou et al., 2018). Several antiinflammatory and non-steroidal drugs are available in treating inflammation and pain; however, there are several side effects reported with the use of nonsteroidal anti-inflammatory medication. Medicinal plants having anti-inflammatory therapeutic activities with little or no side effects are recommended as a healthy alternative therapy to be exploited in the treatment of inflammation (Oguntibeju, 2018).

The anti-inflammatory activity of Khayandirobilde, a limonoid isolated from the stem bark of K. senegalensis, was evaluated against lipopolysaccharide (LPS)-stimulated inflammation in mouse macrophages RAW 264.7 and BV-2 microglial cells (Zhou et al., 2018). Khayandirobilde suppressed several pro-inflammatory mediators in RAW 264.7 and BV-2 microglial cells. Khayandirobilde reduced the production of LPS- induced nitric oxide (NO) in RAW 264.7 and BV-2 with IC50 values of 5.04 ± 0.14 μM and 4.97 ± 0.5 μM, respectively. Additionally, at both protein and mRNA levels, Khayandirobilde decreased LPS-induced interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), which are pro-inflammatory mediators (Zhou et al., 2018). These results suggest that this limonoid is capable of exerting anti-inflammatory activity by preventing inflammatory mediators' expression.

Statement of problem

Diabetes mellitus is an endocrine disease which is rapidly becoming public health problems in Nigeria. Diabetes mellitus is one of the chronic non-communicable diseases. It is a serious complex chronic condition and a major cause of ill health worldwide.

Justification for the study

No modern medicine has reached the adequate level in the treatment of diabetes. Use of plant extract to treat diabetes mellitus is of growing interest as most plant foods contain

many bioactive substances with therapeutic potentials. Khaya anthotheca is a plant readily available and used locally to cure disease in Nigeria because of its less side effects of it and it is easily accessible by the low-income earners. However, limited information is available to the masses about its antidiabetic activity. This research is necessary to investigate the pathogenic effects of methanol fraction of Khaya anthotheca in alloxan induced diabetic wistar rats.

Aim and objectives of the study

To investigate the effects of methanolic fraction of *Khaya anthotheca* in alloxan induced diabetic wistar rats

The objectives of this study are

1. to obtain methanolic extract of *khaya anthotheca*
2. to determine the pathogenic effect and antidiabetics potentials of east African leaves extracts *Khaya anthotheca* in alloxan-induced Albino Rats.

METHODS

Materials

Experimental Animals (Albino rats)

Thirty male albino rats weighing between (150-190g) will be obtained from the animal farm, Natural product research laboratory (NPRL) Bajabure, Adamawa state. Rats were placed at room temperature of 22±2°C and 12/12 periods of light and dark with proper ventilation facility. Rats were acclimatized for one week and given the standard diet and water ad libitum. Standard laboratory protocols for animal studies were maintained as approved by the faculty of pure and applied sciences, Federal University Wukari, Taraba State, Nigeria. They will be maintained on a standard animal pellets (vital feeds, Grand's cereals and oil meal Jos) and water ad libitum. All experiment will be carried out based on the approval of the Animal and Research ethical committee.

Induction of Diabetes

Study location: The research was conducted at the Department of Biochemistry, Federal University Wukari, Taraba State, Nigeria between August 2023 and January 2024. Chemicals: Methanol, alloxan, glibenclamide or insulin were purchased from Sigma

Aldrich, Steinheim, Germany. Other chemicals used in this study were obtained from standard suppliers. Plant collection and identification: The matured roots of khaya anthotheca were collected from a farm in Wukari Local Government Area of Taraba State, Nigeria. And deposited the herbarium unit of the Department of Biological Sciences at Federal University Wukari in Taraba State, the stem-bark were identified down to the species level.

After washing the stem-bark with tap water to get rid of any dirt particles, they were allowed to air dry in the shade to keep the chemical components from being inactivated by UV radiation. Using a mortar and pestle, the dried stem-bark was ground into a fine powder and kept in a dry container. Extraction of plant material: The powdered sample (150 g) was placed into a flask and methanol was used to extract the extract for 7 days, while shaking at intervals and allowed to stand at room temperature. The mixture was filtered using Whatman no. 4 filter paper and concentrated in a Buchi rotary evaporator (Gaithersburg, Maryland, United States). The dried extract was transferred to airtight container, corked and preserved in a refrigerator.

Anti-diabetic study

Experimental design:

Thirty-five albino Wistar rats were distributed into seven groups, each group containing five animals (n = 5). After it was allowed to fast for 24 hrs, Diabetes mellitus will be induced with a single intraperitoneal injection of alloxan monohydrate, at a dosage of 120 mg/kg b. wt

Treatment with the plant extract was administered daily for 28 days as follows:

C Group 1: Normal control (diet/water)

C Group 2: Rats (induced alloxan 120 mg/kg b. wt, +diet/water)

C Group 3: Rats (induced alloxan 120 mg/kg b. wt, +diet/water Omeprazole)

C Group 4: Rats (induced alloxan 120 mg/kg b.wt., +diet/water+100 mg/kg/b.wt., extract)

C Group 5: Rats (induced alloxan 120 mg/kg b.wt., +diet/water+200 mg/kg/b.wt., extract)

C Group 6: Rats (induced alloxan 120 mg/kg b.wt., +diet/water+300 mg/kg/b.wt., extract)

C Group 7: Rats (induced alloxan 120 mg/kg b. wt, +diet/water+400 mg/kg/b.wt., extract).

An 18 h fast will be allowed for all animals, followed by measurement of blood glucose at (time 0) for a baseline reading and then loading glucose (3 g/kg, body weight). This will be followed by the different treatments of either distilled water, plant extract (100 mg/kg), or positive controls, glibenclamide (2.5 mg/kg) or insulin (200 μg/kg). Blood samples will be collected from the tail veins of the animals at 30 min intervals for 2½ hours, using Bayer's Glucometer Elite® (Elite (Pty) Ltd, Health Care Division, Isando, China).

Long term Glucose and Insulin Level Studies

Animals will be orally administered with 100-400 mg/ kg b.wt of *khaya anthotheca* by means of a bulbed steel needle for a period of 28days. Negative control groups will be given an equal volume of distilled water whilst the positive controls will be given glibenclamide or insulin. The animals will be housed individually in separate cages to facilitate the daily measurements of water and food intake at 10:00 h. The weights of the rats will be measured and recorded once every week. Blood glucose levels will be also measured weekly.

Insulin Measurements

Serum insulin concentrations will be determined in blood samples of separate groups of non-diabetic and alloxan-induced diabetic rats (n=5 in each group) following the 28days treatment plan. Measurements will be done using kit (10-1250-10 Mercodia Diagnostics, Germany). Each determination will be performed in duplicate for standards and samples.

Statistical Analysis

Values will be expressed as Mean±standard deviation for three determinations of each experiment. The analysis will be done using the software-SPSS one-way ANOVA. Differences between means will be considered significant when a 2-tailed value of $P > 0.05$.

Table 1. Effect of stem-bark *K. anthotheca* methanol extract on alloxan diabetic induced rats. Mean blood glucose Level of diabetic rats.

Mean fasting blood glucose level post treatment (days)

Treatment	Dose mg/kg	0	3	7	14	21	28
		112.3±10.	116.5±4.2*	122.6±6.4*	123.3±8.3*	126.0±7.5*	125.7±5.5d
B	0.25ml	364.3±72.	387.6±61.2c	420.4±15.7c	455.7±25.8c	487.2±29.1	504.7±7.6c
C	2.5mg/k	399.6±56.7	189.5±45.5	123.6±6.3*	101.2±2.4c*	089.3±6.4	076.6±8.3c
D	100	323.4±16.5	317.5±32.3*	294.7±51.4c	213.78±15.3	172.6±12.8	134.7±19.6
E	200	344.2±16.4	324.7±17.9	302.9±36.2	245.3±33.4	163.3±34.6	122.3±6.6d
F	300	367.5±32.5	282.3±31.9c	225.7±11.6c	209.7±17.8	145.8±19.7	095.4±29.5
G	400	395.4±16.	265.9±21.3	178.8±45.3	125.3±19.3	102.4±11.2	083.8±21.
H	500	429.3±11.	232.6±23.8	129.7±11.9	105.3±12.4	093.4±33.5	069.2±24.

Value with superscripts ^{c} with a group along the row is significantly (P<0.05) higher than zero hours' blood glucose, value with superscript ^{d} within the group along the row are significantly (P<0.05) lower than zero hours' blood glucose value. While value with superscript * between groups along the column is significantly (P<0.05) lower than blood glucose value in the diabetic ^{c}

control group.

Induced Diabetic								
Parameters	**Control**	**Diabetic control**	**glibenclamide**	**Treatment Groups with stem-bark Khaya anthotheca methanol extract**				
				100	200	300	400	500
AST(U/L)	21.55±3.85	31.4±1.42	28.34±0.21	27.11±2.89	22.11±1.22	24.33±1.98	26.77±2.00	24.98±1.10
ALT(U/L)	13.89±0.94	19.23±1.74	24.79±0.41	18.56±3.46	17.21±4.01	19.18±2.12	23.14±1.88	23.66±2.21
ALP (U/L)	28.67±1.26	37.11±1.46	28.56±1.23	21.75±2.99	20.33±3.41	22.15±4.56	23.78±5.23	25.00±5.36
Creatinine	1.00±0.21	1.43±1.45*	0.88±2.05	0.68±1.67	1.11±0.03	1.08±0.04	0.96±0.02	0.77±0.11*
Urea	35.88±6.73	48.77±2.32	38.36±1.64	34.16±3.00	33.22±0.98	31.11±2.88	29.58±1.99	33.21±2.58
Protein	5.88±7.63	8.12±0.43	6.11±0.76	5.79±0.45	5.37±0.78	5.89±0.77	6.00±0.59	6.56±0.26
Albumin	3.40±0.71	4.41±0.52	4.24±0.36	3.67±0.32	3.48±0.44	3.46±0.32	3.12±0.44	3.08±0.14

Animals were treated orally with induced alloxan 120 mg/kg b. wt and *Khaya anthotheca* Stem-Bark Methanol Crude Extract (KASB) at 400 mg/kg/b.wt., for 28 days. The result reveals that *K. anthotheca* methanol stem-bark crude extract exhibited a consistent and substantial (p<0.05) increase of percentage in blood glucose with increase in concentration

RESULTS

The result of the hypoglycaemic study revealed that *K. anthotheca* methanol stem-bark extract exhibited a consistent and substantial ($p<0.05$) hypoglycaemic result.

The effect of the extracts of K. anthotheca Stem-bark extract on the diabetic albino rats fasted for 28days with a dose of 100-500 mg/kg body weight, is shown in Tables 1, The mean blood glucose levels of rats treated with 100,200,300,400 and 500mg/kg bwt of the extract at 0 days' table 1, were 364.3±72.4, 399.6±56.7, 323.4±16.5, 344.2±16.4, 367.5±32.5, 395.4±16.7 and 429.3±11.6; respectively. After three days the blood glucose level of the rats treated with 100mg/kg bwt showed statistically significant decrease compared to zero-day blood glucose value, the value significantly ($P<0.05$) decreased to 316.5±32.3, 324.7±17.9, 282.3±31.9, 265.9±21.3 and 232.6±23.8 at 500mg/kg bwt extract concentration.

All results of biochemical parameters for AST(U/L), ALT(U/L), ALP (U/L), Creatinine, Urea, Protein, Albumin at 500 mg/kg/ bwt show 24.98±1.10, 23.66±2.21, 25.00±5.36, 0.77±0.11*, 33.21±2.58, 6.56±0.26, and 3.08±0.14 respectively when compared with the concentration at 100- 400mg/kg bwt as a while as the controls don't show any significant alarming Level in the concentration levels.

DISCUSSION

Glucose is the simplest metabolic end-product of carbohydrate metabolism which is most readily absorbed into the porta blood from the gastro-intestinal tract following its oral ingestion (Balasubramanian, et al 2021) Therefore, several in vivo acute and chronic drug-induced hyperglycaemic models have been developed and used to investigate the hypoglycaemic effects of medicinal plants with antidiabetic potentials.

The *K. anthotheca* is a medicinal plant found in Africa, used in the treatment of several diseases including malaria, diarrhoea and skin infections. Other pharmacological activities including anti-protozoal anticancer, and neuroprotective activities have been linked to this plant that *K. anthotheca* extract exhibited significant activity against a variety of gram-positive and gram-negative bacteria (Umaru et al.,2024).

Most of the models include oral glucose loading- and nicotine-induced hyperglycaemia (AAab & OOb 2009). The research work on the stem bark of *K. anthotheca* on diabetic

induced rats showed that extracts at dose of 300mg/kg bwt - 500mg/kg bwt is capable to reduce the diabetic blood glucose level. At 500mg/kg the stem-back extract reduced the diabetic glucose level from (429.3±11.6) to a significantly non-diabetic Level of (069.2±24.6*). Since Alloxan is known to destroy pancreatic beta cells, these research findings suggest that the extracts may have extra pancreatic anti-hyperglycaemia mechanism of the secondary to their insulin secretion (Chan & Leung, 2015). Thus, studies on the phytochemical should be carried out for the exploration of the bioactive potential of the plant parts as an agent for antidiabetic.

Table 1 caused no significant alteration in the plasma creatinine urea, protein, and albumin, ALT, AST and ALP measurements of the diabetic rats compared to the control. However, the plasma creatinine measurements were significantly ($p < 0.05$) elevated in diabetic rats not treated. The result showed an observed concentration-dependent decrease in glucose levels in the treated groups with the most significant value was able to increase insulin secretion from the regenerated pancreatic beta cells. This will contribute to the discovery of novel phytochemicals that could aide in combating diabetics that is engulfing the health sector worldwide.

CONCLUSION

The present study has shown that the methanol extract of *K. anthotheca* stem-bark caused significant reductions in diabetic drug-induced hyperglycaemia in albino rats, The results highlight how crucial it is to do additional research and obtain clinical validation to fully utilize this plant's therapeutic potential. Finally, it is worth suggesting that *K. anthotheca* could be a viable option for the creation of cutting-edge remedies for the management of ulcers and bacterial infections. However, more research is needed to confirm these findings and to evaluate the potential clinical efficacy of *K. anthotheca* extracts for the treatment of ulcers.

This study concluded that *Khaya anthotheca* stem-bark extract possesses substantial anti-diabetic activities with an increase in concentration. This research will contribute to the discovery and development of bioactive compounds against hyperglycaemia that have become a menace in less developed countries, as this will offer hope for healthcare improvement and well-being of people. However, more research is needed to confirm these findings and to evaluate the potential clinical efficacy of *Khaya anthotheca* extracts for

the treatment of hyperglycaemia. Further studies are needed to discover the bioactive constituent of the plant responsible for the reported activity as well as other pharmacological activities in clinical trials.

The goal of this research is to increase our knowledge of the effectiveness of natural cures, which may provide, cheaper, safer and more long-lasting substitutes for traditional therapies. This research may provide priceless insights into traditional medicine practices and pharmaceutical development from Khaya anthotheca. This could ultimately improve healthcare outcomes and promote the discovery of new drugs derived from natural sources.

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