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Effect of methanol extract of *cocos nucifera* husk (MECH) in Alloxan-induced toxicity in Wistar male rats

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Abstract

The present study investigated the effect of Methanol extract of *Cocos nucifera* Husk (MECH) in alloxan-induced toxicity in male wistar rats**.** Thirty-six (36) male rats were randomly divided into six experimental groups (n=6). Group 1 was administered distilled water). Groups 2, 3, 4, 5and 6 were made diabetic by a single intraperitoneal dose of 150mg/kg body weight (bwt) of alloxon monohydrate. Group 2 served as diabetic non-treated, Group 3 (positive control) was treated orally with gibenclamide at 2mg/kg bwt. Groups 4, 5, and 6 were treated with MECH extract orally at doses of 62.5mg/kg, 125.0mg/kg, and 250mg/kg body weight for 28 days respectively. The fasting blood sugar (FBS) was taken on days 0, 1, 7, 14, 21, and 28. At the end of 28 days, the serum biochemical parameters were measured (assigned). MECH demonstrated a significant ($P<0.05$) dose-dependent reduction in the fasting blood sugar (FBS) of the diabetic rats as compared to the untreated control group. A decrease of 68.5%, 78.25%, and 47% respectively on day 28. In other words, the highest reduction was seen at 125mg/kg FBS. There was a significant ($P<0.05$) increase in levels of Alanine aminotransferase (ALT), Alkaline phosphatase (ALP) and urea in the alloxan-intoxicated rat when compared with normal control. MECH reduced the level of ALT, ALP, and urea compared with the diabetic control. These findings showed that MECH has significant antidiabetic activity where comparable with glibenclamide. It also may protect against DM-induced hepatorenal injuries in rats.

Keywords: Diabetic; Alloxan monohydrate; Alkaline phosphatase; Alanine aminotransferase

1. Introduction

Diabetes Mellitus (DM) is a group of metabolic disorders of carbohydrate metabolism in which glucose is both underutilized as an energy source and overproduced due to inappropriate gluconeogenesis and glycogenolysis, resulting in hyperglycemia [31].

Diabetes imposes an economic burden in the world, including Catastrophic spending in controlling the disease at the individual level [38]. Demographic Socio-culture and Economic Transitions are driving the increase in the risk and prevalence of diabetes. DM imposes a heavy financial strain on healthcare systems worldwide. It is estimated that 537 million (10.5%) individuals (those aged 20-79 years) worldwide are currently managing the disease. In 2021, the IDF approximated that there were 537 million individuals living with diabetes, making up 10.5% of the global population [17].

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The World Health Organization (WHO) recommends the use of medicinal plants in food items for the treatment of DM [44]. At least four billion people living in developing countries use medicinal plants to treat metabolic diseases such as diabetes [12,10].

The Disease is majorly classified into two types: Type 1 Diabetes (TID) and Type 2 Diabetes (T2D) [8]. However, other forms of the disease do exist. For example, gestational Diabetes (GDM), etc. [1]. The ultimate goal of DM treatment is to achieve and maintain normoglycemia [8]. Traditional plant-based remedies have been used to manage DM and some of these plants have been found to have potential antidiabetic properties [39]. One of such plants is *Cocos nucifera* [13]. Antidiabetic properties of the different part of *cocos nucifera* such as the water, oil, and fruit juice have been reported [26, 27]. The literature revealed *Cocos nucifera* husk to have analgesic [32], antimicrobial [18], antiviral [9], antiparasitic [11] antimalaria [3] and hepatorenal protective [14] activities/properties, etc. Traditionally in Nigeria, *C. nucifera* has been used for the treatment of hypertension and diabetes [15, 34]. As a result of its many traditional medicinal uses, *C. nucifera* husk is frequently mentioned by traditional folkloric medicine practitioners in Benue state. Due to ever-increasing prevalence rates of DM and the need to search for new, cost-effective, safe, and readily available alternatives. Thus, more investigations of medicinal plant products have been recommended. The present hypoglycaemic agent used in the treatment of DM, from available literature did not show enough scientific validation for *C. nucifera* husk traditional use. This study was therefore designed to evaluate the anti-diabetic, Liver, and kidney function of *C. nucifera* husk Extracts in diabetic rats.

1.1. Aim of the study

- To determine the Phytochemical composition of MECH.
- To determine the effect of MECH on the biochemical parameters of alloxan-induced hyperglycaemic rats.

2. Materials and methods

2.1. Plant Collection, identification, and Preparation

Two (2kg) of the Husk of *C. nucifera* husk were collected in Makurdi, Benue State, North Central Nigeria, and identified by MR Teny Waya, a plant taxonomist with a specimen number UAM/FHM/205 deposited at the Forestry herbarium at Joseph Sarwuan Tarka University, Makurdi.

The 100 g of the pulverized Husk materials were pulverized into coarse powder and extracted by cold maceration in 80% aqueous methanol and allowed to stand for 72 hours. The mixture was filtered into a flat-bottomed flask using a muslin cloth. Further filtration was achieved with Whatman No. 1 filter paper to remove the fine and suspended residue. The filtrate was concentrated with a Rotary evaporator and the extract obtained was dried and the percentage yield was calculated.

2.2. Phytochemical analysis

Phytochemical analysis of MECH powder was done to determine the presence of secondary metabolites which include saponins, tannins, alkaloids, flavonoids, oxalate, and cyanogenic glycosides. The analysis of these phytoconstituents was carried out quantitatively using standard procedures.

2.2.1. Alkaloids Determination

The Harborne (1973) [16] Method was used. Five (5) mg of the extract was weighed into a 250 mL beaker and 80 mL of 10 % acetic acid in ethanol was added and covered and allowed to stand for 4 hours. This was filtered and the extract was concentrated on a water bath to one quarter of the original volume. Concentrated Ammonium hydroxide was added dropwise to the extract until precipitation was complete. The whole solution was allowed to settle, and the precipitate was collected and washed with dilute ammonium hydroxide and then filtered. The residue was alkaloid which was dried and weighed.

2.2.2. Flavonoid Determination

The method of Boham and Kopcal-Abyazam (1984) [41] was used. Ten grammes (10 g) of the plant extract was extracted repeated with 100 mL of 80 % aqueous methanol at room temperature. The whole solution was filtered through Whatman filter paper No 42 (125 mm). The filtrate was later transferred into a crucible and evaporated into dryness over a water bath and weighed to a constant weight.

2.2.3. Oxalate Determination

The titration method of Dey and Underwood (1996) [42] was used to determine the oxalate content. One gram (1 g) of the extract was weighed into a 100 mL conical flask where 75 mL of 3N H_2SO_4 was added and stirred for 1 hour. It was then filtered using Whatman No 1 filter paper.

From the filtrate, 25 mL was taken and titrated while hot (80 – 90^{o}C) against 0.1N KMnO4 solution, until a faint pink colour persisted for at least 30 seconds.

2.3. Determination of Cyanogenic Glycoside

The extraction method of Wang as described by Onwuka (2005) [44] was used. A portion (5 g) of the powdered plant material was made into the paste and the paste was dissolved into 50 mL distilled water. The extract was filtered, and the filtrate was used for cyanide determination. To 1 mL of sample filtrate, 4 mL of alkaline picrate was added, and absorbance was recorded at 550 nm and cyanide content was extrapolated from a cyanide standard curve.

2.3.1. Saponin Determination

The gravimetric method of AOAC (2006) [43] employing the use of a Soxhlet extractor and two different organic solvents were used. Five grams (5 g) of dry ground plant material was weighed into a thimble and transferred into the Soxhlet extractor chamber fitted with a condenser and a flat bottom flask. Some quantity of acetone, enough to cause reflux was poured into the flask. The sample was exhaustively extracted of its lipid and interfering pigments for 3 hours by heating the flask on a hot plate and the solvent distilled off. This was the first extraction. For the second extraction, a pre-weighed round bottom flask was fitted into the Soxhlet apparatus (bearing the sample containing thimble) and methanol was poured into the flask. The methanol was enough to cause a reflux. The saponin was then exhaustively extracted for 3 hours by heating the flask on a hot plate after which the solvent was distilled off. The flask was re-weighed. The difference between the final and initial weights of the flask represented the weight of saponin extracted.

2.3.2. Determination of Tannin

The Folin-Denis Spectrophotometric method was used. The method was described by Pearson (1976) [45]. A measured weight of the extract (1.0 g) was dispersed in 10 mL distilled H_2O and agitated. This was left to stand for 30 minutes at room temperature being shaken every 5 minutes. At the end of the 30 minutes, it was centrifuged, and the extract gotten 2.5 mL of the supernatant (extract) was dispersed into a 50 mL volumetric flask. Similarly, 2.5 mL of the standard tannic acid solution was dispersed into a separate 50 mL flask. A 1.0 mL Folin-Denis reagent was measured into each flask followed by 2.5 mL of saturated Na_2CO_3 solution. The mixture was diluted to mark in the flask (50 mL) and incubated for 90 minutes at room temperature. The absorbance was measured at 725 nm in a Genway® model 6000 electronic Spectrophotometer.

2.4. Study Design

Thirty adult male Wistar rats having body weights of 100-118g, were used for this study. They were procured as litters at the age of 6 weeks from the College of Medicine, Benue State University, Makurdi. Nigeria. The rats were kept in plastic cages and acclimatized for 4 weeks in the Department of Veterinary Physiology and Biochemistry Research Laboratory, Jostum. The rats were kept under normal environmental conditions of 12 h dark and 12 h light cycle, with an average temperature of 29°C. They were permitted to acclimatize for seven (7) days before the initiation of the treatment and provided with standard animal feed and clean water ad libitum.

The experimental protocol was carried out following the National Institute of Health's guidelines for the care and welfare of research animals [2].

Thirty-six rats were randomly divided into six groups of six (n=6) animals per group with their weight ranging from 120-150g.

- Group 1were administered distilled water only.
- Group 2 was administered a single dose of 150 mg/kg alloxan monohydrate (150 mg/kg) intraperitoneally (IP)
- Group 3 was administered Alloxan monohydrate and gilbenclemide
- Group 4 rats were administered Alloxan monohydrate and MECH 62.5 mg/kg
- Group5 rats were administered Alloxan monohydrate and MECH 125 mg/kg
- Group 6 rate were administered Alloxan monohydrate and MECH 250 mg/kg

The rats were observed until diabetes was established by the presence of fasting blood sugar (FBS) 7.0 mMol. FBS was assessed using ACCU check advantage 11(Roche Diagnosis, New Jersey, USA).

On the last day of the experiment (Day 28), the rats were humanely sacrificed using cervical dislocation, and blood samples were collected via the Retrobulbar puncture into a plain blood sample bottle for serum biochemistry activities.

2.5. Preparation of serum samples

Another portion of the blood samples were collected in plain bottles and allowed to stand for 3 h to confirm complete clotting. The clotted blood samples were centrifuged at 3000 rpm for 10 min and the clear sera samples were aspirated off and stored frozen at –40 °C for biochemical analyses.

2.6. Biochemical analysis

The biochemical parameters include serum aspartate aminotransferase and alanine aminotransferase, alkaline phosphatase, total proteins, albumin, creatinine, they were analysed using Cobas C311 Roche Chemistry Analyzer (Hoffmann) using the manufacturer's manual.

2.7. Ethical Clearance

Ethical approval was sort from the research and ethics committee of the college of veterinary medicine, Joseph Sarwuan Tarka University, Makurdi, Benue State, Nigeria.

2.8. Statistical analysis

All results are expressed as mean ± standard deviation (Mean ± SD). The data were analyzed by one-way analysis of variance (ANOVA) with Graph pad prism version 8.01

3. Results

3.1. *Quantitative Phytochemical Composition of MECH*

The quantitative phytochemical composition of MECH is presented in Table 1. The result of the phytochemical screening revealed the extract to be high in saponin and flavonoid with a percent (%) concentration of 12.4 and 2.1 respectively and least in oxalate with 0.14%.

Table 1 Quantitative Result of Phytochemical Screening Metabolite of MECH.

S/No.	Phytochemicals	Amount (%)
1	Tannin	0.53
2	Cyanogenic glycoside	0.60
3	Saponin	12.41
4	Alkaloid	1.97
5	Flavonoid	2.10
6	Oxalate	0.14

3.2. Effect of Administration of MECH on Alloxan-Induced Diabetic Rats for 28 days

3.2.1. Fasting Blood Sugar (FBS) Levels

The FBS levels of all rats were taken prior to exposure to alloxan on Day 0 (pre-experimental values), 1, 7, 14, 21, and 28 respectively. The blood glucose data is presented in Table 7. The FBS of pre-experimental animals showed significantly higher ($p<0.05$) values in the untreated control group (i.e., normal control) compared to the rest of the treated groups. However, on Day 1 of DM induction, animals in all the inducted groups showed significantly increased ($p<0.05$) FBS with values of 463.50±78.81, 405.83±63.70, 422.33±88.30, 257.00±53.10 and 233.40±59.10 mg/dL for groups 2, 3, 4, 5 and 6 respectively as compared with untreated control with FBS of 75.33±15.60 mg/dL. After 7 days post-treatment to the end of the treatment protocol, animals treated with MECH at all doses showed a significantly

decreased FBS values compared with the normal control animals except animals in group 6 (MECH at 250 mg/kg bwt, 120.73±20.10 mg/dL) that still showed a significantly higher FBS compared with normal control animals with 67.20±3.14 mg/dL

Table 2 Effect of MECH on Mean FBS in Alloxan-Induced Diabetic Rats

Groups	FBS (mg/dL)					
	Day 0 (pre-exp.)	Day 1	Day 7	Day 14	Day 21	Day 28
1 Normal Control (dH_2O)	99.50±3.02[a]	75.33±15.60[a]	53.00±0.97[a]	64.00±4.48[a]	60.20±5.89[a]	67.20±3.14[a]
2 $DM_{alloxan}$ only	69.75±5.66[b]	463.50±78.81[b]	281.50±43.01[b]	392.50±19.20[b]	281.50±30.3[b]	338.50±42.4[b]
3 $DM_{alloxan}$ + Gilb.	71.50±3.76[b]	405.83±63.70[b]	72.75±4.11[a]	69.50±6.03[a]	95.50±12.3[a]	74.50±11.8[a]
4 $DM_{alloxan}$ + MECH (62.5)	81.67±5.63[b]	422.33±88.30[b]	64.00±13.70[a]	78.75±3.66[a]	63.50±8.50[a]	83.75±14.3[a]
5 $DM_{alloxan}$ + MECH (125)	80.50±5.03[b]	257.00±53.10[c]	70.17±7.00[a]	87.00±5.77[a]	91.17±14.0[a]	72.33±4.67[a]
6 $DM_{alloxan}$ + MECH (250)	69.33±3.23[b]	233.40±59.10[c]	76.20±16.73[a]	100.00±15.9[a]	109.33±67.8[a]	120.73±20.10[c]

Values are mean±SEM, n = 6. Values with different alphabet superscript on the same column are significant at $p<0.05$. dH2O = distilled water, FBS = Fasting Blood Sugar, pre-exp. = pre-experiment day, DMalloxan = DM induced with alloxan, Gilb. = Gilbenclamide, dL = deciliter, mg = milligram, MECH (62.5), MECH (125), and MECH (250) = Methanolic extract of Cocos nucifera husk treated at 62.5, 125, and 250 mg/kg bwt per os respectively.

3.3. The Effect of MECH on Biochemical Parameters of Alloxan-Induced Diabetic Rats

Table 3 Effects of MECH on Biochemical Parameters of Alloxan-Induced Diabetic Rats

Groups	ALT (u/L)	ALP (u/L)	AST (u/L)	TProt. (g/dL)	Creat. (mg/dL)	Urea (mg/dL)
Normal Control(dH_2O)	60.08±5.94[a]	160.80±33.44[a]	201.52±15.62	77.80±1.98	49.20±3.06	5.88±0.16[a]
$DM_{alloxan}$ only	106.35±26.45[b]	531.00±77.78[b]	216.25±33.55	53.00±3.00	54.00±7.00	10.30±0.70[b]
$DM_{alloxan}$+Gilb.	59.57±13.89[a]	131.12±51.10[a]	148.34±47.10	58.18±14.43	42.50±8.95	5.44±1.43[a]
$DM_{alloxan}$+MECH(62.5)	67.20±14.52	249.67±37.25[a]	186.33±7.99	73.67±2.03	52.00±5.20	5.93±0.43[a]
$DM_{alloxan}$+MECH(125)	91.25±8.51	449.25±77.33[b]	275.93±21.21	70.25±3.66	54.00±2.48	5.13±0.17[a]
$DM_{alloxan}$+MECH(250)	58.97±4.12[b]	481.00±68.91[b]	183.97±6.19	65.33±8.37	50.67±2.91	6.63±1.16[a]

Values are mean±SEM, n = 6. Values with different alphabet superscript on the same column are significant at $p<0.05$. dH_2O = distilled water, $DM_{alloxan}$ = DM induced with alloxan, Gilb. = Gilbenclamide, dL = deciliter, mg = milligram, MECH (62.5), MECH (125) and MECH (250) = Methanolic extract of *Cocos nucifera* husk treated at 62.5,125, and 250 mg/kg bwt *per os* respectively. ALT=Alanine aminotransferase, AST=Aspartate amino transferase, ALP=Alkaline phosphatase, Tprot = Total protein, Creat = Creatinine,

The results of the effect of MECH on biochemical parameters are presented in Table 10. The result indicated that there was a significant increase ($p<0.05$) in the mean ALT values of the DM-induced but un-treatment animals (Group 2, 106.35±26.45 u/L) relative to the non-induced and untreated control (Group 1, 60.08±5.94 u/L) and the groups administered MECH at 250 mg/kg bwt with a mean value of 58.97±4.12 u/L. Similarly, there was a significant increase ($p<0.05$) in mean urea values in the DM-induced group without treatment (10.30±0.70 mg/dL) compared to the rest of the treatment groups and normal control with means values of 5.88±0.16, 5.44±1.43, 5.93±0.43, 5.13±.07 and 6.63±1.16 mg/dL for Groups 1, 3, 4, 5 and 6 respectively. Analysis of mean ALP values showed that there was a significant increase

($p<0.05$) in group 2 (DM-induced with treatment) (531.00±77.78 u/L) and groups 5 and 6 induced and treated with MECH at 125 (449.25±77.33 u/L) and 250 mg/kg bwt (481.00±68.91 u/L), compared to normal control animals (160.80±33.44 u/L) and groups induced but treated with Gilbenclamide (131.12±51.10 u/L) and MECH at 62.5 mg/kg bwt (249.67±37.25 u/L) respectively.

4. Discussion

Globally, diabetes has become a great health worry and its prevalence is ever-increasing as the majority consume diets that are predominantly carbohydrates, especially in developing countries [4]. Synthetic oral hypoglycemic drugs used currently are unable to cure this condition and are bedeviled with some side effects, hence the search for alternative and or supplementary medication for diabetes [23]. Numerous studies have demonstrated that a variety of plant extracts effectively lower the glucose level in alloxan-induced diabetic animals to uphold the antidiabetic use of such plants in traditional medicine [37, 22]. These plants are thought to contain some bioactive principles which may be responsible for their anti-diabetic properties. Although several medicinal plants have gained importance for the treatment of DM, many remain to be scientifically investigated [36].

One of the many in-vivo models in laboratory animals is alloxan-induced diabetes. Alloxan induces DM by selectively inhibiting glucose-induced insulin secretion via diabetes of specific glucokinase in the beta cells of the pancreas resulting in insulin-dependent diabetes. It also can induce the formation of free radicals (reactive oxygen species) producing selective necrosis of the pancreatic β cells which are involved in the synthesis, storage, and release of insulin, a peptide hormone that regulates carbohydrate, protein, and lipid metabolism [23, 4].

Plants with antioxidant properties have been known to have hypoglycemic activity in alloxan-induced diabetes due to their ability to subdue the reactive oxygen species (ROS), formation that destroys pancreatic β cells [22]. The quantitative Phytochemical analysis of MECH revealed the presence of flavonoids, tannins, and saponins which are good antioxidants. Table 1 studies have shown that saponins are potential antidiabetic agents [21]. It has been reported that fenugreek saponins an anti-hyperglycemic function by increasing plasma insulin levels [30], restoring insulin response [40] and improving Glucose metabolism [20]. phytochemical analysis of MECH revealed the presence of Flavonoids and tannins which are good antioxidants. (Table 1) Studies have shown that flavonoids such as anthocyanins have hypoglycaemic properties and they exert this effect by lowering the fasting blood sugar levels, which are key indicators of type 2 diabetes. The increase in blood sugar level seen in alloxan-induced diabetes is triphasic in nature [28], this may be the reason for the rising FBS levels seen towards the end of the experiment in the diabetes-induced but untreated group and the groups treated with MECH at 250 mg/kg bw (Table 7). That notwithstanding, MECH appears to have a more potent hypoglycemic effect at lower doses. This may be indicative of the presence of some phytoconstituent that may be interfering with insulin secretion at higher doses.

Serum liver enzymes are good markers of liver injury and are often used to assess the effect of drugs, phytochemical constituents, and xenobiotics [35]. An increase in the serum activity of these enzymes often points to necrosis of hepatocytes and or cholestasis, with elevated serum levels of ALT being more specific for liver damage [35]. In this study allowance induced DM elicited significant increases in ALT ALP and serum urea (Table 10) which is indicative of the effect of allowance on hepatocytes and nephrons and agrees with the work of [24]. In diabetic conditions, the liver becomes insulin resistant, leading to increased glucose production and elevated blood glucose levels, this effect can be attributed to the generation of ROS induced by alloxan administration which was ameliorated by treatment with MECH resulting in decrease serum levels of these enzymes and urea, owing possibly to the antioxidant effect of MECH in diabetic rats. The decrease in total protein in alloxan-induced DM rats but not treated further buttresses the deleterious effect of alloxan on liver synthetic function. This finding agrees with the finding of [19, 5]. The decrease in protein in diabetic rats is one of the clear signs of diabetes (type I and type II) which is a result of inadequate utilization of amino acid in peripheral tissues, and decreased energy generation of adenosine triphosphate (ATP) resulting in low synthesis of protein by the liver. Increase in total protein stem from increases in the albumin and globulin concentration indicated the effectiveness of dose and decrease in glucose concentration, which ultimately increases the protein production. In this study, treatment of diabetic rats with MECH at all doses significantly increases serum total protein agreeing with a previous report [30].

Creatinine and urea are waste products in the blood that are commonly measured to assess kidney function, particularly in individuals with diabetes mellitus [29], invariably they can also be used as useful prognostic markers of renal damage in diabetic patients [6]. Serum Creatinine is the metabolic product of muscle protein while urea is a primary product of protein metabolism and its levels reflect kidney function [20] urea measurement is part of routine diagnostic workups for diabetes, especially in patients with suspected kidney disease [7]. Hyperglycemia is one of the major causes of renal

damage [33]. An increase in blood urea level is seen when there is damage to the kidney increase in blood urea level in the presence of high blood sugar levels in diabetic patients indicates damage to the kidney.

Creatinine value in diabetic rats could not be controlled by MECH at all doses. Overall, our study demonstrated that MECH has antidiabetic potential and could be used for the management of diabetes.

5. Conclusion

Alloxan-induced diabetes is characterized by multiphasic blood glucose response in rats. There was frequent urination and increased glucose levels in comparison to normal control, there was also an increase in ALT, ALP, and serum urea. But after treatment with MECH at varying doses as well as gibenclamide for 28 days, all the parameters became normal, when compared to the diabetic group (untreated). The results of our study prove that MECH is effective against diabetes. In conclusion, MECH showed an ameliorative effect about diabetic complications.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest among all the authors.

Statement of ethical approval

Ethical approval was sought from the research and Ethics committee of the college of Veterinary Medicine, Joseph Sarwuan Tarka University, Makurdi, Benue State, Nigeria.

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