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Effect of *Mangifera Indica* Root Methanolic Extract on Streptozotocin Induced Diabetic Albino Rats

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Abstract

The growing prevalence of diabetes in both developed and developing nations has prompted scientists to intensify their research efforts in identifying potent therapeutic compounds from natural sources. These compounds are aimed at more effectively treating and managing diabetes. The aim of this research is to determine the potentials of Mangifera Indica on induced hyperglycemic rats. The materials and methods : The roots was cut into small pieces, air-dried and 100g of the root powdered soaked , extracted in rotary evaporator, fort albino rats is used. Diabetes was induced in rats by injecting them intraperitoneally (i.p.) with freshly prepared streptozotocin (STZ) dissolved in citrate buffer (0.1 M pH 4.5) after an overnight fast and Hyperglycemia confirmed. Thirty albino rats was randomly divided into six groups, each consisting of five rats: group 1-6. Group 1-3 control groups, NC (Normal non-treated control), DM (Negative control rats), PC (Positive Control) group 4-6 (Mangifera indica treated diabetic rats). The NC and DM (control groups) was given distilled water, while the MI and DM + MI (experimental groups) will

receive Mangifera indica extract at a dose of 100, 200 and 400 mg/kg/b.wt. Results: Day one blood glucose levels was lowered significantly ($p < 0.05$). Day three treatments with standard drug and 100 mg/kg body weight extract lowered blood glucose significantly ($p < 0.05$) close to normal after induction with alloxan. The results of selected liver test indicates that AST decreased significantly, ALT increased significantly, ALP increased significantly, TP decreased significantly, GLB decreased significantly, TB increased significantly, DB increased significantly, INDB increased significantly. The results of kidney function test show that urea increased significantly, no significant difference shown in creatinine, potassium level were raised significantly, chloride and carbon dioxide were elevated significantly.

Keywords: Hyperglycaemic, Activity, Mangifera Indica, Streptozotocin, Albino Rats

INTRODUCTION

The growing prevalence of diabetes in both developed and developing nations has prompted scientists to intensify their research efforts in identifying potent therapeutic compounds from natural sources. These compounds are aimed at more effectively treating and managing diabetes (Gupta et al., 2012). There is a worldwide upsurge of diabetes, attributed to the rapid rise in weight, obesity, and sedentary lifestyles (Zimmet, 2017). Diabetes is a chronic ailment affecting the blood glucose system, marked by a deficiency in insulin production by pancreatic beta cells, leading to sustained high levels of blood sugar. This condition is linked to enduring complications such as retinopathy, nephropathy, neuropathy, and cardiovascular issues (Nellaiappan et al., 2022). Hyperglycemia-induced oxidative stress is associated with the onset and advancement of diabetes and, if left un addressed, can result in severe complications (Matough et al., 2012). Diabetes is anticipated to rank as the seventh primary cause of global mortality by 2030, with projected deaths from diabetes increasing by over 50% in the next decade (Omodanisi et al., 2017).

Traditional medicinal plants have historically played a significant role in the development of novel drug therapies. Research conducted on medicinal plants has served the dual purposes of bringing up new therapeutic agents and providing useful leads for studies directed towards the synthesis of drugs based on the chemical structures of natural products (Lautie et al., 2020). Modern pharmaceutical industries still rely to some extent on the bioactive principle, obtained from plants. Some of these plants include Chromolaena odorata,

Nauclea latifolia, Lawsonia albalam., Morinda lucida, and Tithonia diversifolia (Afolayan et al., 2022).

Mango (Mangifera indica L.) is considered one of the main tropical fruits in the world believed to have originated in Asia (Hirano et al., 2010). It has been reported that China, India, Brazil, Nigeria, Pakistan, Mexico, Thailand, and the Philippines are well-known for mango cultivation with India being the highest mango-cultivating country. World production of mango is approximately 42 million tons per year which is second only to banana production. There are about 1000 mango varieties grown all over the world (Torres-Leon et al., 2016). Mango is known by various names around the world, for example, Manja in Arabic, Mannko in Greek, Am or Ambi in Hindi, Amba in Sinhala, Mangue in French, Mango in Finnish, Mango in Dutch, Mangue in German, Manggu ´ oin ˇ in Chinese, and Mampalam in Tamil (Ghuniyal, 2015).

Despite the common use of mango fruit as a food item, various parts of mango trees have also been used for medical purposes since ancient times, mostly in Southeast Asian and African countries. Various parts of the plant are used as a dentifrice, antiseptic, astringent, diaphoretic, stomachic, vermifuge, tonic, laxative and diuretic and to treat diarrhoea, dysentery, anaemia, asthma, bronchitis, cough, hypertension, insomnia, rheumatism, toothache, leucorrhoea, haemorrhage and piles. All parts are used to treat abscesses, broken horns, rabid dog or jackal bites, tumours, snakebites, stings, datura poisoning, heat stroke, miscarriage, anthrax, blisters, wounds in the mouth, tympanitis, colic, diarrhoea, glossitis, indigestion, bacillosis, bloody dysentery, liver disorders, excessive urination, tetanus and asthma (Abu-Rahma et al., 2018).

It was reported that the plant and its parts were found to have numerous potential such as;

Gastroprotective Effects

Peptic ulcers are mainly present in the lining of the stomach or the duodenum. Nonsteroidal anti-inflammatory drugs, mental or physical stress, alcohol, diet, lifestyle, and antibiotics are considered as main causes of peptic ulcers (Stewart and Ackroyd, 2011). Peptic ulcers are usually treated with proton pump inhibitors that reduce the secretion of gastric HCl. As peptic ulcer cases are rising at an alarming rate worldwide, it is necessary to discover novel methods or drugs that can effectively reduce peptic ulcers. Assessment of gastroprotective effects of different extracts of M. indica has been carried out. A study conducted by Lima et al. (2006) found that a decoction prepared from M. indica flowers

can significantly increase gastroprotective properties in an experimental rat model by reducing gastric juice volume and acidity. Furthermore, Severi et al. (2009) have shown that a decoction prepared from leaves of M. indica reduces gastric lesions induced by HCl, ethanol, and nonsteroidal anti-inflammatory drugs in experimental rat models. The antiulcer potential of ethanol and petroleum ether extracts prepared from mango leaves has also been reported by Neelima et al. (2012).

Akindele et al. (2012) who assessed gastroprotective effects of a drug formulation (DAS-77) which comprises M. indica bark and papaya roots showed a significant reduction of gastric ulcers after feeding with DAS-77 in rat models. Antiulcer activity of an ethanolic extract of mango kernels in combination with vitamin C, ZnSO4, and menadione in pylorus ligation and ethanol-induced ulcers in rat models was evaluated by Nethravathi et al. (2015). Considerable reduction in gastric volume, ulcer score and index, and total acid output was observed after administration of ethanolic extract and the above drug combinations.

Anti-Inflammatory Effects

Several naturally found polyphenols are reported to possess anti-inflammatory effects via inhibition of nuclear factor kappa-B (NF-κB). However, the anti-inflammatory activities of these compounds depend on their chemical structures and their cellular targets. Production of a large number of proinflammatory cytokines (IL-1, 2 and 6 and TNF) increases the expression of enzymes such as COX-2 and iNOS which are associated with anti-inflammations. Ulcerative colitis and inflammatory bowel disease are considered as main diseases that occur due to chronic inflammation (Itzkowitz and Yio, 2004). Several studies have shown that mango extracts can exert anti-inflammatory effects in experimental models of ulcerative colitis.

In a study, treatment with a mango beverage prepared from fruit (Mexican variety) which consists of polyphenols and vitamins has caused attenuation of colitis symptoms by expressing the PI3K/AKT/mTOR pathway (Kim et al., 2016). Another study conducted by the same authors showed that the same mango polyphenols-rich beverage can inhibit the IGF1R/AKT/mTOR pathway in ulcerative colitis (Kim et al., 2016). In another study, aqueous extract of stem-bark extract from M. indica rich in polyphenols and flavonoids was found to attenuate colitis symptoms in a model of colitis (Marquez et al., 2010). Attenuation of symptoms was accompanied by a reduction in COX-2, TNFR-2, TNF-α,

and iNOS levels in colonic tissue. Gout is considered one of the most common causes of inflammatory arthritis. The deposition of monosodium urate crystals on local tissue and joints is the major clinical manifestation of gout. Antigouty arthritis effects of ethanol extract from M. indica leaves have been studied by Jiang et al. (2012). Oral administration of ethanol extract from M. indica leaves has caused a reduction in IL-1β and TNF-α mRNA levels and ankle swelling in a rat with gouty arthritis induced by monosodium urate (Jiang et al., 2012).

Neuroprotective Effects

Neuroprotective efficacy of mangiferin in doxorubicin (DOX)-induced rats has been studied by Siswanto et al., (2016). Brain damage in male Sprague-Dawley rats has been induced by doxorubicin, and mangiferin has been given to brain damage-induced rats for 7 weeks. Results of this study have shown that mangiferin can effectively reverse the brain damage induced by doxorubicin. Cognitive enhancing effects and improvement in memory impairment by M. indica fruit pulp extract (ethanol) were studied by Wattanathorn et al., (2014). To determine cognitive enhancing effects and improvement in memory impairment, male Wistar rats have been administered the neurotoxin AF64A and given the fruit peel extract. Results of the study have shown increased cholinergic neuron density and decreased oxidative stress rates, which illustrates possible cognitive-enhancing effects of M. indica fruit pulp. Neuroprotective activities of methanol and aqueous extracts of M. indica leaf have been studied by Kawpoomhae et al., (2010).

Neuroprotective effects of methanol and aqueous extracts were evaluated by determining the protection of neuroblastoma cells from H2O2-induced oxidative damage and results showed that methanol extract and aqueous extract can effectively protect H2O2-induced neuroblastoma cells from oxidative damage. The liver, a vital organ in the human body, mainly regulates the metabolism and detoxification of toxic substances (Marchesini et al., 2001). It plays an important role by removing reactive oxygen species (ROS) and helps maintain oxidative balance. Several chemical substances that cause hepatotoxicity by inducing oxidative damage and lipid peroxidation have been identified (James et al., 2003).

Hepatoprotective Effects

Hepatotoxicity is currently treated with drugs that can activate the p450 enzyme mechanism either by stopping or inducing the metabolic activity of enzymes (Yan and Caldwell, 2001). Investigation of phytochemicals with hepatoprotective effects and their

mechanism of action has gained much attention. Many authors have investigated the hepatoprotective effects of certain plant extracts/pure compounds including M. indica. Ebeid et al. (2015) have demonstrated hepatoprotective effects of an aqueous extract of leaves of an M. indica variety found in Egypt where they found that the aqueous extract successfully inhibited CCl4-induced hepatocellular toxicity in albino rats. Results were further confirmed by analyzing lipid profiles, high-density lipoprotein (HDL), and malondialdehyde (MDA) levels. An in vitro study carried out by Hiraganahalli et al. (2012) has shown that methanol/acetone extract of M. indica bark can exert hepatoprotective effects in tert-butyl hydroperoxide-induced HepG2 cells in a dose-dependent manner.

Hepatoprotective effects of lupeol and aqueous M. indica pulp extract (collected from Lucknow, India) have been studied in 7,12-Dimethylbenz[a]anthracene (DMBA)-induced Swiss albino mice. Lupeol and mango M. indica extract were found to be effective in the treatment of liver injury caused by oxidative stress (Prasad et al., 2012). Pourahmad et al. (2010) investigated the hepatoprotective effects of an aqueous extract of a mango fruit variety collected from Iran and demonstrated that the extract exerts hepatoprotective effects in cumene hydroperoxide-induced rat hepatocytes. The hepatoprotective effects of an ethanolic extract of a kernel of a Thai M. indica variety have been also reported by Nithitanakool et al. (2009). Significant hepatoprotective effects of the ethanolic extract of kernel have been reported in rats with liver injuries induced by carbon tetrachloride (CCl4).

Antitumoral Effects

Cancer is considered one of the major causes of death in the world and any practical solution to fighting this dreadful disease would be very important in public health (Siegel et al., 2017). It is the main cause of death in economically developed countries and the second leading cause of death in economically developing countries. Cancer is caused by several factors such as chemicals, radiation, tobacco, infectious microorganisms, hormones, gene mutations, and immune conditions. Though modern surgeries have considerably reduced cancer death rates, the use of radiotherapy, chemotherapy, and hormone therapy treatments cannot completely reduce the number of deaths due to cancer. Plant-based treatments have been used in traditional medicine to treat different diseases including cancer since ancient times and several in vitro and in vivo studies have already been reported in literature to validate these uses (Dillard and Bruce German, 2000).

Different organic extracts and decoctions prepared from parts of mango trees and compounds isolated from mango trees have shown anticancer effects. A recent study by Abbasi et al. (2017) demonstrated the antiproliferative effects of fruit peel and pulp of several mango varieties (Royal mango, Thai mango, Egg mango, Luzon Narcissus, Big Tainong, Keitt, Australian mango, and Small Tainong) grown in China. They showed that the acetone extracts of mango peel and pulp exerted antiproliferative effects in HepG2 cells. Another study carried out by Kim et al. (2012) has shown that the ethanolic extract of M. indica peel can induce apoptosis in human cervical adenocarcinoma HeLa cells. Apoptotic effects of the peel ethanolic extract have been studied by analyzing the expression of apoptosis-related proteins Bax, Bcl-2, Bid, and caspases (3, 8, and 9) in this study. Phytochemical investigation of peel ethanolic extract has revealed that it contains some reported anticancer compounds such as quercetin 3-O-galactoside, gallic acid, linoleic acid, alpha-tocopherol, mangiferin gallate, mangiferin, kaempferol 3-glucoside and quercetin-3-Oarabinopyranoside.

Protective effects of ethanolic extracts of mango fruit peel and flesh (a Korean variety) samples in H2O2-induced cytotoxicity in HepG2 cells have also been studied by this research group (Kim et al., 2010). A study carried out by Corrales-Bernal et al. (2014) has shown that aqueous extract of mango fruit flesh possesses antiproliferative effects in human colon adenocarcinoma cell lines (SW480) and mouse models with colorectal cancer. Antiproliferative effects of methanol extracts of peel and flesh of three mango cultivars (Kensington Pride (KP), Nam Doc Mai (NDM), and Irwin (IW)) found in Australia were studied by Taing et al. (2015). They have demonstrated that peel methanol extract of NDM can only inhibit the proliferation of MCF-7 breast cancer cells. Antitumor effects of mango polyphenols-rich fruit flesh extract in human breast cancer xenografts mice have been studied by Banerjee et al. (2015). This study has proven that mango polyphenols-rich fruit pulp extract has the potential to target the PI3K/AKT pathway in breast cancer.

Anticarcinogenic effects of a crude (methanol: acetone: water1: 1: 1) fruit peel extract of some selected mango varieties (Kent, Francis, Atkins, Ataulfo, Tommy, and Haden, found in Brazil) have been evaluated in leukaemia (Molt-4), lung (A-549), triple-negative breast (MDA-MB-231), prostate (LnCap), and colon (SW-480) cancer cells by Noratto et al. (2010). Among the studied mango varieties, two (Ataulfo and Haden) were more sensitive to SW-480 and MOLT4 cells. Moreover, apoptotic effects of Ataulfo and Haden varieties have also been studied in SW-480 cells in this study. Induction of apoptosis by aqueous

extract of mango fruit peel rich in lupeol has been carried out in testosterone-induced mouse prostate and human prostate cancer cells (LNCaP) by Prasad et al. (2007).

Antiproliferative effects of two extracts (pectinase and Soxhlet extracts) of mango flesh found in Australia have been shown in oestrogen receptor-positive (MCF-7) breast cancer cells by Wilkinson et al. (2011). Induction of oxidative stress-mediated apoptosis by ethanolic extract of M. indica seed in triple-negative breast cancer cells (MDA-MB-231) has been reported by Abdullah et al. (2015). In this study, apoptotic effects of ethanolic extract of M. indica seeds were evaluated by analyzing apoptosis-related marker proteins such as Bax, Bcl-2, cytochrome c, and caspases (3, 8, and 9). The involvement of oxidative stress markers such as reactive oxygen species (ROS), glutathione (GSH), and malondialdehyde (MDA) levels in apoptosis has also been studied. In another study carried out by Abdullah et al. (2015), the same research group reported oxidative stress-mediated apoptosis by ethanolic extract of mango seeds in oestrogen receptor-positive breast (MCF-7) cancer cells. Nguyen et al. (2016) have demonstrated the cytotoxic effects of methanol bark extract of M. indica in pancreatic cancer cells (PANC-1). The isolation of two novel cycloartanetype triterpenes, namely, mangiferolate A and mangiferolate B, has also been reported in the same study. Studies on the anticancer effects of mango leaves are limited

Statement of Problem

The rising prevalence of diabetes globally poses significant health challenges, with chronic hyperglycemia leading to severe complications and increased mortality rates. The search for effective and accessible treatments is ongoing, and natural compounds derived from medicinal plants have shown promise in offering therapeutic benefits in various diseases, including diabetes. Among these plants, mango (Mangifera indica) is known to possess a diverse array of compounds that exhibit potential biological properties. However, there is a pressing need to explore and validate the potential therapeutic effects of the methanol root extract of Mangifera indica in addressing hyperglycemia, evaluating its antibacterial properties, and determining its antioxidant capacity in streptozotocin-induced diabetic albino rats. Thus, the purpose of this work to investigate the hypoglycaemic capacity of methanol root extract of mango tree in streptozotocin-induced diabetic albino rats.

MATERIALS AND METHODS

Sample Collection

The root of Mangifera indica will be locally sourced in Wukari Local Government Area of Taraba State, Nigeria.

Extraction of Plant Material

The plant material wasextracted according to the method described by Omotayo et al., (2015). The roots was cut into small pieces, air-dried under the shade pulverized into coarse powder using a wooden pestle and mortar and stored until required for use. 100g of powdered M. indica root was taken into two different beakers. The samples was soaked with 500 ml of methanol and boiled distilled water respectively. The methanol root extract of the mango tree was concentrated to a small volume by the use of a rotary evaporator and dried at 50oC in a water bath. The extract containing the bioactive compounds was stored at - 20oC until the period of analysis.

Experimental Animals and Grouping

Forty (40) albino rats was obtained. They were acclimatized for seven days during which they were fed ad libitum with standard feed and drinking water and was housed in clean cages placed in well-ventilated housing conditions (under humid tropical conditions) throughout the experiment. All the animals receive humane care according to NAS (2011) criteria. They were randomly divided into six groups of five (5) rats.

Drug Administration

Diabetes was induced in rats by injecting them intraperitoneally (i.p.) with freshly prepared streptozotocin (STZ) dissolved in citrate buffer (0.1 M pH 4.5) after an overnight fast. A dosage of 55 mg/kg will be administered. Blood samples was collected from the rat's tail to verify the diabetic condition using a glucometer. Hyperglycemia was confirmed by a consistent glucose level (>18 mmol/L), ensuring that only diabetic rats were included in the study.

Treatment

The thirty albino rats was randomly divided into five groups, each consisting of six rats: NC (Normal non-treated control), NC + MI (Mangifera indica treated control rats), DM (diabetic rats), and DM + MI (Mangifera indica treated diabetic rats). The NC and DM (control groups) was given distilled water, while the MI and DM + MI (experimental

groups) received Mangifera indica extract at a dose of 250 mg/kg/b.wt. The extract was diluted with distilled water and administered orally using a gavage method for 6 weeks.

Anti-hyperglycemic Activity

a. In vitro α-amylase inhibitory assay

The assay was carried out following the protocol reported by Dineshkumar et al. (2010). The assay was performed in triplicate. The α-amylase inhibitory activity was determined using the formula:

$$\frac{(Ac^{+}) - (Ac^{-}) - (As - Ab)}{(Ac^{+}) - (Ac^{-})} \times 100$$

Here, Ac+, Ac−, As, and Ab represent the absorbance values at 595 nm for 100% enzyme activity (solvent with enzyme only), 0% enzyme activity (solvent without enzyme), the test sample (with enzyme), and a blank (test sample without enzyme), respectively.

b. In vitro α-glucosidase inhibitory assay

The in vitro α-glucosidase inhibitory assay was performed following the procedure described by Dineshkumar et al. (2010). and calculated using the formula:

$$\frac{(Ac^{+}) - (Ac^{-}) - (As - Ab)}{(Ac^{+}) - (Ac^{-})} \times 100$$

Here, Ac+, Ac−, As, and Ab is defined as the absorbance at 405 nm, of 100% enzyme activity (only solvent with enzyme), 0% enzyme activity (only solvent without enzyme), test sample (with enzyme), and a blank (a test sample without enzyme), respectively. The reagents used for assessing anti-hyperglycemic activity are of analytical grade. Acarbose (an anti-hyperglycemic drug) will serve as the control in evaluating anti-hyperglycemic activity.

Statistical Analysis

Data was subjected to analysis using SPSS software. The results was expressed as mean ± SD.

RESULTS

Table 1: Fasting Blood Glucose Levels

FBG	Group 1 NC (Normal control)	Group 2 DM (Negative control)	Group 3 PC (positive control)	MI and DM + MI (experimental groups Group 4,5,6.)		
				100 mg/kg extract	200 mg/kg extract	400 mg/kg extract
Day 1	5.65 ± 0.19^{a}	23.78 ± 0.30^{c}	6.23 ± 0.47^{a}	19.17 ± 0.86^{b}	29.18 ± 0.22^{d}	33.21 ± 0.49^{e}
Day 3	5.76 ± 0.21^{a}	24.73 ± 0.58^{b}	5.49 ± 0.37^{a}	5.03 ± 0.24^{a}	29.90 ± 0.32^{c}	33.69 ± 0.55^{d}
Day 7	5.74 ± 0.16^{a}	25.37 ± 1.93^{b}	5.41 ± 0.33^{a}	6.96 ± 0.17^{a}	24.90 ± 0.32^{b}	33.80 ± 0.45^{c}
Day 14	5.25 ± 0.22^{a}	27.07 ± 0.51^{c}	4.78 ± 0.18^{a}	6.56 ± 0.47^{a}	7.40 ± 0.96^{b}	9.45 ± 0.43^{b}

Results are expressed as mean ± standard deviation of group results obtained (n=5).

Means in the same row having different superscripts are statistically significant (p <0.05).

Blood glucose level

Day one blood glucose levels was lowered significantly ($p < 0.05$) close to normal on treatment with standard drug after induction, treatment with 100 mg/kg extract was able to lower blood glucose but not significantly; treatments with 200 mg/kg and 400 mg/kg body weight extract elevated blood glucose significantly ($p < 0.05$) after induction. Day three treatments with standard drug and 100 mg/kg body weight extract lowered blood glucose significantly ($p < 0.05$) close to normal after induction with alloxan, while treatments with 200 mg/kg and 400 mg/kg body weight extract elevated blood glucose significantly ($p < 0.05$) after induction. Day seven treatments with standard drug and 100 mg/kg body weight extract also lowered blood glucose significantly ($p < 0.05$) close to normal, treatment with 400 mg/kg body weight extract elevated blood glucose significantly ($p < 0.05$), while treatment with 200 mg/kg body weight extract did not have significant effect on blood glucose after induction. Day fourteen treatments with standard drug and all the extract showed significant ($p < 0.05$) blood glucose lowering activities to levels close to normal.

Table 2: Liver Function Parameters

Parameters	Group 1 (Normal control)	Group 2 (negative control)	Group 3 (positive control)	Group 4 (100 mg/kg extract)	Group 5 (200 mg/kg extract)	Group 6 (400 mg/kg extract)
AST (IU/L)	45.09 ± 4.1^{d}	11.90 ± 1.16^{a}	12.00 ± 1.11^{a}	34.53 ± 2.65^{c}	23.92 ± 0.59^{b}	26.62 ± 0.66^{b}
ALT (IU/L)	20.00 ± 0.82^{b}	18.11 ± 0.85^{b}	15.15 ± 0.24^{a}	26.38 ± 0.82^{c}	28.06 ± 0.34^{c,d}	33.17 ± 2.46^{d}
ALP (IU/L)	80.21 ± 0.88^{b}	225. 80 ± 6.24^{d}	80.69 ± 2.98^{b}	96.01 ± 1.21^{c}	81.56 ± 2.13^{b}	77.86 ± 1.90^{a}
TP (gm/dL)	14.13 ± 1.09^{d}	12.95 ± 0.75^{c}	14.42 ± 0.52^{d}	10.32 ± 0.82^{a,b}	9.76 ± 0.82^{a,b}	8.70 ± 1.16^{a}
ALB (gm/dL)	9.30 ± 0.09^{c}	8.82 ± 0.65^{c}	11. 60 ± 0.26^{d}	7.16 ± 0.29^{b}	5.40 ± 0.20^{a}	4.55 ± 0.27^{a}
GLB (gm/dL)	4.83 ± 0.19^{b,c}	4.13 ± 0.10^{b}	2.82 ± 0.36^{a}	3.16 ± 0.63^{a}	4.34 ± 0.62^{b}	4.25 ± 0.07^{b}
TB (mg/dL)	4.58 ± 0.54^{a}	4.36 ± 0.28^{a}	6.10 ± 0.35^{d}	5.06 ± 0.26^{b,c}	6.53 ± 0.46^{b}	6.88 ± 0.36^{b}
DB (mg/dL)	3.29 ± 0.24^{b}	1.46 ± 0.19^{a}	4.42 ± 0.24^{c}	3.10 ± 0.12^{b}	4.64 ± 0.45^{c,d}	5.57 ± 0.25^{d}
INDB (mg/dL)	1.29 ± 0.30^{a}	2.90 ± 0.08^{c}	1.68 ± 0.11^{b}	1.96 ± 0.14^{b}	1.89 ±0.01^{b}	1.31 ± 0.11^{a}

Results are expressed as mean ± standard deviation of group results obtained (n=5). Means in the same row having different superscripts are statistically significant (p <0.05). Legend: ALT= Alanine transaminase, AST= Aspartate transaminase, ALP= Alkaline phosphatase, TP= Total protein, ALB= Albumin, GLB= Globulin, TB= Total bilirubin, DB= Direct bilirubin, INDB= Indirect bilirubin.

Concentration of selected liver function parameters

The results of selected liver function indices showed that AST decreased significantly (p <0.05) in all the treatment groups; ALT increased significantly (p <0.05) in group 4, 5 and 6, and decreased significantly in group 3, while group 2 showed no level of significance compared to normal control; ALP increased significantly (p <0.05) in group 2 and 4, decreased significantly (p <0.05) in group 6, while group 4 and 5 showed no significance

compared to normal control. TP decreased significantly ($p < 0.05$) in all groups except group 3 which showed no level of significance; ALB decreased significantly ($p < 0.05$) in group 4, 5 and 6, increased significantly ($p < 0.05$) in group 3, while group 2 showed no level of significance; GLB decreased significantly ($p < 0.05$) in group 3 and 4, while the rest of the groups showed no significant difference. TB increased significantly ($p < 0.05$) in all the treatment groups except group 2 which showed no level of significance; DB increased significantly in group 3, 4 and 6, decreased in group 2, while group 5 showed no significant difference compared to normal control (group 1); INDB increased significantly ($p < 0.05$) in all the treatment groups except group which showed no significant difference.

Table 3: Concentration of selected kidney function parameters of male albino rats

Parameters	Group 1 (Normal control)	Group 2 (negative control)	Group 3 (positive control)	Group 4 (100 mg/kg extract)	Group 5 (200 mg/kg extract)	Group 6 (400 mg/kg extract)
Urea (mg/dL)	42.96 ± 3.36^{a}	70.03 ± 2.42^{e}	56.62 ± 1.49^{d}	47.15 ± 2.57^{b}	50.75 ± 4.52^{c}	46.72 ± 1.45^{b}
Creatinine (mg/dL)	1.35 ± 0.18^{a,b}	1.12 ± 0.07^{a}	1.50 ± 0.03^{b}	1.39 ± 0.04^{a,b}	1.04 ± 0.04^{a}	1.11 ± 0.17^{a}
Sodium (mmol/L)	10.67 ± 0.33^{a}	55.32 ± 2.91^{b}	121. 11 ± 6.23^{d}	119.92 ± 1.84^{d}	91.78 ± 4.45^{c}	55.06 ± 3.90^{b}
Potassium (mmol/L)	5.36 ± 0.30^{a}	7.87 ± 0.61^{b}	4.98 ± 0.23^{a}	7.43 ± 0.52^{b}	9.31 ± 0.21^{c}	11.32 ± 0.04^{d}
Chloride (mmol/L)	87.65 ± 5.07^{a}	126.76 ± 5.72^{e}	100.11 ± 1.80^{c}	116.90 ± 7.87^{d}	100.54 ± 2.17^{c}	94.03 ± 6.81^{b}
CO_2 (mmol/L)	48.22 ± 1.17^{a}	61.46 ± 0.82^{d}	54.82 ± 1.45^{b}	54.65 ± 1.00^{b}	52.30 ± 1.49^{b}	58.45 ± 0.51^{c}

Results are expressed as mean ± standard deviation of group results obtained (n=5).

Means in the same row having different superscripts are statistically significant ($p<0.05$).s

Concentration of selected kidney function parameters

The result of kidney function indices showed that urea increased significantly ($p < 0.05$) in all the treatment groups, except in group 4 which showed no level of significance compared to normal control; creatinine did not show significant difference in all the treatment groups compared to normal control. Sodium increased significantly ($p < 0.05$) in all the treatment groups; potassium levels were raised significantly in all the treatment

groups, except group 3 which showed no level of significance; chloride and carbon dioxide were elevated significantly in all the treatment groups compared with normal control.

DISCUSSION

Results of table 1 of blood glucose showed that administration of standard drug and 100 mg/kg body weight of Mangifera indica root methanolic extract from day one to fourteen were able to display hypoglycaemic activity against Streptozotocin Induced Diabetic to a level almost the same as normal control. Treatments with 200 mg/kg and 400mg/kg body weight of Mangifera indica root methanolic extract showed hypoglycaemic activity only in day 14 of treatment, while day 1 to day 7 treatments did not show hyperglycaemic activity. This showed that the hypoglycaemic activity of Mangifera indica root methanolic is dose dependent. The result of this study is in tandem with the report of Gondi and Prasada (2015), they reported that ethanolic extract of mango fruit peel can successfully reduce blood glucose levels in streptozotocin-induced diabetic rats. A significant decrease in fructosamine and glycated haemoglobin, which are considered status indicators of diabetes, has also been observed after treatment with the ethanolic extract of mango peel. Another study carried out by Gondi et al. (2015) with M. indica fruit peel powder showed a significant reduction of blood glucose levels and diabetes-associated complications in rats. Similar results were obtained in a study carried out with flour prepared from mango fruit pulp (Perpetuo and Salgado, 2003). Irondi et al., (2016), showed that flour supplements prepared with mango kernel effectively reduced blood glucose levels in diabetes rats. Improvement in liver function, blood glucose level, hepatic glycogen, lipid profile, and hepatic and pancreatic malonaldehyde was observed in diabetic rats supplied with flour supplements.

Results of liver function indices showed that treatments after induction of diabetes with Streptozotocin Induced Diabetic significantly lowered serum AST and ALT, treatment with standard drug did no showed significant activity against lowering effect of serum AST and ALT caused by alloxan, treatments with 100 mg/kg, 200 mg/kg and 400mg/kg body weight of *Mangifera indica* root methanolic extract were able to restore serum AST and ALT activities close to normal control; ALP activity was significantly elevated beyond normal upon induction with Streptozotocin, while treatments with standard drug, 100 mg/kg, 200 mg/kg and 400 mg/kg body weight of *Mangifera indica* root methanolic extract were able to

restore serum ALP activities significantly.. Increased serum enzyme activities indicate cellular leakage and a breakdown of the functional integrity of the liver cell membrane (Moore et al., 1985; Imo et al., 2015). Elevated blood ALP level could be due to increased hepatic synthesis of the enzyme (Gómez, et al., 2020), or due to coronary artery disease according to Johnson et al. (2006); Schoppet and Shanahan (2008), since they encourage vascular calcification via the pyrophosphate pathway. Additionally, a high blood ALP level worsens the prognosis for those with coronary artery disease and raises the chance of death (Xiao et al., 2013; Wannamethee et al., 2013). Result of ALT and AST is in tandem with the report of Omotayo et al. (2015) which reported lowering activities of AST and ALT in paracetamol induced oxidative stress rats treated with stem bark extract of Mangifera indica.

Induction of diabetes causes lowering of serum total protein and albumin. Only treatment with standard drug was able to restore serum total protein and albumin almost same to normal, while treatment with all the doses of the extracts did not restore serum total protein and albumin levels. Serum globulin was not affected by treatment with treatments with 200 mg/kg and 400 mg/kg body weight of Mangifera indica root methanolic extract, while treatments with standard drug and 100 mg/kg of Mangifera indica root methanolic extract significantly lowered serum globulin. Total bilirubin was not affected by induction, while all treatment groups significantly elevate total bilirubin; direct bilirubin was significantly lowered upon induction, while treatments with all the doses of the extract and standard drug were able to restore serum levels of direct bilirubin ≥ normal; indirect bilirubin was significantly elevated upon induction, while treatments with standard drug and all the doses of extract were able to restore serum indirect bilirubin. The low levels of serum indirect bilirubin in all the treatment groups, suggests that bile is been expelled properly by the liver.

Results of kidney function parameters showed treatments with standard drug and all the doses of the extract were able to counteract the elevated effect of alloxan in serum urea level by restoring the serum urea levels significantly. Levels of serum creatinine in group all the groups were not affected. Because the kidney is in charge of filtering urea and creatinine out of the blood, urea and creatinine are frequently employ as indicators of renal function (Iseghohi and Orhue, 2017). A high concentration of these metabolites in the serum is a sign of renal impairment. The increased in sodium concentration in all the treatment groups may result to hypernatremia. Hypernatremia can be caused by a variety of

conditions, such as renal illness, inadequate hydration, and water loss via diarrhoea and/or vomiting (walker et al., 1990). Potassium was elevated in all the treatments groups except treatment with standard drug. Serum chloride and carbon dioxide levels were significantly elevated in all the treatment groups, this suggests that the extract did not exert electrolyte lowering activity. High levels of electrolytes in the blood may result to high blood pressure which may in turn increase the risk of cardiovascular diseases

CONCLUSION

Methanolic root extract of *Mangifera indica* has shown a great hypoglycaemic activity at lower dose (100 mg/kg body weight), at higher dosage it only showed mild to moderate hypoglycaemic activity. Hepatoprotective and nephroprotective activities were also exhibited by the methanolic root extracts of *Mangifera indica*. These hypoglycaemic, hepatoprotective and nephroprotective activities displayed by methanolic root extract of *Mangifera indica* supports it usage as a potential antidiabetic, hepatoprotective and nephroprotective agent.

Recommendations

Individual active ingredients responsible for the hypoglycaemic, hepatoprotective and nephroprotective activities displayed the methanolic root extract of Mangifera indica need to be isolated and characterized and the mechanism and mode of action of each isolated ingredient need to be studied.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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