



Journal of
**Pharmacology and
Toxicology**

ISSN 1816-496X



Academic
Journals Inc.

www.academicjournals.com

Hypoglycemic Effect, Biochemical and Histological Changes of *Spondias mombin* Linn. and *Parinari polyandra* Benth. Seeds Ethanolic Extracts in Alloxan-induced Diabetic Rats

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ABSTRACT

The aim of this study was to evaluate the individual and synergistic hypoglycaemic and biochemical effects of the ethanolic extracts of seeds of *Parinari polyandra* and *Spondias mombin* in alloxan-induced diabetic rats. The ethanolic extracts of the seeds of *Parinari polyandra* and *Spondias mombin* were obtained by soxhlet extraction and administered to non-diabetic and alloxan-induced diabetic albino rats. Parameters including blood glucose, alanine aminotransferase (ALT), aspartate transaminase (AST), lipid peroxidation, triglycerides, cholesterol, glutathione and total protein were checked using standard test kits and methods after administration of the extracts. Histological changes in the liver of the animal were also examined. The results obtained revealed that alanine aminotransferase (ALT), aspartate transaminase (AST), lipid peroxidation, triglycerides, cholesterol and glutathione did not change significantly ($p \leq 0.05$) in the animals treated with the plant extracts. Glucose and total protein levels were significantly reduced ($p \leq 0.05$) in the animals treated with the plant extracts. The histological changes showed the presence of fatty cells in the liver of alloxan-induced diabetic control and non diabetic rats administered both *Parinari polyandra* and *Spondias mombin* extracts. The implications of the results obtained especially reduction of glucose by *Parinari polyandra* and *Spondias mombin* is their potential use in management of diabetes and apparent effects on the liver when administered together.

Key words: Medicinal plants, diabetes, alanine aminotransferase, aspartate transaminase, lipid peroxidation

INTRODUCTION

Medicinal plants are widely used in management of diseases all over the world (Aliyu *et al.*, 2007; Adewunmi and Ojewole, 2004). Historically, the use of medicinal plants is as old as mankind and medicine. In Nigeria, several thousands of plant species have been claimed to possess medicinal properties and employed in the treatment of many ailments (Okigbo and Mmeka, 2006).

Diabetes is a disease associated with glucose metabolism resulting from defects in insulin secretion and action (WHO, 1999). It is characterized by hyperglycemia, glucosuria and several microvascular and macrovascular complications (Brownlee, 2001; Virella-Lopes and Virella, 2003). The complications of diabetes are linked to oxidative stress induced by hyperglycemia which

overcomes the body's natural anti-oxidant system (Kikkawa *et al.*, 2003; Udoh *et al.*, 2007). In the later stages of diabetes, lipid metabolism is affected and seen as hyperlipidemia and hypercholesterolemia which are risk factors in arteriosclerosis (Ross, 1999; Schwartz, 2006; Krishnakumar *et al.*, 1999). There is also the possibility of liver damage in diabetes due to increased gluconeogenesis and ketogenesis (Felig *et al.*, 1970). The incidence of diabetes is on the rise and is estimated to be over 150 million worldwide (Wild *et al.*, 2004). There is yet no effective cure for diabetes and the available drugs and insulin currently used in managing the disease are associated with several undesirable side effects (Piedrola *et al.*, 2001; Yaryura-Tobias *et al.*, 2001; Gandhipuram *et al.*, 2006). The undesirable side effects and high cost of anti-diabetic drugs has led to search for plants with hypoglycemic properties and their employment in the management of diabetes (Calixto, 2000; WHO, 2002). Several species of medicinal plants used in traditional treatment and management of diabetes worldwide have been evaluated (Brai *et al.*, 2007; Gondwe *et al.*, 2008). The hypoglycemic properties of plants used in management of diabetes are reported to be due to their content of flavonoids, glycosides, alkaloids terpenoids, plant polysaccharides and other bioactive compounds. The seeds of two medicinal plants namely *Parinari polyandra* and *Spondias mombin* are commonly employed in ethno medicine management of diabetic conditions in Nigeria. *Parinari polyandra* is a tropical plant belonging to the family, Rosaceae and widely used to enhance fertility and relieve painful and inflammatory conditions (Vongtau *et al.*, 2004). Some species of *Parinari* have been claimed to be effective in the treatment of venereal diseases and erectile dysfunctions (Lans, 2007). Preliminary nutritional and phytochemical screening of the plant extracts revealed the presence of flavonoids, tannins, saponin and glycosides (Abolaji *et al.*, 2007; Vongtau *et al.*, 2004). *Spondias mombin* belongs to the tropical genus Anacardiaceae and its leaves and fruits are mostly used in treating various diseases including diarrhea, allergies, inflammatory conditions and microbial infections (Okolie *et al.*, 2008; Ajao *et al.*, 1985). It is also used in managing psychiatric disorders (Ayoka *et al.*, 2005). *Spondias mombin* leaves contain tannins, flavonoids, saponins, alkaloids and phenols (Njoku and Akumefula, 2007). The hypoglycemic activity of the methanolic stem extract of *Parinari polyandra* has been reported (Vongtau *et al.*, 2004). Also, the antidiabetic activity of the methanol leaf extract of *Spondias mombin* has been evaluated (Fred-Jaiyesimi *et al.*, 2009). This study is designed to study the individual and synergistic hypoglycaemic and biochemical effects of the seeds of *Parinari polyandra* and *Spondias mombin* in view of their unorthodox use in the traditional management of diabetes in Nigeria.

MATERIALS AND METHODS

This study was carried out between November, 2009 to February, 2010 at the Department of Biological Sciences, Covenant University, Ota South West, Nigeria.

Collection, processing and extraction of seeds of *Parinari polyandra* and *Spondias mombin*: The seeds of *Spondias mombin* and *Parinari polyandra* were bought from a local market in Ogun State, Nigeria, identified, sorted, air-dried and ground to a coarse powdered form. Hundred grams of each of the plant seeds was extracted with 90% ethanol and the crude extracts concentrated to dryness.

Experimental design: Forty male albino rats aged six weeks old and with an average weight of 45 g were used for the experiment. They were housed in well ventilated cages and given normal rat chow and water *ad libitum*. The rats were randomly distributed into eight groups consisting

of five animals each. Diabetes was induced in rats by administering 250 mg kg⁻¹ of alloxan intraperitoneally and then checking the fasting blood sugar for hyperglycemia after five days. Groups that were not administered alloxan for induction of diabetes were administered normal saline. Rats were orally administered plant extracts (100 mg kg⁻¹) daily for ten days. Groups that were not given plant extracts were administered normal saline which was the vehicle. Group 1 and 2 were the non-diabetic and diabetic controls administered with vehicle. Group 3 and 4 were non-diabetic and administered *Parinari polyandra* and *Spondias mombin* extracts (100 mg kg⁻¹ b.wt.), respectively. Group 5 were non-diabetic and co-administered *Parinari polyandra* and *Spondias mombin* extracts (100 mg kg⁻¹ b.wt.). Group 6 and 7 were diabetic and administered *Parinari polyandra* and *Spondias mombin* extracts (100 mg kg⁻¹ b.wt.), respectively. Group 8 were also diabetic and co-administered *Parinari polyandra* and *Spondias mombin* extracts (100 mg kg⁻¹ b.wt.). The animals were weighed weekly throughout the period of the experiment.

All the animal experiments and handling were carried according to standard protocols approved by animal research ethics committee of the department of biological sciences, Covenant University, Ota, Nigeria.

Collection of blood, organs and tissue samples: At the end of the experimental period, four animals from each group were anesthetized and blood samples collected in heparinised sample bottles. Serum samples were collected in non-heparinized sample bottles and allowed to clot before being centrifuged at 5000 rpm for 10 min. The livers were quickly removed and stored in 10% formyl saline.

Biochemical determinations: Glucose, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined using Cypress diagnostic test kits. Total triglyceride and cholesterol were determined using test kits (Linear chemicals). Total protein was determined by the Lowry method (Lowry *et al.*, 1951). Glutathione was determined using the method of Ellman (1959). Lipid peroxidation was determined by the thiobarbituric acid reactive substances (TBARS) method of Buege and Aust (1978).

Histological examination of liver tissue: Sections of liver tissue from all the groups were processed for histological examination according to procedures described by Disbrey and Rack (1970).

Statistical analysis: The results obtained were expressed as Mean±Standard deviation for triplicate determinations. Analysis of Variance (ANOVA) for a completely randomized design and Duncan's multiple range tests were used to analyse data. Values were considered significant at $p \leq 0.05$.

RESULTS

The effect of administration of *Parinari polyandra* and *Spondias mombin* extracts on weight and the biochemical parameters in non diabetic rats are presented in Table 1. The results of the administration of *Parinari polyandra* and *Spondias mombin* extracts on weight and the biochemical parameters in alloxan-induced diabetic rats are provided in Table 2. Groups significant against the non-diabetic control (Positive control) are signified by (a) and the groups significant against alloxan-induced diabetic control (negative control) are signified by (b).

Table 1: Weight change and biochemical parameters in non-diabetic rats administered *Parinari polyandra* and *Spondias mombin* ethanolic extracts

Parameters	Non-diabetic group			
	Control	Administered <i>Parinari polyandra</i> extracts	Administered <i>Spondias mombin</i> extracts	Co-administered <i>Parinari polyandra</i> and <i>Spondias mombin</i> extracts
Weight change (%)	43.1	35.4	36.0	59.3
Glucose (mM L ⁻¹)	65.92±4.28	44.72±10.72 ^b	42.15±7.67 ^{a, b}	32.02±10.77 ^{a, b}
Protein (mg mL ⁻¹)	4.54±0.56 ^b	4.94±0.71 ^b	4.58±0.91 ^b	1.60±1.10
Gluthathione (mM mL ⁻¹)	0.06±0.01	0.05±0.01	0.05±0.01	0.04±0.01
Cholesterol (mM L ⁻¹)	213.33±5.67	213.33±2.55	216.94±3.44	211.74±2.56
Triglycerides (mg dL ⁻¹)	309.80±8.14	294.49±11.97	309.58±18.61	303.65±20.32
Lipid peroxidation (mg mL ⁻¹)	16.88±2.47	19.44 ±1.63	17.42±2.64	19.12±6.33
Aspartate transaminase (IU L ⁻¹)	42.23±20.68	73.15±37.88	12.13±2.55	9.04±1.46
Alanine transaminase (IU L ⁻¹)	16.52±4.46	22.87±3.90	22.05±9.12	12.25±0.01

Table 2: Weight change and biochemical parameters in alloxan-induced diabetic rats administered *Parinari polyandra* and *Spondias mombin* ethanolic extracts

Parameters	Alloxan-induced diabetic group			
	Control	Administered <i>Parinari polyandra</i> extracts	Administered <i>Spondias mombin</i> extracts	Co-administered <i>Parinari polyandra</i> and <i>Spondias mombin</i> extracts
Weight change (%)	25.6	29.2	47.4	22.9
Glucose (mM L ⁻¹)	76.43±7.20	36.68±7.29 ^{a, b}	41.85±6.80 ^b	66.92±10.97
Protein (mg mL ⁻¹)	1.75±0.52 ^a	4.53±2.08	2.65±0.05	3.10±0.89
Gluthathione (mM mL ⁻¹)	0.07±0.01	0.06±0.01	0.04±0.01	0.17±0.11
Cholesterol (mM L ⁻¹)	218.10±4.96	217.00±3.55	222.62±6.54	216.34±5.43
Triglycerides (mg dL ⁻¹)	335.63 ±16.63	288.20±4.67	273.96±29.17	313.28±28.87
Lipid peroxidation (mg mL ⁻¹)	11.78± 0.50	16.83±2.13	13.20±0.95	13.57±1.62
Aspartate transaminase (IU L ⁻¹)	54.25±24.29	6.41±0.58	14.59±2.92	10.79±3.80
Alanine transaminase (IU L ⁻¹)	14.44 ±4.18	8.75±1.35	9.05±0.88	14.44±6.19

Generally there were no significant percentage weight changes in all the experimental groups but the group administered *Parinari polyandra* and *Spondias mombin* extracts showed the highest percentage increase in weight while the alloxan-induced diabetic rats administered *Parinari polyandra* and *Spondias mombin* extracts had the lowest.

There were significant reductions ($p \leq 0.05$) in glucose concentration in all the groups administered *Parinari polyandra* and *Spondias mombin* extracts except the alloxan-induced diabetic group co-administered both extracts. The changes in total protein in most of the groups were not significant ($p \leq 0.05$) except the alloxan-induced diabetic control and the non-diabetic group administered *Parinari polyandra* and *Spondias mombin* extracts, respectively. There were no significant changes in glutathione, cholesterol, triglyceride and lipid peroxidation levels. The activities of the liver enzymes including AST and ALT were not significantly changed ($p \leq 0.05$) in all the groups.

The histological features of liver tissues of the animals administered *Parinari polyandra* and *Spondias mombin* extracts in all the groups are shown in Fig. 1-8. The liver of the rats in all the

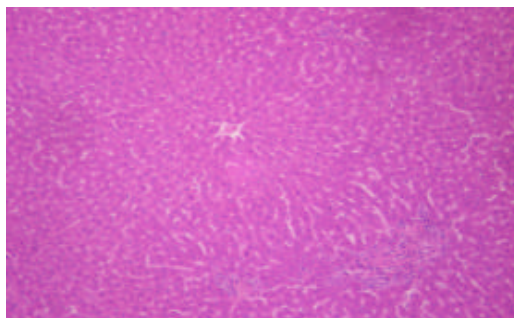


Fig. 1: Photomicrograph of liver of non-diabetic control rats

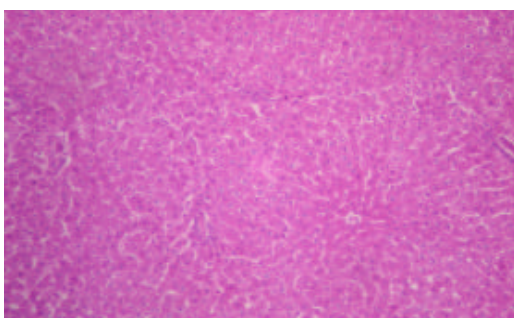


Fig. 2: Photomicrograph of liver of non-diabetic rats administered *Parinari polyandra* extracts

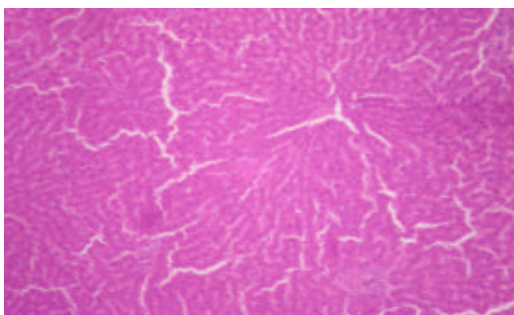


Fig. 3: Photomicrograph of liver of non-diabetic rats administered *Spondias mombin* extracts

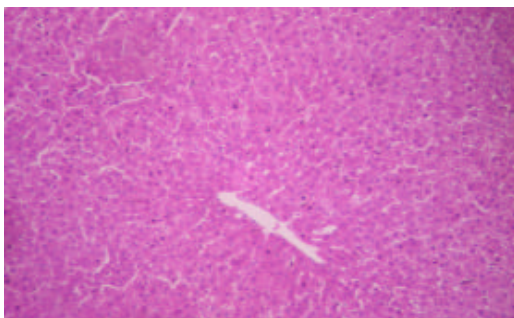


Fig. 4: Photomicrograph of liver of non-diabetic rats co-administered *Parinari polyandra* and *Spondias mombin* extracts

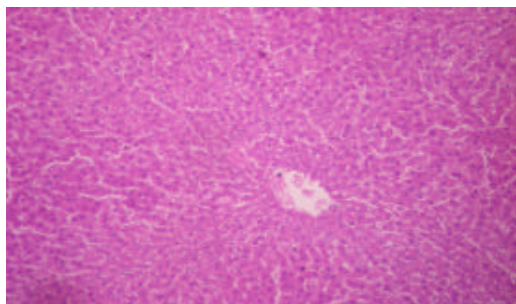


Fig. 5: Photomicrograph of liver of alloxan-induced diabetic control rats

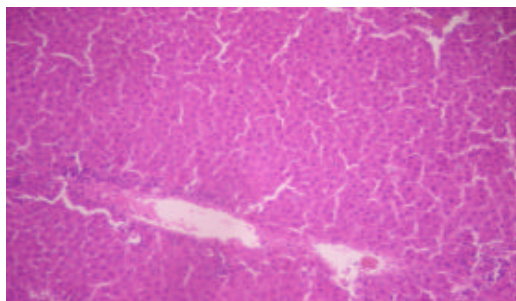


Fig. 6: Photomicrograph of liver of alloxan-induced diabetic rats administered *Parinari polyandra* extracts.

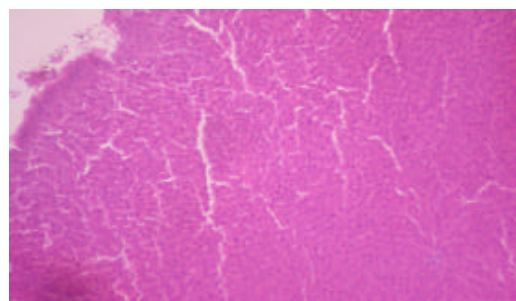


Fig. 7: Photomicrograph of liver of alloxan-induced diabetic rats administered *Spondias mombin* extracts

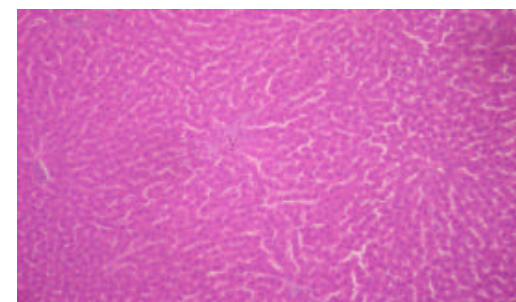


Fig. 8: Photomicrograph of liver of alloxan-induced diabetic rats co-administered *Parinari polyandra* and *Spondias mombin* extracts

groups except those co-administered *Parinari polyandra* and *Spondias mombin* extracts and the alloxan-induced diabetic control (Fig. 4, 5) showed normal histological characteristics with preserved hepatic architecture and hepatocytes arranged in plates. The normal liver was devoid of vascular congestions, necrosis, fibrosis, haemorrhage or fatty changes. The portal tracts contained the hepatic triads (artery, vein and bile duct) and scanty inflammatory cellular infiltrates.

DISCUSSION

The results showed a general increase in body weight of animals with no significant percentage weight changes, indicating that the plants generally were not toxic to the animals.

The oral administration of ethanolic extracts of *Spondias mombin* and *Parinari polyandra* caused a significant reduction in the blood glucose concentration of the diabetic rats. Alloxan induces diabetes by destroying the beta-cells of the Islets of Langerhans in the pancreas leading to reduction in synthesis and release of insulin (Szkudelski, 2001). This model has been used to study the anti diabetic effects of several plant products (Abdel-Barry *et al.*, 1997; Babu *et al.*, 2002). The hypoglycemic properties of numerous medicinal plants have been studied and reported (Adeneye and Agbaje, 2008; Rajagopal and Sasikala, 2008; Maroo *et al.*, 2003; Vats *et al.*, 2002). Reduction in blood glucose by most bioactive compounds from plants might act by one of several mechanisms including stimulation of insulin secretion, increased repair or proliferation of β -cells and enhancing the effects of insulin and adrenalin (Fayed *et al.*, 1998). The possible mechanism by which the ethanolic extracts of *Spondias mombin* and *Parinari polyandra* reduced blood glucose concentration of the diabetic rats may be either by increasing the pancreatic secretion of insulin from the cells of islets of Langerhan's or its release from bound insulin (Pari and Amarnath, 2004). This mechanism of action is suggested for other plants that have been studied (Chaude *et al.*, 2001; Krishna *et al.*, 2004; El-Demerdash *et al.*, 2005; Alarcon-Aguilar *et al.*, 2005).

There was also a decrease in total protein in the alloxan-induced diabetic control which could be attributed to the non-enzymatic glycation of proteins seen in diabetes and which contributes to the long-term complications of the disease (Vlassara *et al.*, 1981). Oral administration of ethanolic extracts of *Spondias mombin* and *Parinari polyandra* significantly reduced total protein concentration in the non-diabetic animals.

Lipid peroxidation is one of the characteristic features of chronic diabetes and insulin secretion is also closely associated with lipoxygenase-derived peroxides (Metz, 1984). TBARS is the most commonly used indicator of lipid peroxidation (Lyons, 1991). Glutathione (GSH) is known to protect the cellular system against toxic effects of lipid peroxidation (Nicotera and Orrenius, 1986). Decreased level of GSH in the liver and kidney during diabetes represents its increased utilization due to oxidative stress (Anuradha and Selvam, 1993). In this study there was no significant difference in the lipid peroxidation and GSH levels in the tissues of all the test groups. This indicates that the extracts maintained the levels of GSH that are utilized during diabetes and hence also stabilized lipid peroxidation. This finding is similar to studies done on some antidiabetic plants (Ravikumar and Anuradha, 1999; Srinivasan *et al.*, 2005; Adewole and Caxton-Martins, 2006).

High cholesterol levels and hyperlipidemia are associated consequences of diabetes (Mironova *et al.*, 2000; Pepato *et al.*, 2003; Odetola *et al.*, 2006). In this study, cholesterol and triglyceride levels were not significantly changed following treatments with ethanolic extracts of *Spondias mombin* and *Parinari polyandra*. This result agrees with other cholesterol modulating effects of several other plants (Rajagopal and Sasikala, 2008; Iweala and Okeke, 2005;

Dhandapani *et al.*, 2002). The stabilization of triglyceride and cholesterol levels in the rats by ethanolic extracts of *Spondias mombin* and *Parinari polyandra* is related to their promotion of utilization of glucose and hence depressed mobilization of fat (Momo *et al.*, 2006). This result implies that the plant extracts may be helpful in reducing the complications of hyperlipidemia and hypercholesterolemia which coexist quite often in diabetics (Sharma *et al.*, 2003).

Aspartate transaminase (AST) and alanine transaminase (ALT) assay are important in the diagnosis of liver damage caused by drug toxicity or harmful chemicals (Nelson and Cox, 2005). In the present study, AST and ALT levels in the test groups did not significantly change. Increase in liver enzymes is an indication of liver damage. However, the histological changes in the liver of the diabetic rats and the non diabetic group co-administered both ethanolic extracts of *Spondias mombin* and *Parinari polyandra* indicated hepatic damage. This means that administration of alloxan and co-administration of the ethanolic extracts of *Spondias mombin* and *Parinari polyandra* alters liver function in diabetes. This suggests a possible harmful synergistic effect by both plants on the liver. This observation is similar to a study by Raji *et al.* (2006) and corroborates the claim that most medicinal preparations in traditional medicines contain a variety of synergistically acting phytochemicals that act on a variety of targets by various mechanisms (Tiwari and Madhusudana-Rao, 2002). The implication of this is the questionable safety especially on the liver associated with the traditional concurrent use of the seeds of *Spondias mombin* and *Parinari polyandra* in management of diabetes. However, the non significant changes in the liver enzymes in groups treated with the individual ethanolic extracts of *Spondias mombin* and *Parinari polyandra* suggests no apparent toxicity to the liver and hence improving its functions and enhancing transport of glucose to ameliorate diabetes (Bhandarkar and Khan, 2004). Several plants employed in the management of diabetes do not express liver toxicity (Muthulingam, 2010; Hossain and Bhattacharya, 2006).

Generally, the biological effects of ethanolic extracts of *Spondias mombin* and *Parinari polyandra* are not unconnected with their active principles including alkaloids, flavonoids, tannins, glycosides which have been reported to have hypoglycaemic, hypolipidemic, hypocholesterolemic, antioxidant properties amongst others (Oladele *et al.*, 1995).

The results of the present study clearly indicate that the ethanolic extracts of seeds of *Spondias mombin* and *Parinari polyandra* have glucose lowering effects on alloxan-induced diabetic rats. It also reveals the possible hepatotoxic effect of co-administration of both *S. mombin* and *P. polyandra* extracts as commonly practiced in unorthodox traditional management of diabetes in Nigeria. Further studies are in progress to isolate the active principle and elucidate the exact mechanism of action of *S. mombin* and *P. polyandra*.

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