

Effects of Repeated Administration of *Terminaliamacroptera* (Guill. & Perr.) Stem Bark Extracts on the Glycaemic, Lipidaemic and Antioxidant Benchmarks of Wistar Albino Rats

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Abstract

Background: *Terminaliamacroptera* (TM) is one plant that is used by locals in some parts of Nigeria to treat diabetes mellitus. This study examined the hypoglycaemic property of aqueous (AE) and ethanol extracts (EE) of TM stem bark and their effects on lipid and antioxidant status of normoglycaemic rats.

Materials and Methods: Four groups (n=4) of female Wistar albino rats were used. The blood glucose (BG) of the rats were determined after respective oral administration of 200, 400 and 600 mg/kg b. w. of extract doses for 28 days. Control animals were administered distilled water (4 ml/kg b. w.) for an equivalent period. BG concentrations were determined with glucometer while serum lipids were determined by approved spectrometric protocols. Hepatic antioxidant status of groups with the most hypoglycaemic and hypolipidaemic effects were examined respectively.

Results: The results showed that 600 mg/kg b. w. AE had the most effective time-point BG reduction [49.67 (± 1.03) mg/dl] below mean basal value [73.00 (± 6.42) mg/dl] at termination of experiment (p<0.05). However, only 200 mg/kg b. w. of both extracts showed correlated decremental area over curve (dAOC) and positively modified the lipid profiles and at least maintained normal antioxidant status.

Conclusion: TMSB extracts possessed hypoglycaemic and hypolipidaemic properties that may attract further investigations for use as an antidiabetic agent.

Key Word: Antioxidants, hypoglycaemia, hypolipidaemia, *Terminaliamacroptera*, area over curve.

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I. Introduction

Terminaliamacroptera Guill. & Perr. is a member of the Combretaceae plant family that grows along the Savannah region of West Africa¹. The plant bears a white flower that develops into chambered seed surrounded by a thin circular wing². The flower of the shrub has been revealed to contain flavonoids^{3,4,5} while a number of benzoic and cinnamic acids were found in the stem and root bark extracts of the plant by Kone *et al.*⁶.

Other phytochemicals found in the stem bark, root and leaves extracts of the plant include flavonoids, chlorogenic acid⁷, terminolic acid⁸, triterpenoids⁹, phenolic glucoside, vanillic acid 4-O-β-D-(6'-O-galloyl) glucopyranoside¹⁰, tannins^{11,12}, anthroquinones, cyanogenic glycosides¹³, flavonoids, alkaloids and saponins^{13,14}.

TM was also discovered to contain complement-fixing polysaccharides¹⁵. A previous proximate analysis had shown that the stem bark of the plant has low amount of lipid (0.53%) and high amount of nitrogen free extract (73.01%)¹³.

The stem bark and roots of the plant have shown high fidelity index in ailment treatment^{16,17}. Specifically, the bark of the plant has been reportedly used for the treatment of diarrhoea and dysentery^{1,18}. Foliages of *T. macroptera* stimulate increase in feeding habit of rabbits¹⁹. Moreso, the leaves' decoction is used to treat hepatitis and fungal infection¹⁷. Other pharmacological activities possessed by the plant include anti-*Neisseria gonorrhoeae*¹², anti-*Helicobacter pylori*²⁰ and anti-*staphylococcus aureus*²¹.

Experiments done with mice showed that the aqueous extract of TMSB possesses anxiolytic and antipyretic activities²². Usman *et al.*¹⁴ was able to show that EE of TMSB did not contain steroidal anti-inflammatory agents, but instead non-steroidal anti-inflammatory principles which were thought to inhibit serotonin and histamine produced from carrageenan induced inflammation. Immunological properties were also shown in a recent study, to be displayed by high doses of plant's aqueous stem bark extract in female Wistar albino rats while low doses of EE exhibited increased erythropoietic effects²³. The numerous pharmacological activities displayed by the plant are believed to be connected to their screened phytochemicals.

Interestingly, traditional medical practitioners have reportedly used *Terminaliamacroptera* stem bark (TMSB) among other plants in the treatment of hyperglycaemic challenges^{24,25,26}. This has been partly supported in a study that stated that lower doses of the TMSB polar stem extracts may be useful in the management of obesity²⁷. A more recent study of TMSB had shown that it possessed time-point reductions in mean basal blood glucose level (MBGL) under single dose administrations²⁸. However, this property remained to be fully established until investigated under repeated dose administration and the plant's effects on lipid metabolism and antioxidant benchmarks are evaluated. It is important to note that the administration of any hypoglycaemic agent should not induce hyperlipidaemia or oxidative stress²⁹. This concern is apt because plants extracts show pharmacological activities that are limited in effect to a narrow range of doses, beyond which negative side effects may set in.

This study therefore attempted a model of repeated administration for 28 days to concretize the debatable blood glucose (BG) depression previously reported for the extracts. A further clarity on the intrinsic activity of the extracts would be confirmed by how the extracts modified the lipid and antioxidant profiles. This will in earnest reveal the effectiveness of the administered doses.

II. Material and Methods

All chemicals and reagents were of analytical grade (98 – 99.8% purity) and were purchased from certified dealers. Equipment used include ELISA microplate reader (Spectramax 340 PC molecular device), water-bath (NL-420S, New Life Medical Instrument, England), UV-Vis 722s spectrophotometer (Kyoto, Japan), centrifuge (model: 406B, Techmel&Techmel, USA), mettler H80 weighing balance, glucometer (Accu-Chek Active, Model: GC, Roche, Mannheim, Germany), chemical balance (K-500BH, S. Mettler) and freeze dryer (FD-10M, PEC MEDICALS, USA).

Preparation of Plant Extract

The aqueous (AE) and ethanol extracts (EE) of TMSB powdery sample were prepared by conventional solvent extraction method in a ratio of 1 to 4 of distilled water and ethanol respectively for three days. Plant's source and identification (UBHT 0232) were as previously reported¹³.

Experimental Animals

Female rats (*Wistar* albino strain) were supplied by the animal unit of Anatomy Department, School of Basic Medical Sciences, University of Benin, Benin City and were maintained in well ventilated wooden cages sealed with wire knits above and below. The rats were of approximate weight range of 220 – 250 g and were maintained under standard laboratory conditions of temperature 24°C (± 2°C). The animals were exposed to 12 hours daylight and 12 hours darkness. They were allowed access to standard pelletized mash and fresh tap water *ad libitum* while acclimatization lasted for one week in the animal house of Biochemistry Department, University of Benin prior to commencement of experiment. The research was conducted in accordance with the internationally accepted principles for laboratory animal use and care as found in the European Community guidelines³⁰.

Hypoglycaemic Study

All investigations were conducted between 6 am and 8 am to eliminate the influence of diurnal variations in body temperature and plasma hormone levels. A population of 28 *Wistar* albino rats were randomized into 7 groups comprising 4 rats each as shown below:

Group 1: Normal control (distilled water, 4 ml/kg b. w.).

Group 2: AE 200 group (200 mg/kg b. w. aqueous extract).

Group 3: AE 400 group (400 mg/kg b. w. aqueous extract).

Group 4: AE 600 group (600 mg/kg b. w. aqueous extract).

Group 5: EE 200 group (200 mg/kg b. w. ethanol extract).

Group 6: EE 400 group (400 mg/kg b. w. ethanol extract).

Group 7: EE 600 group (600 mg/kg b. w. ethanol extract).

These were fasted 12 hours overnight prior to MBGL determination and at weekly intervals. Appropriate test doses (predetermined from preliminary investigation) were singly administered orally per day to the rats by means of gavage. Blood samples were collected 3 hours after dosing, on day one and at weekly intervals from tail vein for 4 weeks using glucometer (Accu-Chek Active, Model: GC, Roche, Mannheim, Germany).

Hypoglycaemic effects were determined by the compressed models of previous researchers^{31,32,33,34} as $tAUC = (Y - \frac{1}{2}S)t$ for total areas under the curve (at equal time interval). Y in the formula represented the total concentration of glucose determinations, $\sum_i^f(y)$; S represented the sum of initial (y_i) and final (y_f) determinations; t represented equal time interval between determinations. Area under baseline (AUB) at equal

time interval was calculated with the formula, $AUB = \text{initial determination } (y_i) \times \text{total determination time } (T) = y_i (n-1)t$. Incremental area under curve ($iAUC$) at equal time interval was calculated with the formula $iAUC = (Y' - \frac{1}{2}S')t + \frac{1}{2}(\alpha' + z')$ where Y' represented total increment in concentration of BG determinations, $\sum_{i=1}^{n-1} (y_i')$; S' was the sum of initial (y_i') and final increment (y_f'). The initial incremental area ($y_i't_i$), above fasting blood sugar was indicated by α' ; z' represented the final incremental area ($y_f't_f$) above the fasting blood sugar; t_f' represented the time taken for final increased glucose level to return to baseline $[(y_f't_f) / (y_f' + y_i'^*)]$ while $y_i'^*$ represented the initial decrement below baseline value. The above formulae were then integrated to determine the decremental area over curve, $dAOC$ ²⁸.

Biochemical Study

The blood samples of the rats were harvested on the 28th day of the experiment by cardiac puncture and biochemical assays carried out on them to determine concentrations of serum total cholesterol³⁵, triacylglycerol³⁵, serum high density lipoprotein³⁶ while serum low density lipoprotein was calculated by the formula of Friedwald *et al*³⁷. Antioxidant parameters estimated include superoxide dismutase, SOD³⁸ catalase³⁹ and reduced glutathione, GSH⁴⁰.

Statistical Analysis: All the data were statistically analyzed for variance and significance by student's *t*-test followed by Tukey post hoc test for multiple comparison using SPSS (Statistical Package for Social Sciences Inc., USA) version 23. All results were expressed as mean \pm SEM and *p* values were set at < 0.05 for significant differences.

III. Results

Figure 1a shown below contained the dose response curve of AE of TMSB administered daily over 28 days. AE at concentration of 600 mg/kg b. w. significantly reduced BG concentration below MBGL ($p = 0.035$).

Figure 1a shown below contained the glucose decrement area caused by AE of TMSB administered daily for 28 days. The administered dose of 200 mg/kg showed the most glucose decrement area ($p = 0.01$) when compared with control group due to elimination of differential MBGL.

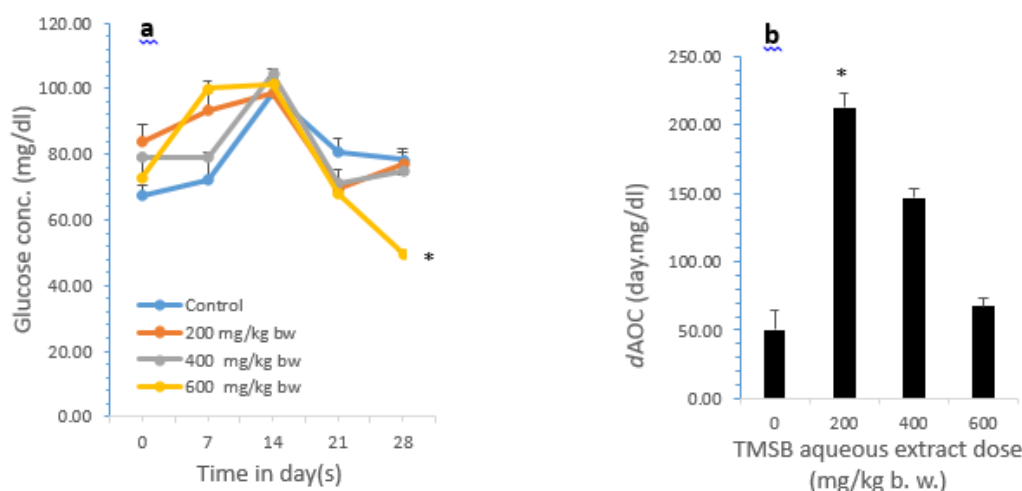


Figure 1(a) Glycaemic profiles of rats administered single daily doses of aqueous extracts (AE) of *Terminalia macroptera* stem bark for 4 weeks. **(b)** Decremental area over glucose curve ($dAOC$) induced by doses of AE.

Figure 2a shown below contained the dose response curve of EE of TMSB administered daily over 28 days. Administered dose of 200 mg/kg b. w. caused the most time point reduction below baseline value on the 28th day of experiment ($p=0.001$, compared with MBGL). EE at 600 mg/kg b. w. also caused a reduction below MBGL ($p=0.008$) though less than 200 mg/kg b. w.

Figure 2b showed the glucose decrement area caused by EE of TMSB administered daily for 28 days. The group dosed with 200 mg/kg b. w. showed the most glucose disposal ($p=0.028$) over 28 days of administration.

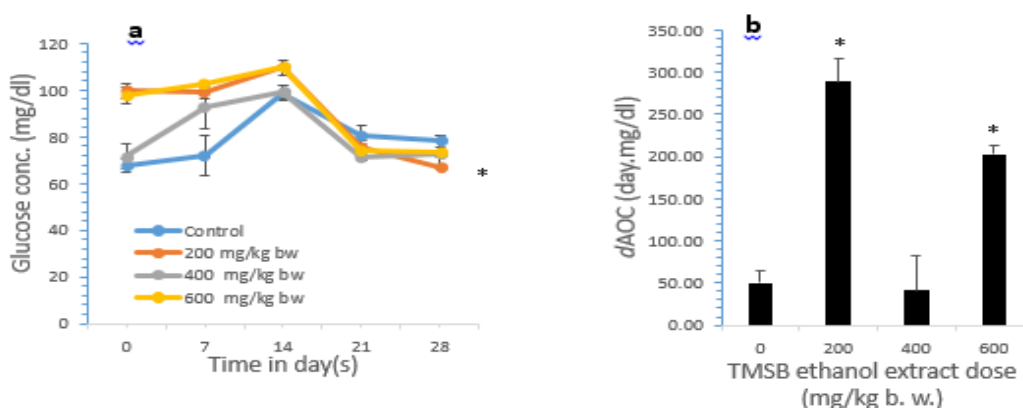


Figure 2(a) Glycaemic profile of rats administered single daily doses of ethanol extracts (EE) for 4 weeks. (b) Decremental AOC induced by doses of EE.

Table 1 shown below contained the lipid profiles in rats administered AE of TMSB on daily basis for 28 days. The 200 mg/kg b. w. AE dose had the most effective modification across the lipid parameters.

Table 1. Lipid profile of rats administered aqueous extract of *Terminaliamacroptera* stem bark for 28 days.

Dose of AE (mg/kg)	Control	200	400	600
T. chol (mg/dl)	132.69 ± 5.34 ^a	106.16 ± 5.46 ^b	166.31 ± 1.82 ^b	77.00 ± 7.17 ^b
Trig. (mg/dl)	125.65 ± 1.05 ^a	90.97 ± 3.46 ^b	155.54 ± 13.57 ^a	66.16 ± 3.94 ^b
HDL-chol (mg/dl)	35.26 ± 3.24 ^a	40.41 ± 2.31 ^a	48.93 ± 1.53 ^a	20.62 ± 2.08 ^b
LDL-chol (mg/dl)	76.49 ± 9.86 ^a	45.32 ± 3.56 ^b	83.17 ± 0.90 ^a	42.48 ± 7.56 ^b

Mean on the same row with different superscripts (ab) differ significantly ($p < 0.05$) for $n = 4$. AE=Aqueous extract, T. chol: total cholesterol, Trig.: triacylglycerol, HDL-chol: high density lipoprotein cholesterol and LDL-chol: Low density lipoprotein cholesterol.

Table 2 shown below contained the lipid profile in rats administered EE of TMSB on daily basis for 28 days. Significant reduction in the levels of total cholesterol, triglyceride and LDL-cholesterol were observed in animals administered 200 mg/kg b. w.

Table 2. Lipid profile of rats administered ethanol extract of *Terminaliamacroptera* stem bark for 28 days.

Dose of EE (mg/kg)	Control	200	400	600
T. chol (mg/dl)	132.69 ± 5.34 ^a	95.55 ± 2.33 ^b	129.41 ± 6.63 ^a	149.38 ± 7.57 ^b
Trig. (mg/dl)	125.65 ± 1.05 ^a	61.52 ± 2.58 ^b	74.87 ± 1.33 ^b	158.44 ± 6.83 ^a
HDL-chol (mg/dl)	35.26 ± 3.24 ^a	29.69 ± 1.43 ^a	32.99 ± 1.72 ^a	36.29 ± 0.58 ^a
LDL-chol (mg/dl)	76.49 ± 9.86 ^a	53.56 ± 3.07 ^b	67.04 ± 3.71 ^a	87.30 ± 6.99 ^a

Mean on the same row with different superscripts (ab) differ significantly ($p < 0.05$) for $n = 4$. EE=Ethanol extract, T. Chol: Total Cholesterol, Trig.: triacylglycerol, HDL-chol: high density lipoprotein cholesterol and LDL-chol: low density lipoprotein cholesterol.

The administered doses of 200 and 600 mg/kg b. w. of both extracts reflected lowering of BG, but only 200mg/kg b. w. of both extracts showed better moderations of lipid profiles than 400 and 600 mg/kg b. w. when compared with normal control. It was only reasonable to investigate the antioxidant status of the effective doses of the respective extracts only.

Antioxidant Effects of the Extracts with Correlated Hypoglycaemic and Hypolipidaemic Properties

Table 3 contained the antioxidant status of rats administered 200 mg/kg of AE and EE of TMSB for 28 days respectively. Antioxidant activities were comparable with those of control group except for GSH concentration of EE administered group that was significantly elevated above the concentration of control group.

Table 3: Antioxidant status of rats administered 200 mg/kg extracts of *Terminalia macroptera* stem bark.

Dose/Group	Control	200 mg/kg AE	200 mg/kg EE
SOD (U/g wet tissue)	97.76 ± 5.81 ^a	110.69 ± 2.37 ^a	75.39 ± 10.49 ^a
CAT (U/g wet tissue)	30.63 ± 2.88 ^a	21.24 ± 0.47 ^b	34.78 ± 6.47 ^a
GSH (nmol/g wet tissue)	0.12 ± 0.01 ^a	0.13 ± 0.01 ^a	0.18 ± 0.01 ^b

Results were expressed as mean value ± SE for $n = 4$ determinations. Statistical differences between control and tests at $p < 0.05$ were indicated by different lower case alphabets. AE = aqueous extract, EE = ethanol extract, SOD = superoxide dismutase, CAT = catalase and GSH = reduced glutathione.

IV. Discussion

Hypoglycaemic changes that occur when plant extracts are administered to normoglycaemic test animals could be very transient and somewhat difficult to capture due to homeostatic regulation. In this study, besides determination of terminal time-point reduction in BG, overall decrease in glucose pool below MBGL was resolved by utilizing the formula for $dAOC$ ²⁸, previously condensed from the work championed by earlier researchers^{31,32}. The $dAOC$ summed up all the time-point reductions below fasting blood sugar. It also corrected for possible errors by eliminating differences in MBGL.

The significant time-point reduction caused by 600 mg/kg AE must have come from an accumulated effect of the extract. This hypoglycaemic effect was exhibited after four weeks of administration. The decrease in BG was unsupported by $dAOC$ because rats had relatively low initial MBGL. Consequently, its $dAOC$ was less than that of 200 mg/kg b. w. AE which had higher MBGL above control baseline.

In a similar manner, EE doses showed depression in BG which were in agreement with their $dAOCs$ because the initial MBGL of the test groups were higher than those of control animals. The effects were however less compared to that of the highest administered dose of AE. Although, the mechanism of action of TMSB extract was unknown, the observation was not different from what has been recorded in a number of other plants reported to have hypoglycaemic effects⁴². In fact, *Alstonia boonei* stem bark extract had been reported by Kumar *et al* significantly prevent a rise in BG level in experimental animals⁴³. The effect of TMSB could be attributed to the reduction in the activity of regulatory glucogenic enzymes and possible stimulation of more insulin molecules by the rich phytochemical contents⁴⁴. The reductions in BG were in consonance with the effect of the plant's extract previously reported to cause moderate food intake-to-body mass conversion²⁷. However, with respect to Hayes postulation about such occurrences, the decreased glucose concentration of the tested animals that went beyond the usual 10-15 mg/dl, most likely registered a hypoglycaemic effect by the administered extracts^{27,45}.

Although, 600 mg/kg b. w. AE showed an applaudable time-point reduction, its effect in causing decreased HDL cholesterol levels negated its effectiveness. This findings supported the argument of Dimmitt and his/her co-researchers that small doses portend the balance with checks on overdose associated risks⁴¹. The effectiveness of 200 mg/kg b. w. AE was shown in its ability to moderate the concentration of HDL-cholesterol at the end of the experimental period while it cut down other lipid molecules.

Fat deposits in lipid stores were well moderated by AE and EE at dose 200 mg/kg. Although, we did not investigate the mechanism behind the hypolipidaemic property, the glory of the attribute remained to be shared by phytochemicals that have been shown to be in abundance in the stem bark. Available literature have pointed to these phytochemicals in possessing cholesterol reduction properties⁴⁶. These phytochemicals may have suppressed the synthesis of triglycerides leading to their low concentration in the blood, which in turn enhanced increased protein content of lipoproteins. The resultant effect of this was increased uptake of LDL by their receptors^{47,48}. Although, the concentration of HDL-chol were not elevated, they were however maintained within normal range. This observation consequently proved EE to be more effective in managing lipid benchmarks.

This research was also designed to investigate the antioxidant effects of the effective doses that displayed hypolipidaemic properties. SOD and catalase protect the body cells from superoxide anions and excess free radicals as well as hazardous agents that can stimulate cell death⁴⁹. The ability of the extracts in moderating the activities of SOD and catalase was seen in the close to normal enzyme activities observed in the tested groups, except for 200 mg/kg AE-treatment group that exhibited a significant decrease in the activity of the latter. This may be connected to the possible exogenous assistance provided by the phytochemicals inherent in the extracts⁵⁰. This result was in consonance with the findings of Olorunnisola *et al.*⁵¹

GSH depletion in pathophysiological state has been extensively investigated. GSH depletion promotes generation of reactive oxygen species and oxidative stress with the consequent destruction of the architectural and structural integrity of cell⁵². Our study showed that administration of 200 mg/kg b. w. of extracts increased GSH content. The extract being a mixture of phytochemicals rich in polyphenols provided a supportive role to the endogenous antioxidants. The leaves of TM had earlier been shown to contain strong radical scavenging

activities⁵³. Flavonoids, tannins and alkaloids were implicated in this extract's attribute.^{54,55}. Consequently, these phytochemicals have been reported to play second line defence antioxidant functions^{49,56}.

V. Conclusion

The study showed that 600 mg/kg b. w. AE of TMSB effectively induced hypoglycaemic condition in normoglycaemic rats. However, 200 mg/kg b. w. of both AE and EE which had mild hypoglycaemic effect were able to modify the lipid profile while they provided maintenance effect to the activities of the antioxidant enzymes. This study will help to give an appropriate start dose for antidiabetic evaluation. Studies are currently on to examine the plant's possible antidiabetic effects in rat models.

Conflict of Interest: The authors declared no conflict of interest.

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