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Original Research Article

Antioxidant Potentials of *Terminalia catappa* Seed Extract and Metformin on the Liver and Kidney of Diabetic Wistar Rats

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ABSTRACT

The antioxidant effects of *Terminalia catappa* ethanol seed extract in the liver and kidneys of diabetic Wistar rats induced with streptozotocin was investigated. Thirty rats weighing 140 g – 180 g were randomly divided into five treatment groups. The normal control (NC) and 50 mg/kg b.w streptozotocin-induced diabetic control (DC) groups received placebo, while the treated groups included 500 mg/kg b.w metformin only group (G), 500 mg/kg b.w *T. catappa* seed extract only group (E) and combined 250 mg/kg b.w dose each of Metformin and *T. catappa* seed extract (GE). Administration was via oral gavage for 21 days. The animals were sacrificed and the effect on antioxidant enzymes and lipid peroxidation in the kidney and liver tissue homogenates were evaluated. The results obtained showed that treatment with *T catappa* seed extract and metformin significantly ($p<0.05$) improved glutathione, (GSH) levels in hepatic tissues in the diabetic rats while no significant effect was observed in the kidneys. Further, renal and hepatic levels of glutathione peroxidase and superoxide dismutase showed significant reduction ($p<0.05$) in the untreated diabetic group, an observation that was reversed following treatment with *T. catappa* seed extract and reference drug, metformin. Additionally, treatment with *T. catappa* and metformin was observed to significantly decrease the levels of malondialdehyde (MDA) in both hepatic and renal tissues. Conclusively, *T. catappa* has antioxidant activities and is a potential candidate to manage diabetes related oxidative stress.

Keywords: Antioxidant potential; *Terminalia catappa*; Metformin; Liver tissues; Kidney tissues; Diabetic Wistar rat.

Introduction

Diabetes mellitus is a chronic condition characterised by metabolic derangement that ensues from either insulin deficiency or a combination of insulin resistance and its deficiency.[1] This metabolic syndrome is regarded as a global epidemic with approximately 537 affected adults as at 2022, and a future projection of 783 million affected individuals by 2045.[2] There are currently no known cures for diabetes and management options are limited to the use of conventional synthetics agents such as insulin, sulfonylureas, thiazolidinediones[3]. Sadly, these options are either associated with undesirable side effects or are not readily accessible to people of low-income demographics and even when available are expensive[3]. Therefore, the need for sourcing alternative and readily accessible antidiabetic agents with minimal side effects associated with their use is expedient.

One consequence of sustained and poorly managed hyperglycaemia is oxidative stress which depletes the activities of the antioxidant defence system, thereby promoting generation of free radicals. [4, 5]

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To this end, incorporating antioxidants as part of antidiabetic therapeutic intervention may be effective in curbing the incidence of hyperglycaemia-induced oxidative stress, thus limiting the rate of developing diabetes related complications or preventing them,[6–8]. In developing nations including sub-Saharan African countries like Nigeria, there is significant reliance on traditional herbal medicines due to cultural practices, religious beliefs, economic constraints, or limited availability of conventional medical treatments[9–11]. These herbal medicines including plant derived medicines over time, have been investigated to contain vast amounts of bioactive compounds with wide-spread therapeutic effects.[12] One of such herbal based agent is the tropical almond, *Terminalia catappa Linn* which has been utilized by several individuals throughout history to address a variety of health conditions and reportedly possess pharmacological activities such as anti-hyperglycaemic properties, as well as antioxidant effects.[3] Additionally, an earlier study on the antidiabetic activity of *T. catappa* revealed the glucose modulating effects of different solvent preparation (aqueous, methanol, petroleum ether) of the fruit extract in alloxan-induced diabetic Wistar rats.[13,14] Furthermore, *T. catappa* fruit extract and decoction prepared with its dried leaves have shown hypocholesterolemic effects in rats.[14, 15] A more recent study of its phytochemical composition has shown the presence of significant phenolic compounds including gallic acid, chlorogenic acid, ellagic acid, quercitrin, isoquercitrin, quercetin, and kaempferol to be present in the leaf, fruits and seeds of *T. catappa*.[13] Also, while the flavonoids and polyphenols were found in significant quantities, catechin, caffeic acid, epicatechin, and rutin occurred in minute amounts.[16] However, despite the rich antioxidant content of *T. catappa* seed, its impact on diabetes-induced oxidative stress, particularly in the kidneys and liver tissue is yet to be investigated, thus, the present study sought to fill this knowledge gap by treating experimental diabetic rats with either the

ethanolic extract of *T. catappa* as monotherapy or in combination with a reference drug, metformin.

Materials and Methods

Collection of nuts and preparation of crude extracts
Almond fruits were manually collected from the University of Calabar and Cross River University of Technology in November 2021. Dr Effa of Plant and Ecological studies department, University of Calabar authenticated the fruits before they were deposited in a herbarium with voucher specimen number Bot/Herb/UCC/056. 2500 g of the fruits were sun dried for 21 days and manually dehulled using clean stones. The nuts were then cut into bits and dried under room temperature (25 – 29ºC). This was followed by the pulverization and suspension of the dried nuts in absolute ethanol in the ratio of 1:2, solute to solvent and thereafter, stirred thoroughly to mix and allowed for 48 hours at room temperature to ensure sedimentation. This was followed by filtration with a chess cloth and subsequently with Whatman No. 2 filter paper. The filtrate obtained was then concentrated in a rotary evaporator at 25 – 30ºC and the resulting concentrate was evaporated to complete dryness in a water bath at a temperature range of 45ºC to 50 ºC yielding a dried oily extract. The weight of the extract was 880 g and the percentage yield calculated was calculated to be 35%.

Experimental design and induction of diabetes
Thirty male and female albino rats between140 – 180 g body weight were purchased from the animal facility of Biochemistry Department at University of Calabar were housed in well-ventilated cages and had access to water and feed *ad libitum*. Standard laboratory conditions at 27 ± 2 °C with 12- hour light / dark cycles and humidity at 55 ± 5 % was maintained throughout the course of the experiment.[3]

Following a 7-day acclimatization period, food was withdrawn from the experimental animals for 16-18 hours, but they had free access to water prior to the induction of diabetes which was achieved by a single dose 50 mg/kg b.w streptozotocin (Sigma St. Lousi, M.S., USA) injection administered intraperitoneally.[4] Prior to use, STZ was dissolved in 0.1 M sodium citrate buffer, at pH 4.5 as previously described.[17] To confirm successful induction of diabetes, blood drawn from single puncture of tail vein was tested using a glucometer (Accucheck®) and the experimental animals that presented with blood glucose level above 200 mg/dl after 72 hours were selected for the experiment.[17]

The experimental design consisted of 6 animals randomly distributed into 5 groups including: normal control, untreated diabetic control, reference drug only (G), reference drug + *T. catappa* seed extract (GE) and *T. catappa* seed extract only (E). Animals in NC and DC groups received distilled water as placebo while animals in G, GE and E groups were treated with the 500 mg/kg b.w metformin only, a combination of metformin + *T. catappa* seed extract at 250 mg/kg b.w each and 250 mg/kg b.w *T. catappa* seed extract only, respectively as previously dtermined.[4] Treatment was achieved by oral gavage and lasted for 21 days. Following the 21 days treatment duration, the animals were anaesthetized using ketamine (50 mg/ml) prior to sacrifice and thereafter, the liver and kidneys were harvested and used for biochemical assay. The study adopted the National Institute of Health (NIH) publication (1985) guidelines for laboratory animal care and use throughout the experimental period and ethical approval to undertake animal experiment was obtained from the Faculty Animal Ethics Committee, Faculty of Basic Medical Sciences, University of Calabar, Calabar, Cross River State, Nigeria.

Biochemical analysis
Preparation of tissue homogenate
The organs (kidneys and liver) weighing 0.2 g was homogenized in 1.8 ml of ice-cold homogenizing buffer comprising 125 mM mannitol, 1 mM EGTA and 5 mM HEPES in a pH of 7.2. Homogenization was carried out using a Teflon pestle homogenizer in a homogenizing cup. The whole content was transferred into a 2 mL Eppendorf micro tubes and subsequently centrifuged at 3000 rpm for 10 minutes. The supernatant was separated and stored at -20 ºC until used for the analysis of antioxidant parameters.

Estimation of malondialdehyde activity in renal and hepatic tissues
The method used in this analysis was earlier reported by Buege and Aust [22]. Briefly, 0.5 mL of kidneys or liver tissue homogenate mixed with 0.5 mL saline and 1 mL of 10 % TCA was centrifuged for 20 minutes at 3000 rpm. Thereafter, 0.25 mL TBA reagent was added to 1 mL of the protein free supernatant, thoroughly mixed and allowed to boil at 95 ºC for 60 minutes. The resulting mixture was then allowed to cool at room temperature before the absorbance was measured using a spectrophotometer at 532 nm.[18]

Estimation of reduced Glutathione (GSH) activity in renal and hepatic tissues
This assay was based on an earlier method as reported by Ellman.[19] Summarily, 0.5 mL of tissue homogenate was precipitated with 2 mL of 5 % TCA solution and centrifuged. 1 mL of Ellman's reagent and 4 mL of 0.3 M disodium hydrogen phosphate was added then to the 2 mL supernatant recovered from the centrifugation step. The intensity of the yellow colour formed was read in a spectrophotometer at 412 nm and amount of tissue GSH was expressed as µg/mg of tissue proteins.

Estimation of glutathione peroxidase activity in renal and hepatic tissues
This assay was performed in the tissue samples based on the reduction of H_2O_2 by GPx through the consumption of GSH as reported earlier by Ellman.[19] In brief, 0.2 ml tris buffer, 02 mL EDTA and 0.1 mL sodium azide was added to 0.5 ml of tissue homogenate. Thereafter, 0.2 ml of GSH and 0.1 mL H_2O_2 solution was added to the mixture and incubated for 10 minutes at 37 ºC after mixing thoroughly. 0.5 ml of 10 % TCA was added to the mixture to stop the reaction and the tubes were centrifuged. The Ellman,[19] method was used to assess the concentration of GSH in the resulting supernatant and GPx activity was thereafter expressed as µmol of GSH consumed in one minute per mg of tissue proteins.

Determination of superoxide dismutase (SOD) activity and renal and hepatic tissues
Superoxide dismutase activity was determined using a biochemical method known as pyrogallol,[20]. In this assay, a 100 µL of SOD buffer comprising 100 mM carbonate buffer and sodium carbonate with pH 10.2 was pipetted into a clean Eppendorf tube followed by the addition 830 µL distilled water and 50 µL of sample. This was incubated for 10 minutes at room temperature. 20 µL Pyrogallol was the added and absorbance reading taken immediately at zero minute and repeated per minute for 3 minutes using 1.0 mL plastic cuvette at 420 nm against a reagent blank containing no sample zero minute and repeated per minute for 3 minutes using a 1.0 mL plastic cuvette at 420 nm against sample free reagent blank. SOD activity was expressed as s Unit/min/mg of tissue proteins.

Statistical analysis
The data obtained was by analysed a one-way analysis of variance (ANOVA) using Graph Pad Prism® version 8 and Microsoft Excel program version 2013. The data were presented as the mean ± standard error of the mean (SEM) and statistical significance was assessed at a 95 % confidence level ($p < 0.05$).

Results and Discussion

Effect of T. catappa seed extract on relative and absolute organ weights
We investigated the impact of seed extract obtained from *T. catappa* and metformin on relative and absolute weights of the liver, heart, kidneys and pancreas. From our results (*figures 1 and 2*), no significant changes ($p>0.05$) in relative and absolute weights was noted for the heart and pancreas both untreated diabetic control and treated diabetic groups compared to the healthy animals in the normal control group. On the contrary, liver and kidney weight were elevated in the untreated diabetic control group relative to the normal group and this was significant at $p<0.05$.

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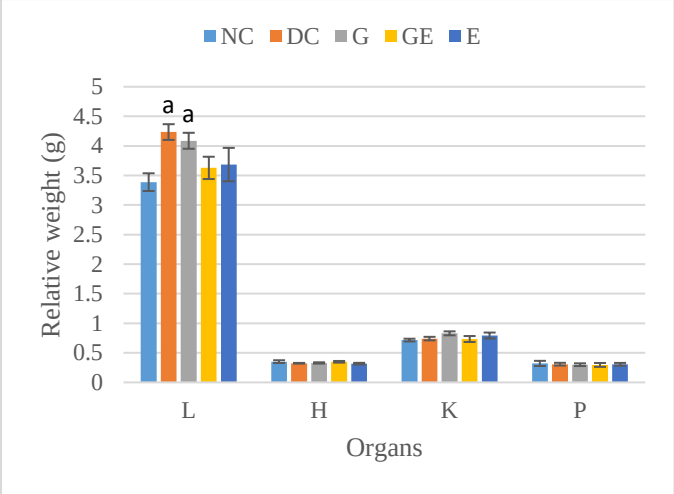

Figure 1: Relative weights (g) of organs/tissues. L = Liver, H = Heart, K = Kidney and P = Pancreas. NC = Normal control, DC = Diabetic control, G = Metformin, GE = Metformin + Extract and E = Extract. a = P < 0.05 vs NC. Values are expressed as Mean ± SEM, n = 6.

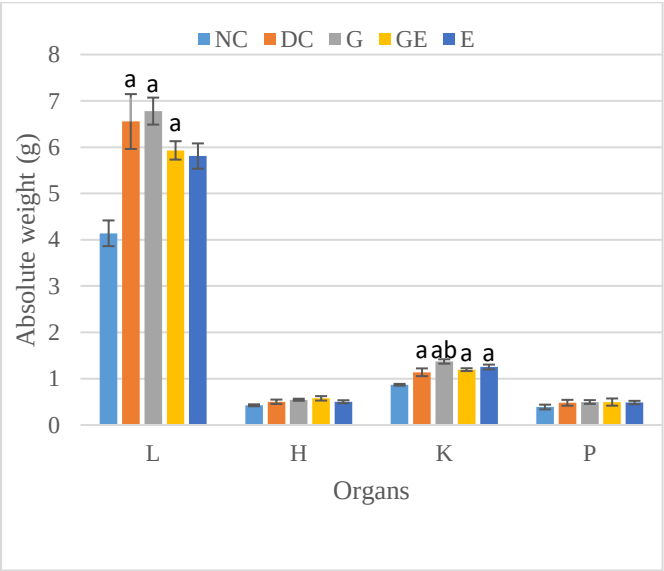

Figure 2: Absolute weights (g) of organs/tissues. L = Liver, H = Heart, K = Kidney and P = Pancreas. NC = Normal control, DC = Diabetic control, G = Metformin, GE = Metformin + Extract and E = Extract. a = P < 0.05 vs NC, b = P < 0.05 vs DC. Values are expressed as Mean ± SEM, n = 6.

It is known that hyperglycaemia and insulin resistance, the hallmarks of type 2 diabetes correlate with elevated accumulation of fats and triacylglycerol in the liver, resulting in fatty liver.[1,17] Therefore, the observed enlargement of the liver in the diabetic group may be ascribed to raised influx of fatty acids to the liver triggered by hyperglycaemia and insulin resistance. Interestingly, treatment with *T. catappa* seed extract ameliorated the weights of both liver and kidney. This suggests that the seeds of *T. catappa* may have modulatory effect on diabetes-induced distortion of organ weight.

Effect of T catappa seed extract on GSH, GPx and SOD activities in the liver and kidneys

In healthy normoglycaemia state, the antioxidant defence mechanism comprising of both enzymatic (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx, glutathione transferase (GSH) and non-enzymatic (glutathione (GSH) and vitamins E and C) act in synergy to prevent oxidative stress and its deleterious consequences.[21] Generally, the superoxide radical is enzymatically converted to hydrogen peroxide which is eventually converted to water and oxygen by GPx and CAT.[21] However, diabetes mellitus progresses with a compromise in redox balance, resulting from increased generation of reactive oxygen species (ROS), consequently producing oxidative stress.[21] Sustained hyperglycaemia further exacerbates this state by suppressing both organ and tissue-based antioxidant defence system, thus promoting oxidative stress and favouring the progression of type 2 DM and related complications.[17] We investigated how *T. catappa* seed extract and its combination with metformin impacted antioxidant enzymes and lipid peroxidation in the present study and from our observation on *figure 3*, GSH activity was significantly elevated in both liver and kidneys in the untreated diabetic control group. Interestingly, this observation was reversed in all treatment groups that received either metformin, *T. catappa* extract or a combination of both. Although this observation was insignificant at p<0.05 except for the group that received the combined treatment, an interesting trend was observed and is worthy of note. GSH is a cysteine-containing peptide synthesized within the cells from its constituent amino acids has been reported to have significant antioxidant effects resulting from the thiol group attached to its cysteine moiety that confers it with the capacity to act as a reducing agent that can be reversibly oxidized and reduced.[22,23] Also, GSH is vital for maintaining antioxidant status within cells. Our finding for GSH level following treatment is similar to one report by Saroja *et al*.[24] who reported that *T. catappa* triggered elevation of GSH in treated experimental animals compared to the controls. It is plausible to suggest that *T. catappa* enhanced GSH level by interrupting the chain reaction of reactive oxygen species by acting either as a hydrogen donor or by transferring electrons.[25] Also, it is possible that the result observed for the kidneys may have been a reflection of the degree of oxidative stress or metabolic dysfunction.

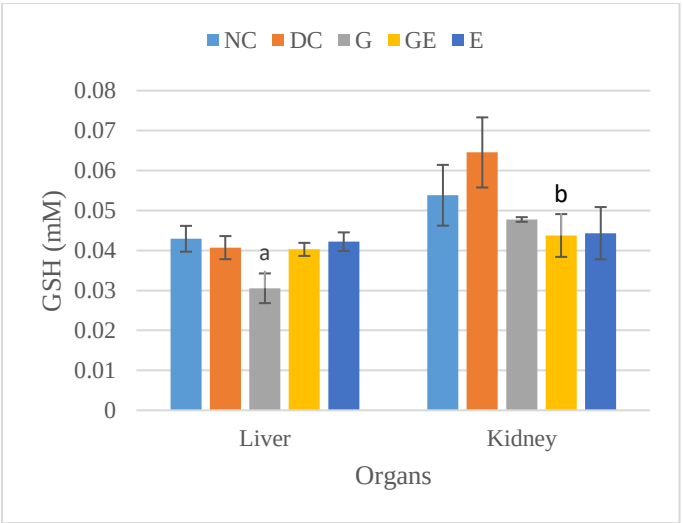

Figure 3: Concentration of reduced glutathione (GSH) in the kidney and liver tissues. NC = Normal control, DC = Diabetic control, G = Metformin only, GE = Metformin + Extract and E = Extract only. a = P<0.05 vs NC, b = P < 0.05 vs DC. Values are expressed as Mean ± SEM, n = 6.

Furthermore, from the results obtained for the effect of seed extract from *T. catappa* on renal and hepatic levels of GPx, it was evident that the untreated diabetic control group presented reduced GPx activity compared to the normal control and upon treatment, an insignificant

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(p>0.05) elevation was observed in all treatment groups compared to the diabetic group additionally, although an inconsistent trend was observed in renal GPx activity following treatment, it was evident that the animals that received *T. catappa* seed extract only presented a significant elevation in GPx activity compared to other treatment groups and the untreated diabetic control that showed significantly low levels of GPx (*figure 4*). The antioxidant protective potential of glutathione peroxidase is dependent on the presence of selenium.[26] GPx acts by oxidizing the selenol moiety of a selenocysteine residue of GPx by hydrogen peroxide.[27] Selenium as a mineral element is listed as an ingredient in many multivitamins and other dietary supplements.[16] This implies that the seed extract under study may probably contain selenium as an antioxidant bioactive principle that can potentially enhance or mimic the activity of GPx. Selenium was reported as part of the mineral content in addition to the phenolic compounds (polyphenols and flavonoids), alkaloids and other essential minerals like Cu, Zn, Fe and Mn in *T. catappa*.[28] Increased GPx activities in both kidney and liver, although mostly insignificant following the treatment with *T. catappa* extract showed a similar trend with previously reported findings,[25] which indicated remarkable reductions of GPx in STZ induced diabetic rats treated with *T. catappa* seed extract.

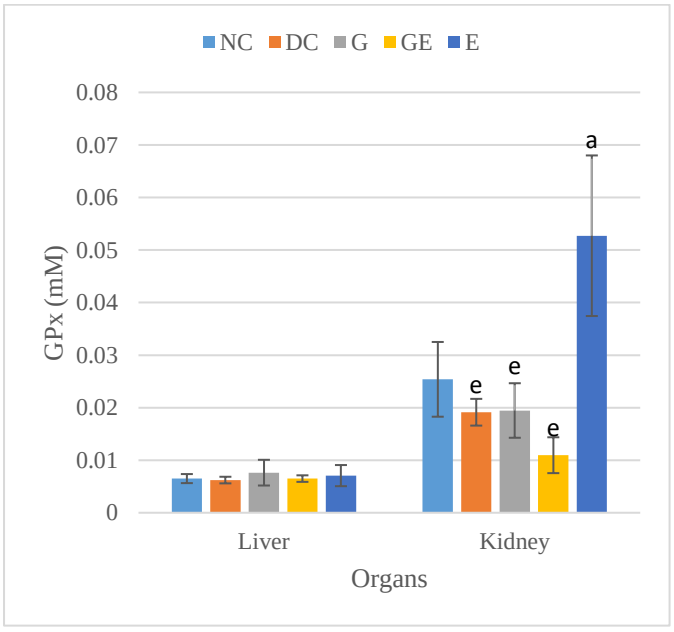

Figure 4: Glutathione peroxidase (GPx) activity (mM) in the kidney and liver tissues. NC = Normal control, DC = Diabetic control, G = Metformin only, GE = Metformin + Extract and E = Extract only. a = *P*< 0.05 vs NC and e = *P*< 0.05 vs E. Values are expressed as Mean ± SEM, n = 6.

Similarly, hepatic SOD activity showed significant elevation at p<0.05 in the untreated diabetic group relative to normal control and treated experimental groups (*figure 5*). This may have been an initial physiological response to streptozotocin induced oxidative stress caused by elevated generation of the superoxide radical reported to be particularly linked to cellular dysfunction.[29] Upon treatment, we observed that although SOD level significantly increased across all groups compare to normal control, *T. catappa* only group and the group that received a combination of extract and metformin showed a greater impact on improving SOD level compared to the reference group. Again, renal SOD activity declined significantly (p<0.05) in the untreated diabetic control group compared to the normal control and treatment group and was reversed following treatment with *T. catappa* seed extract and metformin, with a higher impact observed for the group treated with a combination of the seed extract and metformin. This observation agrees with an earlier study on the antioxidant effects of *T. catappa* seed extracts and its isolated compounds in diabetic Wistar rats.[30]

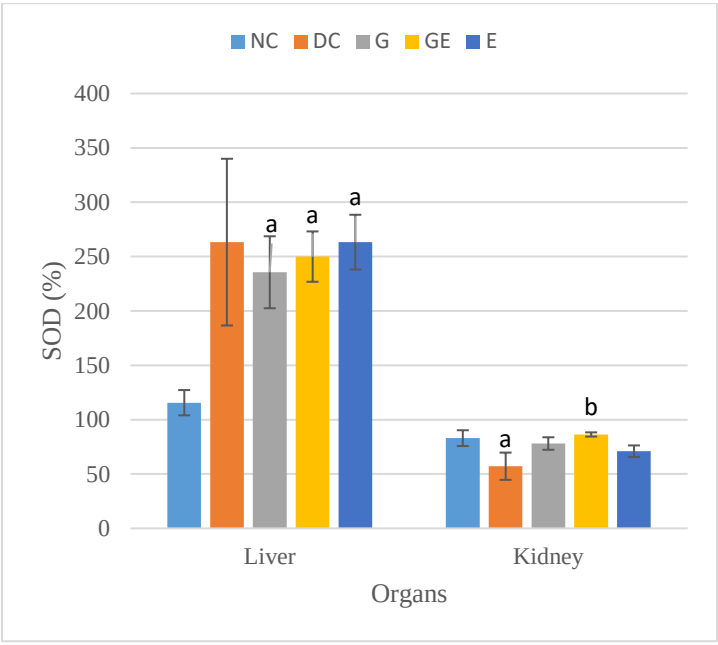

Figure 5: Superoxide dismutase (SOD) activity (%) in the kidney and liver **tissues**. NC = Normal control, DC = Diabetic control, G = Metformin only, GE = Metformin + Extract and E = Extract only. a = *P*< 0.05 vs NC and b = *P*< 0.05 vs DC. Values are expressed as Mean ± SEM, n = 6.

Effect of *T. catappa* on lipid peroxidation in the liver and kidneys

As presented on figure 6, while the activity of MDA in the liver increased significantly (p<0.05) in the untreated diabetic group compared to normal control, treatment with *T catappa* extract and the combination of *T. catappa* seed extract and metformin reversed the elevation and this was comparable to normal control and significant at p<0.05. Surprisingly, it was observed that the reference drug, metformin significantly elevated the activity of MDA comparable to animals in the normal control group. For the kidneys, MDA concentration increased significantly in the untreated diabetic animals and the animals that received metformin and *T. catappa* seed extract alone compared to the normal control group. The distortion in the concentration of antioxidant enzymes revealed in the present study is concomitant with increase in MDA concentration observed in the diabetic animals and is an indication of distorted antioxidant defence, predisposing to the observed oxidative stress. Interestingly, the combination of metformin and *T catappa* seed extract significantly (p<0.05) decreased MDA level compared to all treated groups. The impact of *T. catappa* seed extract alone on the activity of MDA in the liver and kidneys was inconsistent in the present study and it was evident that a combination of *T. catappa* seed extract and metformin presented a better effect on decreasing MDA level and this is consistent with literature.[31] Again, *T. catappa* seed extract has been reported to contain significant concentration of phenolic compounds including triterpenoids like ursolic acid and asiatic acid that are potent scavengers of both hydroxyl radicals and peroxyl radicals, thus preventing lipid peroxidation.[25] Additionally, one study reported that 2,23 - dihydroxy ursolic acid (DHUA), a potent triterpenoid antioxidant was the major bioactive compound in *T. catappa*.[31] It is plausible to suggest that the presence of DHUA as well as mineral elements including Zn, Cu, Mn contained in the seed extract which are cofactors for SOD, may have contributed to the observed antioxidant effect of *T. catappa* and its impact on modulating oxidative stress in this study.

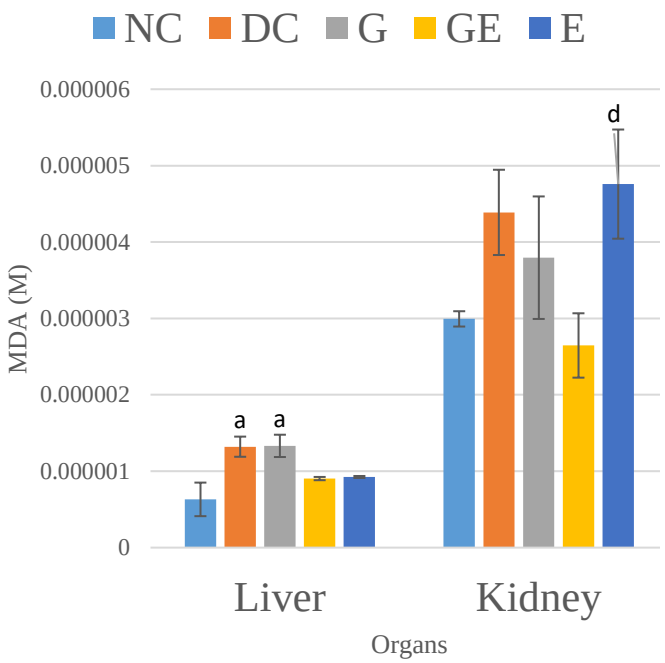

Figure 6: Malondialdehyde (MDA) concentration in the kidney and liver tissues. NC = Normal control, DC = Diabetic control, G = Metformin only, GE = Metformin + Extract and E = Extract only. a = $P < 0.05$ vs NC and b = $P < 0.05$ vs DC. Values are expressed as Mean ± SEM, n = 6.

Conclusion

The presented study investigated the antioxidative potential of *T. catappa* seed extract and metformin on the liver and kidneys of diabetic Wistar rats. The findings revealed that *T. catappa* seed extract ameliorated hyperglycaemia-induced oxidative stress and organ compromise in diabetic Wistar rats, either as monotherapy or in combination with metformin. It is therefore concluded that the extract from *T. catappa* seeds possesses significant antioxidative effects and may be used in combination with metformin to manage oxidative stress and related complications associated with type 2 diabetes mellitus.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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