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Hepatoprotective Effect of *Andropogon gayanus* against Paracetamol- and Carbon Tetrachloride-Induced Liver Toxicity in Rats

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ABSTRACT

Andropogon gayanus has found use in tropical Africa for its vast medicinal properties including liver healing potentials. This study investigated the efficacy of *Andropogon gayanus* extract in paracetamol- and carbon tetrachloride-mediated hepatic injury in rats. Two models were employed to study the toxicity. The first was with 3 g/kg of paracetamol orally on day four and secondly with 1 mL/kg carbon tetrachloride intraperitoneally (1:1 in olive oil) on the third and fourth day, respectively. The efficacy of the extract was tested using varying doses of 200, 400 and 800 mg/kg, respectively for five days. After drug treatments, animals were subjected to humane death while blood sample was taken for determination of liver function markers [(alanine aminotransferase (ALT), aspartate aminotransferase (AST), alanine phosphatase (ALP), and bilirubin) with level of oxidative stress by assessing (malondialdehyde (MDA), catalase (CAT), gluthathione (GSH) and superoxide dismutase (SOD)] while the liver was excised for histological studies. With an estimated LD_{50} value of greater than 5000 mg/kg, the extract is said not to be toxic. Phytochemistry showed that tannins, triterpenes, saponins, flavonoids, glycosides and alkaloids were present. Pre-treatment with extract at 400 mg/kg as well as 800 mg/kg showed significant ($p \leq 0.05$) reduction in all serum liver markers with significant ($p \leq 0.05$) amelioration of oxidative stress when compared to the toxicity control. Results from this research could indicate that methanol extract of *Andropogon gayanus* possesses antioxidant and hepatoprotective potentials and may be beneficial for the treatment of liver diseases.

Keywords: *Andropogon gayanus*, Carbon tetrachloride, Paracetamol, Oxidative stress, Liver, Toxicology.

Introduction

The liver is one of the principal organs in the body and is involved in synthesis, metabolism, storage and detoxification.[1] It's role in the metabolism of xenobiotics makes it particularly susceptible to severe toxicities which are often in form of circulatory, neoplastic, and microbial insults.[2,3] Diseases of the liver are widespread and lead to a lot of deaths worldwide. These diseases are predominantly hepatitis due to viral infections, alcohol-mediated liver injury, liver cirrhosis and liver cells carcinoma.[3,4] Adequate therapeutic measures are hence required to reduce the incidence and associated deaths. Orthodox drugs available for the management of liver diseases usually predispose to adverse effects especially after prolonged use.[5] In addition, due to high cost; they are often not easily accessed by rural dwellers.[6] Hence, newer therapeutic options that are more accessible and affordable with fewer side effects have been sought for by studying medicinal plants.[6,7]

Andropogon gayanus Kunth also known as Gamba grass in English is a widely accessible and used plant medicine of the Poaceae family. It is a nutritive forage[8] locally known as *Gamba* or *Tsaure* and *Eruwa ako* among the Hausa and Yourba natives of Nigeria respectively. Ethnomedicinal uses of this plant from folkloric claims across Africa have been documented. Some of such findings from past decades showed that it has been used as a purgative by locals in Senegal, and for the amelioration of cough and bronchitis in Central African Republic. In addition, it is used for treatment of diarrhoea, hiccups and for wound healing in Nigeria.[9] Furthermore, it is used for its analgesic and antifungal properties in Mali[10] and for its nasal decongestive potentials among natives of Niger Republic.[11] Although there is dearth of documented evidence validating these claims, the safety profile[12] and antinociceptive[13] activities have been established. Currently, there is no scientific validation for the use of *Andropogon gayanus* for the management of liver diseases; hence, this study investigated the hepatoprotective potentials of methanol extract of *Andropogon gayanus* in paracetamol- and carbon tetrachloride induced hepatic injury.

Materials and Methods

Drugs and chemicals

Carbon tetrachloride (Sigma Chemicals Co, USA), olive oil (Metaluni S.P.A., Italy), paracetamol analar grade powder (Sigma Chemicals Co, USA), Silymarin (Micro Labs Limited, India), formalin solution (Sigma Chemicals Co, USA), Randox® analytical kits (Randox Laboratories Ltd., UK), methanol extract of *Andropogon gayanus* (MEAG).

Animals

Male Wistar rats of between 162-170 g in weight were purchased at Pharmacology and Toxicology Departmental Animal House,

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University of Nigeria, Nsukka. They were transported in cages to Gregory University animal house and were given 15 days for acclimatization prior to the study. They were housed in clean plastic cages with saw dust beddings and with constant supply of food and water. The study was in accordance with ethical directives (2010/63/EU) for animal handling proposed by the European parliament and in line with the Gregory University ethical considerations for animal use and care.

Collection of plant material

Andropogon gayanus fresh leaves were fetched on a cold evening in July 2018 within Samaru Zaria, Kaduna state. Identification and authentication by a botanist were ensured by comparing with a previous voucher number 247 in the Department of Plant Sciences.

Extraction of plant

Freshly collected leaves were dried at room temperature for 14 days and thereafter pounded to powdered form with aid of a mortar and pestle. The powdered material (980 g) was transferred into a jar of 1000 mL aqueous methanol. This was left to stand for 48 hours within which shaking of the jar was done within intervals and filtered thereafter. Using an evaporator, the obtained filtrate was evaporated at a regulated temperature of 40-60°C until dryness was achieved, and a dark greenish semi-solid extract was obtained. Percentage yield was calculated as shown in equation 1:

$$percentage\ yield = \frac{\text{weight of dried extract} \times 100}{\text{weight powdered plant}} \quad \text{.....Equation 1}$$

Phytochemical screening

This was done using a previously established protocol.[14]

Acute toxicity study

The two phased method for acute toxicity testing described by Lorke was used.[15] Initially, 9 rats equally assigned to 3 groups were treated with MEAG at 10 mg/kg, 100 mg/kg and 1000 mg/kg respectively via the oral route. The rats were closely monitored for 24 hours for possible manifestation of symptoms of toxicities or mortality. The second phase had three rats with each receiving the extract orally at 1600, 2900 and 5000 mg/kg respectively. They were also monitored in a similar manner as the rats in the initial phase.

Paracetamol toxicity model

The protocol previously employed by Mohammed et al was adopted.[7] Six groups made up of five rats were used. The first group were normal control and treated with 1 mL/kg of distilled water. Second group were toxicity group treated with 3 g/kg of paracetamol on day 4. Group 3 rats received 100 mg/kg silymarin for five days with 3 g/kg of paracetamol on day 4 an hour before paracetamol. Rats in groups 4, 5 and 6 received MEAG at 200 mg/kg, 400 mg/kg and 800 mg/kg respectively for 5 days and with 3 g/kg of paracetamol on day 4 an hour before MEAG. All rats were treated orally across all groups. The rats were euthanized 48 hours after the last paracetamol treatment, and blood samples were collected from jugular veins into anticoagulant free vacutainers and centrifuged at 4000 rpm in a test tube. The obtained serum was used to determine levels of hepatic markers [aspartate aminotransferase (AST), total bilirubin (TB), alkaline phosphatase (ALP), and alanine aminotransferase (ALT)] and oxidative stress level [superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT), with lipid peroxidation product, malondialdehyde (MDA)] using protocols described in the kits (Randox Laboratories Ltd., UK) as adopted previously.[16]

Carbon tetrachloride-induced hepatotoxocity

A protocol earlier proposed was adopted.[6] Thirty rats were shared equally into six groups. Group one was maintained as normal and treated with 1 mL/kg of distilled water. Group two served as the toxicity control, receiving carbon tetrachloride (1:1 in olive oil) on days three and four. Those in the third group received 100 mg/kg silymarin for five days. In addition, they received carbon tetrachloride on days 3 and 4 an hour prior to silymarin administration. Groups 4, 5 and 6 were treated with MEAG at 200 mg/kg, 400 mg/kg and 800 mg/kg respectively for five days, and CCl_4 (1:1 in olive oil) on days 3 and 4 an hour before extract administration. CCl_4 was administered via the *i.p*. route while other treatments across the groups were done orally. Animals from all groups were humanely sacrificed by chloroform inhalation 48 hours after the last CCl_4 treatment and blood samples via jugular veins were collected into anticoagulant free vacutainers. Serum was obtained by spinning in a centrifuge. Serum hepatic markers with antioxidant profile (similar to paracetamol model) were assessed using description it the kits (Randox Laboratories Ltd., Ardmore, UK) as previously adopted.[16]

Liver histology

At the end of paracetamol induced-toxicity model, the liver of the rats were excised and preserved as previously described.[17] The liver tissues were dehydrated through varying concentration of ethanol and thereafter embedded in paraffin. The tissues were then cut into sections with an approximate thickness of 6 µm by means of a microtome. Staining was done with haematoxylin and eosin (H&E) and thereafter viewed microscopically for possible alterations in histoarchtecture.[18]

Statistical analysis

Data were initially subjected to Levene's test for homogeneity and thereafter, statistical relationship was determined with One Way ANOVA and Bonferroni tests using SPSS version 22. *P* values of less than or equal to 0.05 were considered significant. Liver and antioxidant markers were shown as mean and standard error of mean.

Results and Discussion

The methanol leaf extract of *Andropogon gayanus* obtained was a sticky and dark greenish semi-solid substance with a distinct sweet smell. The extract gave a percentage yield of 2.1% $^{w}/_{w}$ which is similar to previous reports.[12] Phytochemistry of *Andropogon gayanus* showed that cardiac glycosides, triterpenes and saponins were present. Others are flavonoids, tannins, glycosides and alkaloids while steroids and anthraquinones were not detected. This result corroborates previous findings where similar constituents were reportedly present in the root extracts.[13] Phytochemicals found in plants confer on them their characteristic pharmacological activities. These constituents may be responsible for the observed hepatoprotection and antioxidant activities observed in this study.

The use of plant-based therapy for various ailments in Tropical Africa is a common occurrence even without validating efficacy and safety. The LD_{50} value of *Andropogon gayayus* was above 5000 mg/kg. This agrees with recent report[13] where the root extract was shown to have similar LD_{50} value. The acute toxicity study gives an insight to the relative safety of the plant. This may signify some degree of safety as no observable sign of toxicity was recorded after oral acute administration in rats.[15] LD_{50} may not accurately represent the exact level of toxicity or safety of a substance; however, it is an important tool used to determine safety margins and does not preclude need for complete toxicological examination.[19]

Effect of *Andropogon gayanus* extract on markers of liver function in paracetamol-induced liver toxicity is shown in Table 1. All markers for liver function (AST, ALT, ALT and bilirubin) were shown to be higher significantly ($p \leq 0.01$) in rats that received paracetamol alone when compared to normal rats, indicating liver toxicity. Abnormally high levels of these markers above normal range have been used as markers for determining liver toxicity.[20] However, treatment with paracetamol in combination with either silymarin or 400 mg/kg and 800 mg/kg of MEAG, produced significantly ($p \leq 0.01$) lower serum hepatic markers when compared to treatment with paracetamol alone. This implies that the extract offers a dose dependent amelioration of liver toxicity in paracetamol-induced liver toxicity. Histological results are shown in Figure 1. The result show evidence of toxicity after treatment with paracetamol, manifested as moderate necrosis and kuffer cell hyperplasia (Figure 1b). Treatment with MEAG at 400

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mg/kg and 800 mg/kg shows amelioration in toxicity with slight pyknosis of the nucleus (Figure 1e) and slight hepatocellular necrosis (Figure 1f) respectively in a similar manner as that shown by silymarin (Figure 1c).

One of the hallmarks of hepatocellular damage is loss of functional and structural integrity of the parenchymal cells.[21] This may result in leakage within the cells to release liver enzymes into circulation which manifested as elevation of serum hepatic markers as observed after administration of paracetamol as a single agent in this study. Although incidence of paracetamol-mediated hepatic toxicities are rarely reported in humans at therapeutic doses; its role in liver damage in animal models especially at higher doses has been established and has found use as a model for studying liver diseases.[21,22,23] The major pathway in the metabolism of paracetamol includes conjugation with both sulphuric acid and glucuronic acid. When administered at normal therapeutic doses, a fraction of paracetamol is metabolised to produce *N*-acetyly-*p*-benzoquinone imine (NAPQI) by cytochrome P450. NAPQI is a toxic and highly reactive species which is normally detoxified with gluthanione (GSH) by means of conjugation to produce a non-toxic mercapturic acid which is excreted in urine.[24] At higher doses however, the very toxic NAPQI accumulates due to saturated conjugation pathways with consequent depletion of endogenous antioxidant mechanisms to expose the liver cells to oxidative stress. This could result to deleterious liver injury characterized by eosinophilic cytoplasm with nuclear pyknosis in addition to lesions within the hepatic cells.[24,25]

Effect of the extract on oxidative stress in paracetamol-induced toxicity is shown in Table 2. Treatment with paracetamol alone showed significantly ($p \leq 0.01$) lower antioxidant markers (CAT, SOD and GSH) and significantly ($p \leq 0.01$) higher oxidative stress marker (MDA) when compared to normal. Treatment with paracetamol either in the presence of silymarin or the extract at 400 mg/kg or 800 mg/kg showed significant ($p \leq 0.05$) difference in these markers when compared to treatment with paracetamol alone. This may imply that the observed hepatoprotection was due to the antioxidant potentials of the extract. This is because methanol extract of *Andropogon gayanus* dose dependently inhibited lipid peroxidation and improved endogenous antioxidant levels in a similar pattern with improving markers for liver function. This could be a benefit of the presence of phytochemical constituents which confers the antioxidant and hepatoprotective potentials on the plants. Presence of phytochemicals in plants is responsible for their biological activities.[26] Some of the constituent of the extract such as tannins, flavonoids and triterpenes have been previously reported to possess hepatoprotective properties.[1] In addition phenol and flavonoid rich plants and compounds have been reported to exert natural antioxidant effects.[27,28] This may explain the observed antioxidant and hepatoprotection produced by the extract in paracetamol-induced liver toxicity. Similarly, silymarin is a polyphenolic flavonoid derived from *Silybum marianum* which has shown different pharmacological potentials like anti-inflammatory, hepatoprotective and as an antioxidant as shown in this study.

Carbon tetrachloride is a clear liquid with toxicity potentials affecting various organs and systems in the body. The extent of carbon tetratchloride-mediated liver toxicity depends on the duration of exposure and the dose which ranges from 0.1 to 3mL/kg when administered via the intraperitoneal route leading to centrilobular necrosis, liver steatosis and cirrhosis.[29] Effect of *Andropogon gayanus* on liver function markers in CCl_4-induced liver toxicity is shown in Table 3. In this model also, markers for hepatic toxicity were all significantly ($p \leq 0.01$) elevated in the toxicity control rats in comparison to normal rats. This is similar to other reports from similar studies where hepatic markers were elevated after treatment with CCl_4.[28] Carbon tetrachloride induces hepatotoxicity through bioactivation of a liver rich membrane protein CYP2E1 cytochrome enzyme, which leads to the formation of trichloromethyl free radicals and reactive oxygen species (ROS). These ultimately result in protein oxidation through lipid peroxidation-mediated oxidative stress to bring about hepatocellular damage.[29] In addition, inflammatory mediators activated from macrophages of hepatic origins are released to exacerbate CCl_4-mediated hepatic damage.[30] Pre-treated rats with either the standard drug or with the extract at 400 mg/kg or 800 mg/kg respectively resulted in significantly ($p \leq 0.05$) lower serum levels of the markers in comparison to toxicity control rats similar to result obtained in the paracetamol model. The extract at 200 mg/kg produced only a mild protection from CCl_4-mediated liver injury, showing lower levels of markers which do not significantly differ from toxicity control. Although the extract of *Andropogon gayanus* did not show any hepatoprotection at low dose against CCl_4-induced hepatotoxicity, higher doses were shown to ameliorate hepatoxicity. In addition, there were evidences to suggest that the hepatoprotection was due to its antioxidant potentials.

Effect of the extract on antioxidant profile in CCl_4-induced toxicity is shown in Table 4. In this study, increase in lipid peroxidation was significant ($p \leq 0.01$) in rats that received only CCl_4, with significant ($p \leq 0.01$) decrease in endogenous antioxidant reserve. This confirms earlier reports that implicates oxidative stress in CCl_4-mediated liver.[28,30] The extract significantly ($p \leq 0.05$) and dose dependently improved endogenous antioxidant reserve as well as decreased lipid peroxidation. This could be as a result of the phytochemical constituents such as tannins, triterpenes, and flavonoids which have been reported to possess antioxidants and hepatoprotective activities.[26] Plant organs such as stems, fruits, leaves, seeds and flowers are shown to be common reservoirs for flavonoids. This could explain the antioxidant and hepatoprotective effects produced by the leaf extract of *Andropogon gayanus* in both paracetamol and carbon terachloride-induced liver toxicity respectively.

Table 1: Effects of methanol extract of *Andropogon gayanus* on paracetamol-induced hepatotoxicity

Groups	AST (U/L)	ALP (U/L)	ALT (U/L)	TB (µmol/L)
Normal control	41.37 ± 1.26	43.44 ± 0.91	32.57 ± 1.26	6.21 ± 1.28
PCM (toxicity control)	84.27 ± 1.65**	96.38 ± 1.08**	71.71 ± 1.66*	22.16 ± 1.55**
SLY + PCM	44.21 ± 1.61$^{\#}$	47.81 ± 1.33$^{\#}$	40.74 ± 1.23$^{\#}$	8.45 ± 1.75$^{\#}$
MEAG (200) + PCM	64.56 ± 0.98*	70.81 ± 1.43*	62.77 ± 1.87*	18.22 ± 1.22*
MEAG (400) + PCM	50.56 ± 1.22$^{\#}$	50.19 ± 1.90$^{\#}$	44.72 ± 1.65$^{\#}$	14.92 ± 1.25*
MEAG (800) + PCM	46.21 ± 1.00$^{\#}$	47.75 ± 1.65$^{\#}$	38.22 ± 1.54$^{\#}$	9.76 ± 1.88$^{\#}$

Data = mean ± SEM, n = 6, * represents $p \leq 0.05$ in comparison to normal control, ** represents $p \leq 0.01$ in comparison to normal control, $^{\#}$ represents $p \leq 0.01$ in comparison to toxicity control. Data analysed by One Way ANOVA and Bonferroni's tests, values are significant at $p \leq 0.05$. SLY = silymarin, MEAG = methanol extract of *Andropogon gayanus*, PCM = paracetamol

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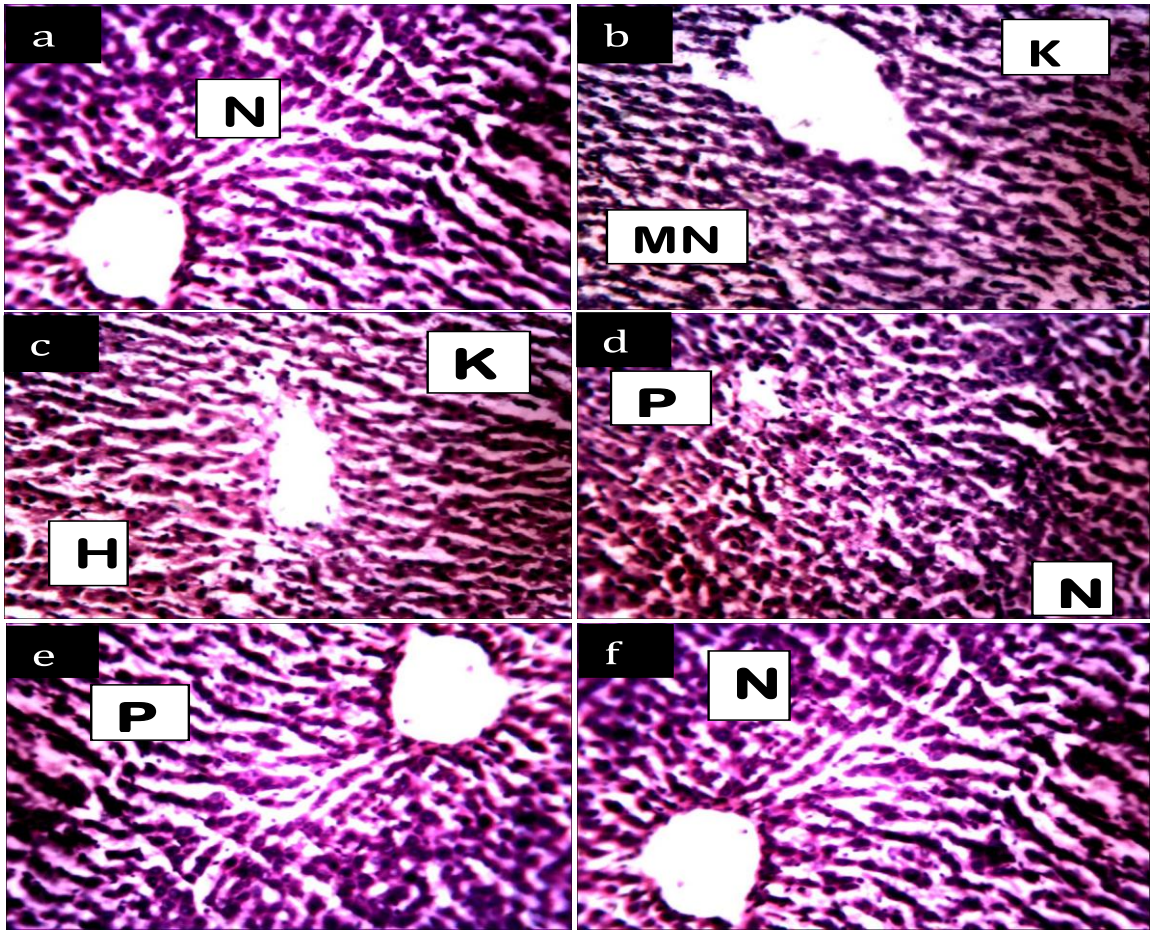

Figure 1: Effect of *Andropogon gayanus* on liver histology in paracetamol-induced hepatotoxicity (H&E) × 250
Fig 1a; Rat liver section treated with 1mL/kg distilled water showing normal (N) features; Fig 1b: Section of liver of rat treated with PCM showing hepatocellular necrosis (MN) with Kuffer cell hyperplasia (K); Fig 1c: Rat liver section treated with SLY+PCM showing slight hepatocellular necrosis (N) with Kuffer cell hyperplasia (K); Fig 1d: Section of rat liver treated with MEAG 200mg/kg + PCM showing moderate hepatocellular necrosis (N) with slight pyknosis of the nucleus (P); Fig 1e: Section of rat liver treated with PCM + MEAG 400mg/kg showing slight pyknosis of nucleus (P); Fig 1f: Liver section of rat that received PCM + MEAG 800 mg/kg showing slight hepatocellular necrosis (N)

Table 2: Effects of methanol extract of *Andropogon gayanus* on antioxidants levels in paracetamol-induced hepatotoxicity

Groups	MDA (µg/mL)	CAT (U/L)	SOD (U/L)	GSH (U/L)
Normal control	1.78 ± 0.03	42.76 ± 1.26	45.45 ± 1.65	20.16 ± 1.00
PCM (toxicity control)	29.67 ± 0.11**	13.16 ± 1.10**	10.01 ± 0.75*	7.16 ± 1.54**
SLY + PCM	2.41 ± 0.02$^{\#}$	38.11 ± 1.98$^{\#}$	43.07 ± 1.88$^{\#}$	18.01 ± 1.18$^{\#}$
MEAG (200) + PCM	17.48 ± 0.18*	26.41 ± 1.79*	28.75 ± 1.09*	10.29 ± 1.31*
MEAG (400) + PCM	7.33 ± 0.10$^{\#}$	48.36 ± 1.30$^{\#}$	40.51 ± 1.58$^{\#}$	16.68 ± 1.28$^{\#}$
MEAG (800) + PCM	3.70 ± 1.92$^{\#}$	43.88 ± 1.71$^{\#}$	43.68 ± 1.56$^{\#}$	18.17 ± 1.01$^{\#}$

Data = mean ± SEM, n = 6, * represents $p \leq 0.05$ in comparison to normal control, ** represents $p \leq 0.01$ in comparison to normal control, $^{\#}$ represents $p \leq 0.01$ in comparison to toxicity control. Data analysed by One Way ANOVA and Bonferroni's tests, values are significant at $p \leq 0.05$. SLY = silymarin, MEAG = methanol extract of *Andropogon gayanus*, PCM = paracetamol

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Table 3: Effects of methanol extract of *Andropogon gayanus* on liver markers in carbon tetrachloride-induced hepatotoxicity

Groups	AST (U/L)	ALP (U/L)	ALT (U/L)	TB (µmol/L)
Normal control	39.97 ± 0.22	42.34 ± 1.31	35.23 ± 0.76	5.01 ± 1.98
CCl_4 (toxicity control)	85.33 ± 1.08**	98.21 ± 1.22**	79.83 ± 0.49*	21.56 ± 1.65**
SLY + CCl_4	45.01 ± 0.11#	46.56 ± 1.76#	40.74 ± 1.23#	8.45 ± 1.75#
MEAG (200) + CCl_4	68.24 ± 1.88*	66.91 ± 1.98*	61.19 ± 1.07*	18.22 ± 1.22*
MEAG (400) + CCl_4	51.33 ± 1.10#	49.99 ± 2.00#	48.22 ± 1.86#	16.29 ± 0.09*
MEAG (800) + CCl_4	47.08 ± 1.71#	47.55 ± 1.78#	41.87 ± 1.37#	9.22 ± 1.06#

Data = mean ± SEM, n = 6, * represents $p \leq 0.05$ in comparison to normal control, ** represents $p \leq 0.01$ in comparison to normal control, # represents $p \leq 0.01$ in comparison to toxicity control. Data analysed by One Way ANOVA and Bonferroni's tests, values are significant at $p \leq 0.05$. SLY = silymarin, MEAG = methanol extract of *Andropogon gayanus*, CCl_4 = carbon tetrachloride

Table 4: Effects of methanol extract of *Andropogon gayanus* on antioxidants levels in carbon tetrachloride-induced hepatotoxicity

Groups	MDA (µg/mL)	CAT (U/L)	SOD (U/L)	GSH (U/L)
Normal control	1.97 ± 0.01	43.64 ± 1.02	48.54 ± 1.87	22.11 ± 1.69
CCl_4 (toxicity control)	27.33 ± 0.08**	11.12 ± 1.09**	9.11 ± 0.65*	9.86 ± 1.74**
SLY + CCl_4	3.21 ± 0.01#	38.96 ± 1.33#	41.77 ± 1.87#	18.44 ± 1.42#
MEAG (200) + CCl_4	18.24 ± 0.08*	25.11 ± 1.98*	26.28 ± 2.01*	13.32 ± 1.63*
MEAG (400) + CCl_4	8.73 ± 1.00#	49.86 ± 1.70#	41.89 ± 1.03#	17.78 ± 1.86#
MEAG (800) + CCl_4	4.10 ± 1.01#	44.85 ± 1.88#	45.97 ± 1.22#	20.67 ± 1.65#

Data = mean ± SEM, n = 6, * represents $p \leq 0.05$ in comparison to normal control, ** represents $p \leq 0.01$ in comparison to normal control, # represents $p \leq 0.01$ in comparison to toxicity control. Data analysed by One Way ANOVA and Bonferroni's tests, values are significant at $p \leq 0.05$. SLY = silymarin, MEAG = methanol extract of *Andropogon gayanus*, CCl_4 = carbon tetrachloride

Conclusion

Methanol leaf extract of *Andropogon gayanus* has shown hepatoprotective and antioxidant potentials in this study. The observed antioxidant properties may in part be responsible for the hepatoprotection. This suggests that the extract may be of benefit in the management of liver diseases or conditions where oxidative stress is implicated.

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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