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Characterization of anti-plasmodial, analgesic and anti-inflammatory fraction of *Maytenus senegalensis* (lam.) Exell leaf extract in mice

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Abstract

Background: The treatment inadequacy and toxicity associated with conventional anti-malarial, anti-inflammatory and analgesic drugs has called for the search of alternatives from medicinal plants, particularly, their phytochemicals with inherent pharmacological properties. In the present study, purified fraction of *M. senegalensis* leaf was evaluated for antimalarial, anti-inflammatory and analgesic properties.

Method: Antimalarial study was conducted against *Plasmodium chabaudi* and *Plasmodium berghei* using 4 days suppressive test, while anti-inflammatory and analgesic studies were conducted using egg albumin induced paw oedema and acetic acid induced pain model respectively. Sub-acute toxicity was assessed using serum biochemical parameters following 3 weeks administrations of the purified fraction.

Results: The purified fraction of *M. senegalensis* leaf shows dose dependent antiplasmodial activity with percentage curative effects of 15.24 ± 0.89 , 45.70 ± 3.43 and 48.50 ± 4.56 at 75, 150 and 300 mg/kg bw against *Plasmodium chabaudi* and % curative effects of 44.25 ± 3.21 , 72.74 ± 6.54 and 76.30 ± 8.32 respectively against *Plasmodium berghei*. The purified fraction exhibited 53.16 ± 4.09 and 60.76 ± 7.54 anti-inflammatory effect, $43.35 \pm 4.98\%$ and $44.83 \pm 3.86\%$ analgesic effect at 75 and 150 mg/kg bw respectively. GC-MS analysis confirmed the presence of 20 α -3-hydroxy-2-oxo-24-nor-friedela-1(10),3,5,7-tetraen-carboxylic acid-(29)-methylester, 2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro- and 3-hydroxy-20(29)-lupen-28-ol and a terpenes (phytol) as the major antimalarial compounds in the fraction. The purified fraction increases the serum total proteins and transaminases concentrations but had no effect on serum levels of sodium, potassium, chloride, alkaline phosphatase, triglyceride and glucose in the mice.

Conclusion: The purified fraction of *M. senegalensis* leaf exhibited promising antimalarial, analgesic and anti-inflammatory activities. Thus, could serve as a template for the synthesis of new drug.

Keywords: Anti-plasmodial, Anti-inflammatory, Analgesic, *Maytenus senegalensis* (lam.) Exell

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Introduction

Malaria is an infectious protozoic and parasitic disease caused by five *Plasmodium* parasites: *vivax*, *falciparum*, *malariae*, *Knowlesi* and *ovale* [1]. More than half of the world's population are at risk of malaria, with about 212 million new case and 429, 000 death annually [2]. Sub-Saharan Africa accounts for over 90% of the malaria cases and deaths predominantly in children of age below five years and pregnant women [2]. Poor rural dwellers in tropical and subtropical areas are highly vulnerable to this attacked owing to the favorable and ideal climatic condition for the reproduction and development of vectors, and parasites [3]. In addition, drug resistance is one of the major challenges facing malarial eradication program world wide [4].

Inflammation and pains are gaining research popularity owing to the etiologic role they play in various human diseases [5]. Dexamethasone, opioids, morphine and aspirin and other drugs have been established for the management of pain and inflammation; however, these drugs have recorded limited success due to unintended effects such as gastric lesions caused by non-steroidal anti-inflammatory drugs [6, 7]. Thus, the search for drugs alternative from natural product is recommended.

Natural products contain metabolite that has therapeutic values for uses in the managements of several diseases [8, 9]. The therapeutic effect plants are however, associated with their secondary metabolites they contain, particularly the alkaloids, terpenoids, and flavonoids, which are known to play defensive role in plants but exhibited different pharmacological effects in human/animals [10].

Maytenus senegalensis (Lam.) Exell is an African medicinal plant, commonly used traditionally for the treatment of a number of ailments, including rheumatism, snakebites, diarrhoea, eye infection, and dyspepsia [11]. Previous study has demonstrated that the extracts from various parts of *M. senegalensis* possess in vitro anti-plasmodial, anti-leishmanial, and antibacterial activities [12]. However, literature survey revealed dearth of scientific information on the pharmacological activities of purified fraction. The present study, therefore evaluated the antiplasmodial analgesic and anti-inflammatory effects of purified fractions from *Maytenus senegalensis* (Lam.) Exell leaf extract in mice.

Materials and methods

Experimental animals

A total of ninety (90) adult swiss albino mice weighing 25.34 ± 0.98 g were obtained from National Veterinary Research Institute (NVRI), Vom, Plateau State of Nigeria. The mice handling and experimentation was in concordance with the guidelines for laboratory animal

use and care as contained in the European Convention on Animal Care Guidelines and Protocol.

Parasite

Plasmodium chabaudi and *Plasmodium berghei* NK65 chloroquine-sensitive strain was obtained from National Institute of Pharmaceutical Research and Development (NIPRD) Abuja, Nigeria and maintained in the laboratory by serial passage in mice.

Sample preparation

The plant *Maytenus senegalensis* (Lam.) Exell was collected from Bida, Niger state. The plant was authenticated by a botanist, from Department of Biological sciences, Federal university of Technology Minna, Nigeria. The leave was cleaned and air-dried at room temperature. The dried leave was pulverized into a coarse powder using mortar and pestle. The pulverized sample was stored in air-tight container.

Extraction and purification of *Maytenus senegalensis* (lam.) Exell fraction

Maytenus senegalensis (Lam.) Exell leaf (50 g) powder was moistened with 200 mL of 95% ethanol, alkalified with 200 mL of ammonia solution and macerated for 24 h followed by extraction with ethanol. The ethanol extract was filtered, concentrated and treated with 1.0 N hydrochloric acid. The filtrate was further alkalified with ammonia solution and the extract was obtained by fractionation in separating funnel using chloroform [13]. The fraction was purified and subjected to thin layer chromatography to obtained the pure fraction (0.6 g) for structural elucidation [13].

Anti-Plasmodial screening of the purified fraction of *Maytenus senegalensis* (lam.) Exell

Four days (4) suppressive test were used to evaluate the antimalarial properties of the purified fraction of *Maytenus senegalensis* (Lam.) Exell as described by Jigam et al. [14]. A total of 15 *P. berghei* infected mice were randomly grouped into five (I- V) of 3 mice each. Groups I – III animals were treated with 75, 150 and 300 mg/kg body weight each of purified fraction. Groups IV and V received normal saline (2 ml/kg body weight) and chloroquine (5 mg/kg body weight) to serve as negative and positive controls respectively. The same procedures (Four days (4) suppressive test) were repeated for *Plasmodium chabaudi* All the treatments were done orally for 4 consecutive days. Daily parasitaemia count was carried out by preparing a Giemsa stained-thin film and viewed under microscope as described by Jigam et al. [14].

$$\% \text{inhibition} = \frac{\text{Mean parasitemia in negative control} - \text{Mean parasitemia in treated}}{\text{Mean parasitemia in negative control}} \times 100$$

Anti-inflammatory study

Anti-inflammatory activity of the purified fraction was tested using egg albumin induced paw oedema in mice according to the methods of Winter et al. [15]. A total of twelve (12) mice were randomly grouped into four (A- D) of 3 mice each and were administered a single dose of 75 and 150 mg/kg bw of the purified fraction, 150 mg/kg.bw acetylsalicylic acid and 2 ml/kg bw normal saline respectively 30 min before the injection of the albumin into the right hind limb. The percentage inhibition of oedema was calculated for each dose using the formula:

$$\% \text{inhibition} = \frac{\text{Mean increase in paw in negative control} - \text{Mean increase in paw in treated}}{\text{Mean increase in paw in negative control}} \times 100$$

Analgesic study

Analgesic effect was assessed according to the method described by Nwafor et al. [16]. A total of twelve (12) mice were randomly grouped into four (A- D) of 3 mice each and were administered a single dose of 75 and 150 mg/kg bw of the purified fraction, 150 mg/kg.bw sodium diclofenac and 2 ml/kg bw normal saline respectively for 60 min before they were challenged with 0.75% v/v acetic acid. Group D (control group) received 2 mL/kg body weight of normal saline. The number of abdominal constrictions induced by acetic acid were counted after 5 min. Observations were made over 10 min and mean value for each group was calculated. Percentage inhibition of abdominal constriction by the purified fraction and sodium diclofenac were determined in relation to the control.

$$\% \text{inhibition} = \frac{\text{Mean increase abdominal const.in negative control} - \text{Mean increase in abdominal const.in treated}}{\text{Mean increase in abdominal const.in negative control}} \times 100$$

Toxicological study

Animals (5 each) were dosed 0 (control), 75 mg/kg and 150 mg/kg bwt of purified fraction of *Maytenus senegalensis* (Lam.) Exell orally for 3 wks. Procedures described by Shittu et al. [17] was followed during blood sample collection and serum preparation for biochemical analysis. Serum biochemical parameters including alkaline phosphatase (ALP), Aspartate transaminase (AST) and alanine transaminase (ALT) were determined as described previously [18]. The concentrations of serum total proteins [19], sodium, potassium, and chloride [20] were determine using standard methods.

Gas chromatography and mass spectroscopy (GC-MS) analysis of bioactive compounds

The purified fraction of *Maytenus senegalensis* (Lam.) Exell was subjected to Gas Chromatography and Mass Spectroscopy for the determination of bioactive volatile compounds as described previously [21].

Data analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) One-way Analysis of Variance (ANOVA) followed by Duncan Multiple Range Test (DMRT). Data were expressed as means \pm SEM of triplicate determinations. Significant was considered at $p < 0.05$.

Results

Antiplasmodial

The purified fraction of *M. senegalensis* leaf shows dose dependent antiplasmodial activity against *Plasmodium chabaudi* (Table 1) and *Plasmodium berghei* (Table 2). The purified fraction had curative effects of $15.24 \pm 0.89\%$, $45.70 \pm 3.43\%$ and $48.50 \pm 4.56\%$ at 75, 150 and 300 mg/kg bw against *Plasmodium chabaudi* (Table 1) while curative effects of $44.25 \pm 3.21\%$, $72.74 \pm 6.54\%$ and $76.30 \pm 8.32\%$ respectively against *Plasmodium berghei* (Table 2).

Anti-inflammatory

The purified fraction of *M. senegalensis* leaf exhibited dose dependent inhibition egg albumin-induced paw oedema with percentage inhibition of 53.16 ± 4.09 and 60.76 ± 7.54 at 75 and 150 mg/kg bw respectively while ASA exhibited 63.29 ± 5.98 inhibition of paw oedema (Table 3).

Analgesic effect

The purified fraction of *M. senegalensis* leaf exhibited dose dependent abdominal constrictions with percentage inhibition of 43.35 ± 4.98 and 44.83 ± 3.86 at 75 and 150 mg/kg bw respectively while sodium diclofenac (SD) exhibited 74.88 ± 6.87 inhibition of paw oedema (Table 4).

Biochemical parameters

Sub-chronic administration of the purified fraction of *M. senegalensis* significantly ($p < 0.05$) increase the concentrations of transaminases (aspartate transaminase and alanine transaminase), and proteins when compared with the untreated control. However, sodium, potassium, chloride, alkaline phosphatase, triglyceride and glucose concentrations were not ($p < 0.05$) significantly altered by treatment with purified fraction of *M. senegalensis* (Table 5).

Table 1 Antiplasmodial activity of purified fraction of *M. senegalensis* leaf against *Plasmodium chabaudi* Infected mice

	Doses (mg/kg bw)	1	2	3	4	5	6	Mean Parasitaemia	% suppression
MS	75	130.56	120.87	134.09	100.05	88.06	79.67	108.98 ± 6.83	15.24 ± 0.89 ^a
	150	79.05	86.55	80.05	58.03	60.43	54.08	69.53 ± 3.45	45.70 ± 3.43 ^b
	300	80.04	84.35	70.55	60.55	49.55	56.56	66.54 ± 5.98	48.50 ± 4.56 ^b
CQ	5	36.05	42.05	58.05	40.50	22.55	18.05	21.55 ± 2.35	83.50 ± 8.89 ^c
NS	2 ml/kg	136.05	140.55	150.46	122.05	102.05	118.55	128.05 ± 9.89	

Data are MEAN ± SEM of triplicate determinations. Values followed by different superscript are significantly different ($p < 0.05$)

MS: *Maytenus senegalensis* (Lam.) Exell

CQ: Chloroquine

NS: Normal saline.

GC-MS of the purified fraction of *Maytenus senegalensis* (lam.) Exell

The results pertaining to gas chromatography and mass spectroscopy (GC-MS) analysis led to the identification of 13 compounds from the gas chromatography (GC) fractionations. The chromatogram of purified fraction of *Maytenus senegalensis* (Lam.) Exell is shown in Fig. 1. The results were tabulated in Table 6. The results revealed that the presence of 3-hydroxy-20(29)-lupen-28-ol (12.95%), 20 α -3-hydroxy-2-oxo-24-nor-friedela-1(10), 3,5,7-tetraen-carboxylic acid-(29)-methylester (6.0%), 2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro- (7.0%), and phytol (1.44%) as the major phytochemicals in the purified fraction of *Maytenus senegalensis* (Lam.) Exell. Other compounds identified in minute amounts include n-Hexadecanoic acid (0.207%), 9,12-Octadecadienoic acid, methyl ester (1.67%), cis-Vaccenic acid (0.490%), 6-Methyl-cyclodec-5-enol (0.66%) each with different biological activities (Table 6).

Discussion

The anti-plasmodial potency of some plants has been associated with the presence of some secondary metabolites such as alkaloids [9]. Findings presented in Table 3 shows that the purified fraction of *M. senegalensis* demonstrated a good antimalarial

activities, in concordance with the classification of Munoz et al. [22], which stated that the antiplasmodial agent are classified on the basis of the percentages parasite inhibition as moderate, "good", and "very good when there is percentage inhibition of above 50% at metabolite concentration of 500, 250 and 100 mg/kg bwt. However, the antiplasmodial effects of the purified fraction at 150 and 300 mg/kg bw not significantly difference ($p > 0.05$), this may suggest that the maximum anti malaria effect of the purified fraction was achieved at 150 mg/kg. The proposed mechanism of antiplasmodial effect of the purified fraction could be by the elevation of erythrocytes oxidation and inhibition of the plasmodium protein synthesis, a mechanism that has been attributed to antimalaria activities of some phytoconstituents [23].

Evidence for the anti-inflammatory properties of flavonoids and alkaloids have been reported by several studies using different models of inflammation [24–26]. The significant anti-inflammatory effects demonstrated by the purified fraction of *M. senegalensis* leaf could be mechanistically explained by the fact that phytochemicals are known to inhibit the enzymes involved in the production of inflammatory mediator including cyclooxygenase and 5-lipoxygenase pathways [27].

Table 2 Antiplasmodial activity of purified fraction of *M. senegalensis* leaf against *Plasmodium berghei* Infected mice

	Doses (mg/kg bw)	1	2	3	4	5	6	Mean Parasitaemia	% suppression
MS	75	60.36	66.25	70.25	64.25	65.25	78.25	67.83 ± 5.43	44.25 ± 3.21 ^a
	150	28.25	34.05	36.25	29.05	34.05	38.25	33.17 ± 3.45	72.74 ± 6.54 ^b
	300	30.05	34.05	25.05	26.25	32.25	26.05	26.83 ± 2.90	76.30 ± 8.32 ^b
CQ	5	15.05	18.36	26.25	31.25	16.25	20.05	21.05 ± 3.45	82.74 ± 7.56 ^c
NS	2 ml/kg	122.05	120.07	115	116.25	131.25	126.67	121.67 ± 7.54	

Data are MEAN ± SEM of triplicate determinations. Values followed by different superscript are significantly different ($p < 0.05$)

MS: *Maytenus senegalensis* (Lam.) Exell

CQ: Chloroquine

NS: Normal saline

Table 3 Effect of purified fraction of *M. senegalensis* leaf on oedema

Extract	Doses (mg/kg bw)	20	40	60	80	100	120	Mean	Inhibition (%)
MS	75	0.32 ± 0.05	0.38 ± 0.02	0.38 ± 0.03	0.36 ± 0.02	0.38 ± 0.04	0.38 ± 0.04	0.37 ± 0.04	53.16 ± 4.09 ^a
MS	150	0.30 ± 0.03	0.36 ± 0.04	0.34 ± 0.02	0.30 ± 0.06	0.28 ± 0.03	0.30 ± 0.02	0.31 ± 0.02	60.76 ± 7.54 ^b
ASA	150	0.30 ± 0.02	0.30 ± 0.02	0.26 ± 0.04	0.28 ± 0.02	0.32 ± 0.02	0.30 ± 0.03	0.29 ± 0.06	63.29 ± 5.98 ^b
NS	2 mL/kg	0.80 ± 0.04	0.80 ± 0.03	0.76 ± 0.05	0.78 ± 0.03	0.82 ± 0.05	0.80 ± 0.05	0.79 ± 0.03	

Data are MEAN ± SEM of triplicate determinations. Values followed by different superscript are significantly different ($p < 0.05$)
 MS: *Maytenus senegalensis* (Lam.) Exell
 ASA: Acetylsalicylic acid
 NS: Normal saline

The present study revealed that the purified fraction of *M. senegalensis* leaf significantly decreased the acetic acid induced pain in mice. This study showed that the purified fraction of *M. senegalensis* leaf contains active analgesic component [28]. This finding is in concordance with previous studies on morphine alkaloid fraction of *Stephia glabra* known as Gindarudine, which showed significant analgesic effect when tested by the same method [29]. The significant analgesic and anti-inflammatory effects of the purified fractions of *M. senegalensis* leaf extracts in vivo is noteworthy. Plants with these added pharmacological phenomena in conjunction with antiplasmodial effects are better antimalarials than plants with the later potential only [30, 31].

Biochemical parameters have been widely used as an indicator of pathological condition, toxicology or safety of a test substance, treatment outcome and general health status of animals [32–35]. Among these biochemical parameters, transaminases, alkaline phosphatases, proteins, lipid profile and electrolyte are the most widely employed in assessing the liver and kidney integrity following plant extract administration to animals [33]. Alterations in the normal activities or concentrations of these biochemical parameters are conventional indicators of any of the following conditions; renal or nephrotic impairments, hepatocellular injury, cellular leakage, loss of functional integrity of cell membrane, biliary cirrhosis or liver hepatitis [32]. Consequently, the concentrations of triglyceride, sodium, potassium,

chloride, alkaline phosphatase and glucose concentrations were not significantly ($p < 0.05$) altered by treatment with 75 and 150 mg/kg bw *M. senegalensis* purified fraction. This is an indication that the functional integrity of kidney is well preserved and that the purified fraction of *M. senegalensis* does not induced any form of pathological conditions to the kidney. The increases in transaminases (aspartate transaminase and alanine transaminase), and proteins concentration is an indication that the liver integrity is not well preserved. The purified fraction might have interfered with the equilibrium in protein metabolism in favor of anabolism. Such drastic increase in protein levels could, negatively affect cellular homeostasis and consequently effect the health of the animals [36, 37].

GCMS analysis of the purified fraction confirmed the presence of 20 α -3-hydroxy-2-oxo-24-nor-friedela-1(10), 3,5,7-tetraen-carboxylic acid-(29)-methylester, 2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro, 3-hydroxy-20(29)-lupen-28-ol and a terpenes (phytol) as the major constituents of the fraction. The antimalarial activities of these compounds have been previously documented, in addition phytol have also been reported for anti-inflammatory activities.

Conclusion

The purified fraction of *M. senegalensis* leaf exhibited promising antimalarial, analgesic and anti-inflammatory activities. Thus, could serve as a template for the synthesis of new drug.

Table 4 Effect of purified fraction of *M. senegalensis* leaf on abdominal constrictions in mice

Extract	Doses (mg/kg bw)	20	40	60	80	100	120	Mean	Inhibition (%)
MS	75	20.50 ± 1.98	20.56 ± 1.07	26.50 ± 2.87	21.05 ± 1.08	28.56 ± 3.78	23.00 ± 1.89	23.00 ± 1.89	43.35 ± 4.98 ^a
MS	150	19.55 ± 0.98	22.51 ± 2.87	18.56 ± 1.09	26.55 ± 0.89	27.56 ± 4.87	22.40 ± 0.97	22.40 ± 0.97	44.83 ± 3.86 ^a
SD	150	9.00 ± 0.25	8.56 ± 1.09	11.05 ± 0.05	10.21 ± 0.56	13.32 ± 0.99	10.20 ± 0.78	10.20 ± 0.78	74.88 ± 6.87 ^b
NS	2 mL/kg	36.50 ± 3.89	38.55 ± 4.86	42.55 ± 3.87	40.06 ± 4.89	47.50 ± 6.07	40.65 ± 8.09	40.65 ± 8.09	

Data are MEAN ± SEM of triplicate determinations. Values followed by different superscript are significantly different ($p < 0.05$)
 SD: sodium diclofenac
 MS: *Maytenus senegalensis* (Lam.) Exell
 NS: Normal saline

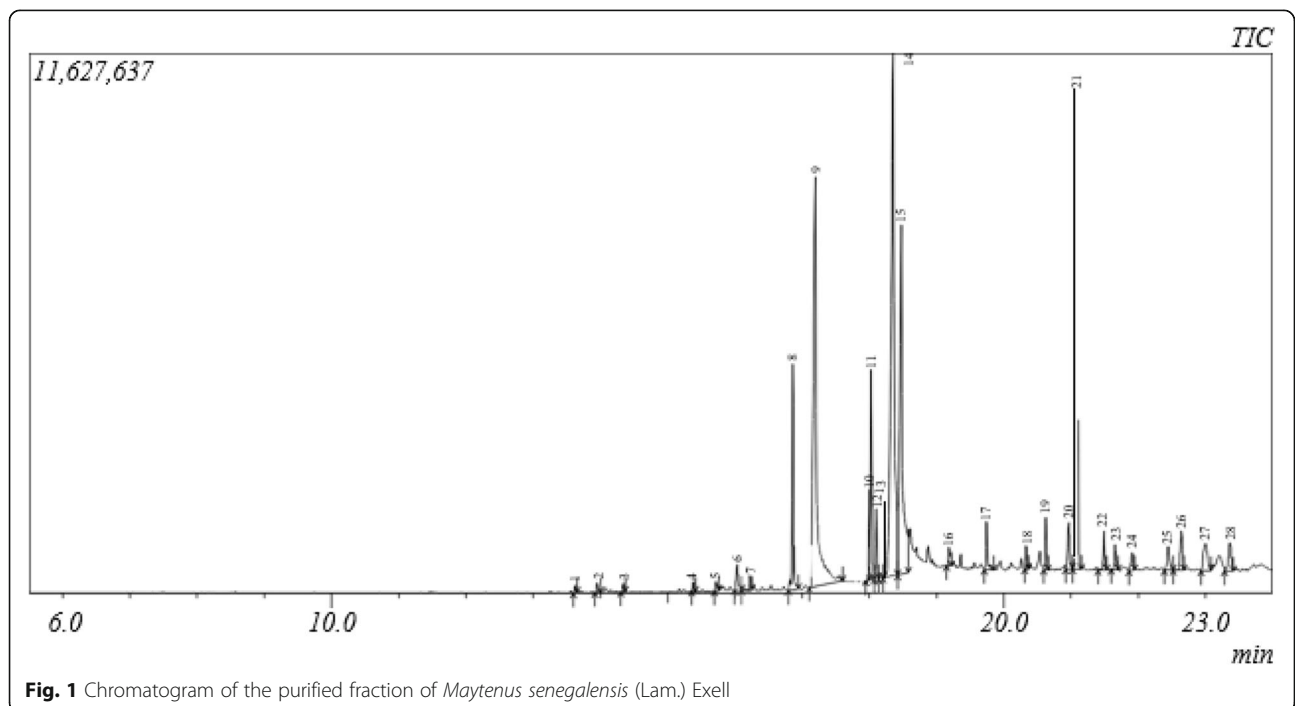
Table 5 Effect of purified fraction of *M. senegalensis* leaf on biochemical parameters in mice

	Control (normal saline)	75 mg/kg bw	150 mg/kg bw
Weight (g)	26.51 ± 0.78 ^a	27.85 ± 1.23 ^a	28.23 ± 0.98 ^a
Glucose (mg/dL)	107.64 ± 2.90 ^a	109.03 ± 3.87 ^a	117.36 ± 5.98 ^a
Tag	170.97 ± 3.89 ^a	170.93 ± 5.98 ^a	173.70 ± 7.09 ^a
Prot (g/dL)	4.66 ± 0.04 ^a	5.20 ± 0.13 ^b	5.41 ± 0.43 ^b
SGOT	9.50 ± 0.67 ^a	13.50 ± 1.03 ^b	21.75 ± 2.98 ^c
SGPT	6.25 ± 0.56 ^a	11.00 ± 0.76 ^b	18.00 ± 0.65 ^c
ALP	34.5 ± 2.90 ^a	37.25 ± 2.90 ^a	36.09 ± 3.98 ^a
Sodium	134 ± 5.09 ^a	132.5 ± 7.97 ^a	135.97 ± 9.67 ^a
Potassium	3.35 ± 0.54 ^a	3.60 ± 0.43 ^a	3.24 ± 0.21 ^a
Chloride	101.5 ± 6.98 ^a	103.25 ± 4.89 ^a	108.78 ± 5.89 ^a

Data are Mean ± SEM of triplicate determination. Value followed by different superscript alphabet along the row were significantly different ($p < 0.05$)

Table 6 Phyto-Components identified in the purified fraction of *Maytenus senegalensis* (Lam.) Exell

Peak#	Retention Time	Peak Area%	Height %	Compound Name
1	13.624	0.13	0.26	Dodecanoic acid, methyl ester
2	13.953	7.0	0.33	2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro-
3	15.379	6.0	0.31	20α)-3-hydroxy-2-oxo-24-nor-friedela-1 (10),3,5,7-tetraen-carboxylic acid-(29)-methylester
4	16.031	0.66	0.89	6-Methyl-cyclodec-5-enol
5	16.227	0.38	0.50	3,7,11,15-Tetramethyl-2-hexadecen-1-ol
6	17.197	0.207	14.07	n-Hexadecanoic acid
7	17.992	1.67	3.13	9,12-Octadecadienoic acid, methyl ester
8	18.101	1.44	2.43	Phytol
9	18.170	1.52	2.80	Methyl stearate
10	18.355	0.490	17.94	cis-Vaccenic acid
11	20.336	0.47	0.79	2-methyltetracosane
12	21.095	12.95	16.42	3-hydroxy-20 (29)-lupen-28-ol
13	21.493	0.88	1.33	d-Xylose, diheptyl mercaptal



Acknowledgements

The authors appreciate the funding support of Tertiary Educational Fund of Nigeria and Federal University of Technology Minna.

Conflict of interest

The authors declared no conflict of interest exist.

Authors' contributions

This work is a collaboration of all the authors. All authors read and approved the final manuscript.

Funding

This research is supported by Research grant to Prof Ali Audu Jigam et al. 2019 (TETFUND/FUTMINNA/2016–2017/6TH BRP/17).

Availability of data and materials

All data are available in the manuscript.

Ethics approval and consent to participate

The principles governing the use of laboratory animals as laid out by the Federal University of Technology, Minna Committee on Ethics for Medical and Scientific Research and also existing internationally accepted principles for laboratory animal use and care as contained in the Canadian Council on Animal Care Guidelines and Protocol Review were duly observed.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 8 November 2019 Accepted: 6 August 2020

Published online: 14 August 2020

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