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(RESEARCH ARTICLE)

Musanga cecropioides (Urticaceae) stem-bark mitigates sodium valproate –induced pantoxicity derangement in albino rats

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Abstract

Sodium valproate (SVPA) is indicated for the management of partial and generalized epilepsy with major limitation of pan-toxicity. *Musanga cecropioides* stem-bark (MCS) is used in ethnomedicine for multiple health benefits. The aim of the study was to test the ameliorative effect of MCS extract on SVPA-induced damage in rodent. The rats were administered with SVPA (500 mg/kg b.w. followed by MCS (50, 100, and 200 mg/kg b.w.) and reference drug, vinpocetine (25 mg/kg b.w.) orally and sub-acutely. The protective effects of MCS extract on their weights, hematological, biochemical, lipid, kidney and electrolytes profiles parameters were examined. Following rats sacrifice, the liver, kidney and lungs were subjected to histopathological analysis. The study indicated that SVPA significantly up-regulated the liver function enzymes ($P< 0.001$), lipid profile ($P< 0.01$-0.001), kidney function ($P< 0.05–0.01$) and electrolytes ($P< 0.01–0.001$) biomarkers and elicited gross alterations of measured indices. However, this effects were dose dependently reversed by MCS extract with higher hepatoprotective percentages, for liver enzymes (77-261%), lipid profiles (74–133%), electrolytes (59-169%) and kidney function (82–154%) compare to vinpocetine values of 63–103%, 80- 127%, 70–161% and 27-78%, respectively. No significant alteration in hematology and relative organ weights. The effect on histopathology corroborated biochemical study. Vinpocetine exhibit no therapeutic effect on the histopathological alteration of liver and kidney but only on the lungs. The presence of potential active ingredients in MCS extract confirms it as an alternative adjunctive therapy in abrogating SVPA – induced pan-toxicity derangement in rats.

Keywords: *Nauclea latifolia* stem-bark; Valproic acid; Vinpocetin; Hepatotoxicity; Nephrotoxicity; Pulmonary-toxicity

1. Introduction

Valproic acid (2-propylpentanoic acid) is a branched short chain fatty acid derived from naturally occurring valeric acid extracted from *Valeriana officinalis* [1, 2], but it was first synthesized in 1882 [3]. The anticonvulsant effect was discovered serendipitously eighty years after usage of VPA as an organic acid [4]. The esterified product of valproic acid, sodium valproate (SVP) is the highly prescribed drug treatment for partial and generalized epilepsy globally [5], but also used primarily in the management of a number of pathologies, seizures, bipolar disorder, mood, anxiety

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and psychiatric disorders and prophylaxis of migraine [6, 7, 8, 9]. Recent work confirming SVPA- induced cell retardation lead to its use in treatment of leukemia and other form of cancers [10, 11]. The drug, SVPA, have been investigated to have a role in HIV and HIV - Associated Neurocognitive Disorders (HAND) [12, 13] and also offer neuroprotection for neurodegenerative diseases: Alzheimer's and Parkinson's and prion diseases [14, 15]. Variability in VPA tissues concentration have been observed in different organs (brain and kidney) and the plasma suggestive of variable tissue transport mechanism [5]. The low permeability of SVPA to the brain necessitates a relatively high daily dosage which posit adverse effects such as bone marrow suppression [16], lethargy [5], hepatotoxicity [17], nephrotoxicity [18], teratogenicity and developmental toxicity [19, 20], neurotoxicity [21] , hematotoxicity [22], pancreatitis [23], and numerous idiopathic effects which in the offspring might lead to autistic spectrum disorder [24, 25]. The drug carries a black box warning for life-threatening adverse drug reactions (ADR) including hepatotoxicity, teratogenicity and pancreatitis [26]. The major limitation of SVPA are its side effects varying from sedation, fatigue, tremor, gastrointestinal symptoms, weight gain [27, 28], long-term adverse symptoms associated with SVPA are metabolic disorders such as hyperinsulinemia, insulin resistance, hyperleptinemia and leptin resistance resulting in weight gain, dyslipidemia, menstrual irregularities, hyperandrogenism and polycystic ovarian syndrome [29]. Hyperammonemia is also a documented adverse drug reaction of SVPA treatment, although this is successfully resolved by co-administration of SVPA with carnitine [30]. Carnitine is prescribed officially to mitigate the adverse effects of SVPA [30].

Vinpocetine the reference drug utilized for this study is an apovincaminic acid ethyl ester, a semi-synthetic derivative of vincamine, an alkaloid extract derived from the periwinkle plant *(Vinca minor).* Vinpocetine is available for management of cerebrovascular and cognitive disorders [31]. In literature limited toxicity data for vinpocetine is reported. The oral median lethal dose (LD_{50}) of vinpocetine in rats is approximately 500 mg/kg [32]. Toxicity of vinpocetine was investigated by [32] in a multiple studies in rats. Report indicated that sub-chronic gavage exposure to vinpocetine at doses between 25 and 100 mg/kg elevated salivation, liver, and thyroid weights especially with the highest dose. But with intraperitoneal injection of 5 or 25 mg/kg for 3 months, mortality was recorded. In a similar report chronic gavage exposure, at doses between 25 and 100 mg/kg, no adverse effects were stated [32]. Oral bioavailability of vinpocetine in rats was 52% suggesting extensive first pass metabolism [33]. Vinpocetine is recently reported to exhibit hepatoprotective effects [34], nephroprotective effects [35], cardio-protective [36], gastroprotective effect [37]; vinpocetine significantly reduces inflammatory pain by targeting oxidative stress, cytokine production and NF-κB activation at both peripheral and spinal cord levels [38]. It exhibit both antioxidant and anti-inflammatory property [34]. These hepatoprotective, nephron-protective, cardio-protective, gastro-protective, anti-inflammatory and antioxidant effect of vinpocetine necessitated consideration for use as reference compound in this study.

Musanga cecropioides (Urticaceae) is known as corkwood (English), Parasoiler (French), Aga or Agbawo (Yoruba, Nigeria), Onru (Igbo, Nigeria) and Uno (Efik, Nigeria) [39]. Corkwood is a very rapidly growing evergreen tree with an umbrella-shape crown. It grows up to a height of 18-45 meter. The straight cylindrical bore can be about 5 cm in diameter with stilt or prop roots that are 2-3 meters tall. It grows in secondary forests in recent clearings, on superficially damp soils, common on old farm, in closed forests, but rare in rain forests; swamp forests; along rivers, often in pure regular stands at elevations of near sea level to about 1200 meter. The bark is intricately layered and become brown on exposure. The outer part exudes a red-brown juice. This juice is mixed with maize pap and then eaten in the belief that it is a galactogogue. Women consuming it over a period of several days experience an increased milk flow and even those who have no child to breastfeed can experience a flow of milk. The sap of this plant has been investigated and found to contain the female hormone estrogen and the sap is a galactogogue that can stimulate milk flow. The plant is said to have analgesic properties and is used in the treatment of asthenia and loss of appetite. The terminal bud is crushed and taken often with the sap added to calm attacks of epilepsy and insanity [39]. Folkloric use of MCS for treatment of hepatic injuries resulting from acute gastric poisonings, infective hepatitis or other liver diseases has been reported [40]. Pharmacological activity of MCS extract reported include: hypotensive, vasorelaxant and angiotensin enzyme blockade [41], toxicological safety [42], hypoglycemic and antidiabetic effect [43], anti-diarrheal [44], acute hepatoprotective activity [45].

No protective subacute, subchronic and chronic data on VPA-induced toxicity by MCS extract to the best of our knowledge. This is the first report of the subacute protective evaluation of MCS extract in SVPA–induced multifocal toxicity derangement on the hematological and biochemical profiles and the hepatotoxicity, nephrotoxicity,

pulmonary-toxicity and histomorphological alteration of the cytoarchitecture in Wistar albino rats following oral subacute repeated dosing for 28 days.

2. Materials and methods

2.1. Drugs, chemicals and equipment

Sodium valproate (Unither, France), Vinpocetine (Cognitol®, Tyonex, Nigeria) purchased from Luckpharm Pharmacy International (Nigeria) Limited, Rivers State, Nigeria; *n*-hexane 85% (Loba Chemie, Mumbai, India); methanol 99.8% (Loba, Chemie, India); Centrifuge (Techmel and Techmel, MI, USA); Water bath (TT-6 Techmel and Techmel, MI, USA); Analytical balance TH60 (Labscience, England, UK), Spectrophotometer model SM-23 D (Surgifield Medical, England, UK), auto-hematology analyzer model MY-B002B (Maya Medical Equipment Limited, China) and rotary evaporator (Shenke® R-205, Shangai Shenshun Biotechnology Co. Ltd, China).

2.2. Plant collection, authentication and preparation

Fresh *Musanga cecropioides* stem-bark (MCS) was collected within the University of Port Harcourt and identified by Dr. Oladele Adekunle, a taxonomist of the Forestry Department, University of Port Harcourt, Nigeria in June, 2018. A voucher specimen (UUH 2001) of the stem bark is deposited at the herbarium of the Department of Pharmacognosy, University of Uyo, Uyo, Nigeria. This was air-dried for 2 weeks and pulverized. The pulverized stem bark (500g) was soaked in *n*-hexane for 24 hours for defatting. This was filtered and then soaked in methanol for 72 hours to obtain methanolic crude extract which was concentrated using Rotary evaporator (R-205, Nanjing, China), and then placed in thermostatic water bath set at 55 °C (TT-6,Techmel and Techmel, MI, USA. The sticky residue was weighed using Lab-Science Analytical Balance (TH60, England, UK). The yield (8.9%) was obtained. Phytochemical screening of the plant stem-bark extract was executed at the laboratory of Pharmacognosy and Phytotherapy Department, University of Port Harcourt. The bioactive agents screened include: flavonoids, alkaloids, triterpenoids, saponins, cardiac glycosides, tannins and phlobatannins using standardized protocol [46].

2.3. Animal, animal care and handling

Forty male Wistar albino rats weighing 160-180 g were obtained from the Animal House, Department of Physiology, University of Port Harcourt, and River State, Nigeria. The animals were acclimatized for 14 days under standard husbandry condition at temperature of 25 °C and 45-55% relative humidity, with 12 hours each of dark and light cycles. The animals were fed pelleted diet (Eastern Premier Feed Mills Ltd, Lagos, Nigeria) and water *ad-libitum* under strict hygienic condition. The animal study was approved by the Institutional Animal Care and Use Committee with approval code (No. UPHAEC/2018/089) in February 2018. The animal procedures were in accordance with the "Guide and Care and Use of Laboratory Animals" National Research Council, 2011) and study conducted with strict compliance with Food and Drug Administration Good Laboratory Practice Regulation, 1987).

2.4. Acute toxicity

The LD_{50} of the MCS extract was evaluated by the technique of Lorke [47]. Albino rats (180–190 g) of either sex were used. Each of these eight doses, 10, 100, 500, 1000, 1500, 2000, 3000, and 4000 mg/kg were administered intraperitoneally to three rats per group. The treated animals were monitored for 24 h for mortality and general signs of toxicity. From the results, four different doses of 500, 1500, 3000, and 4000 mg/kg were chosen and administered intraperitoneally to another four groups of three rats. The treated animals were again monitored for 24 h. The LD_{50} was calculated as the square root of the multiplication of the least dose that kill all the animals and the highest dose that does not kill any animal or the geometric mean of the lowest dose causing death and the highest dose causing no death.

2.5. Drug administration

The MCS, valproate and vinpocetine ®) (the reference drug) were administered orally per kg of body weight once daily for 28 days. Sodium valproate (SVPA) (500 mg/kg) was administered one hour prior to the administration of the control drugs or extracts respectively for animals in groups 2 to 6. The MCS extract and vinpocetine 25 mg/kg

were solubilized in 2% Tween 80 (Polysorbate 80). The various experimental groups utilized for the study are as follows-

2.6. Experimental study protocols

The animals were divided into six (6) groups of seven (7) animals each according to block randomization plan. All the drugs were administered orally per kg body weight for a period of 28 days.

Group 1 (Normal control): received distilled water 10 mL/kg.
Group 2 (Diseases control group): received SVPA 500 mg/kg body weight and followed by 2% Tween 80 with 10 ml/kg distilled water
Group 3 (Experimental group): received SVPA 500 mg/kg and 50 mg/kg extract of MCS extract
Group 4 (Experimental group): received SVPA 500 mg /kg and 100 mg/kg extract of MCS
Group 5 (Experimental group): received SVPA 500 mg/kg and 200 mg/kg MCS extract
Group 6 (Reference control group): received SVPA 500mg/kg and Vinpocetine 25 mg/kg
The rats were administered SVPA (500 mg/kg b.w) and one hour later; distilled water, MCS or vinpocetine was administered adopting standard procedure [48].

Hepatotoxicity and nephrotoxicity percentage (%) was deduced using formula as below:

$$\text{Toxicity percentage (\%)} = \left[\left(\frac{\text{SVPA—W(negative control)}}{\text{W(negative control)}}\right) \times 100\right]$$

Hepatoprotective and nephroprotective activity (%) was calculated as follows:

$$\text{Protective activity (\%)} = \left[1 - \left(\frac{\text{MCS} - \text{W}}{\text{SVPA} - \text{W}}\right)\right] \times 100$$

Where, MCS, SVPA, and W are experimental variables estimated in the rats treated with valproic acid plus MCS (Test groups), valproic acid (diseases control group) and distil water treated animals (negative control) respectively.

The rats were anaesthetized with diethyl ether and the jugular vein lacerated with a sterile scalpel and the blood collected into sterile sample bottles and allowed to clot for 10 minutes at room temperature for serum formation. The serum was collected using micropipette after centrifugation at 3000 rpm for 5 minute. The serum were kept frozen at – 80 ºC until used for the various liver function tests, lipid profile and kidney function analysis within 12 hours of collection.

2.7. Hematological analysis

Hematological analysis was executed using automated hematology analyzer, model MY-B002B (Maya Medical Equipment Limited, Beijing, China). The hematological parameters analyzed include: HGB (hemoglobin), PCV (packed cell volume), RBC (total red blood cell), WBC (total white blood cell), PLT (platelet), , MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), NEU (neutrophils), LYM (Lymphocytes), MEB (monocytes), MID (mid-range percent of monocytes, eosinophils, and basophils), MPV (mean platelet volume), RDW-SD (red cell distribution width- standard size), RDW- CV (red blood cell distribution width – coefficient of variation), RDW (red cell distribution width and platelet larger cell ratio (P-LCR). The analysis followed earlier reported procedure [49].

2.8. Biochemical assays

The levels of liver enzymes were estimated in serum using established earlier reported protocol. Alkaline phosphatase level was determined by the procedure of Roy, et al. [50]; plasma aspartate and alanine transaminases by the methodology of Reitman and Frankel [51]; serum determination of total bilirubin in the samples was based on Jendrassik and Grof, [52] using Mindray test kit the level of plasma albumin (ALB) concentration in the sample was evaluated by Bromocresol green (BCG) method following the procedure of Doumas et al. [53]; total protein (TP) by Biuret method of Flack and Woollen [54]; the high density lipoprotein-cholesterol(HDL-C) was obtained by the direct method of Lopes-Virella et al.[55]. The level of total cholesterol in the sample was determined using cholesterol- oxidase-peroxidase (CHOD-POD) method by Allain et al. [56] and Roeschlau method [57]; triglycerides

(TG) by Burtis and Tietz, [58]; the electrolytes, sodium (Na^+) and potassium (K^+) was by the methodology of Maruna [59]; chloride (Cl^-) by the colorimetric procedure of Schoenfeld and Lewellen [60]; bicarbonate (HCO_3^{2-}) by the methodology of Henry et al., [61]; serum creatinine and urea were estimated by the procedure of Varley and Alan [62].

2.9. Histopathological evaluation

After animal sacrifice the liver, kidney and lungs were abstracted from the experimental groups (1 – 6) and labelled. They were fixed in 10 % formal-saline. The rotary microtome model Leica RM2125 RT was used to section the tissues into 4-5 µm cross-sections. Hematoxylin and eosin stains were utilized in staining optimization of all slides for 48 hours following the protocol of Kiernan [63]. Discernible morphological changes in well stained slides were examined under the light microscope after mounting in a mixture of distyrene (polystyrene), plasticizer (tricresyl phosphate) and xylene, generally called DPX mountant (Atom Scientific, Manchester, UK). The kidney tissue slides were stained with modified Grill's Hematoxylin and Eosin stain after representative tissue of various samples have collected for standard processing into paraffin-embedded tissue blocks. The high power field (400 x magnifications) was utilized in the histological observation.

2.10. Statistical analysis

The data were analyzed using one-way analysis of variance (ANOVA) and were expressed as Mean ± SD. Values $P< 0.05$ were considered significant. Further comparison among groups was made according to post hoc Turkey's test. P values < 0.05 were considered significant.

3. Results

3.1. Phytochemical screening

The phytochemical analysis of the MCS extract is presented in the Table 1 above. The presence of saponins, alkaloid, flavonoids, glycosides, tannins, phlobatannins and cardiac glycoside were observed in the concentrations indicated.

Table 1 Phytochemical constituents present in *Musanga cecropioides* methanolic stem bark extract

Constituents	Test	Observation
Saponins	Benedict's test	+
	Emulsion test	+
	Frothing test	+
Alkaloids	Draggendorff	++
	Mayer	+
	Wagner	++
Flavonoids	Ferric Chloride	+++
	Lead acetate test	+++
Reducing sugar		
Hexose	Benedict's test	+
Keto	Fehling's test	+
Pentose	Fehling's test	+
Monosaccharide	Molish test	+
Tannins	Ferric chloride	++
	Bromin water	++
Phlobatannins	1% HCl	+
Cardiac glycosides	Keller-Kiliani	+++
	Salkowski	++

(+) presence in low concentration; (++) present in moderate concentration; (+++) presence in high concentration

3.2. Acute toxicity

The results of acute toxicity (LD_{50}) showed that the extract at 5 g/kg did not produce any oral toxicity in rats after 14 days of treatment. No behavioral sign of toxicity. Narcolepsy did not reveal any visible signs of toxicity.

3.3. Effect on body weights

The MCS methanolic extract effects on body weights is presented in Table 2 below. The study revealed significant increase of weight in Group 1 in week 3 ($P< 0.001$) and in the final weight ($P< 0.05$); in group 2 from week 2 ($P< 0.01$) and in the final weight ($P< 0.001$); in group 3 from week 1 to week 4 and final weight ($P< 0.001$); in group 5 from week 4 ($P< 0.05$) and final weight ($P< 0.001$); in group 6 from week 1($P< 0.05$), week 3 and week 4 ($P< 0.001$) and final weight ($P< 0.01$) when compared to the initial weight of animal. Besides following intoxication with SVPA, significant decrease in weight in Group 2 from week 1 ($P< 0.05$), week 3 ($P< 0.001$) and in the final weight ($P< 0.05$) when compared to group 1. Also, there was significant elevation in weight in Group 3 in week 1 ($P < 0.001$), week 3 ($P< 0.05$) and week 4 ($P< 0.01$); in group 5 from week 1 ($P < 0.05$), week 2 through to the final weight ($P< 0.001$) when compared to the diseases control group.

3.4. Effect on relative organ weights of rats

Effect on relative organ weight is shown in Table 3 below. No observable significant effect was noted on the relative organ weights.

3.5. Effect on hematology

The effect on hematology is shown in Table 4 below. No significant effects observed on hematology by MCS extract.

3.6. Effect on biochemical function

The result (Table 5) indicates that SVPA intoxication in the experimental rats produce significant alteration in liver function enzymes. The SVPA intoxication produce significant ($P< 0.001$) increase in GGT (138%), AST (57%), ALT (62%), ALP (12%), TBIL (53%) and CBIL (24%), but a significant ($P< 0.001$) decrease in TP (15%), ALB (40%) compared to the negative control substantiating the establishment of hepatotoxicity, liver insults and impingement in the diseases control group (Group 2). However, the post-treatment with MCS extract significantly and dose dependently ameliorated the observed hepatotoxicity by providing higher percentage of hepatoprotection for GGT (91%, 107%, 77%), AST (101%, 108%, 94%), ALT (125%, 112%, 115%), ALP (261%, 112%, 136%), TP (30%, 91%, 127%), ALB (104%, 89%, 134%), TBIL (129%, 78%, 96%), CBIL (296%, 133%, 175%) at the utilized doses of 50, 100, 200 mg/kg b.w., respectively. The reference control drug produce significant ($P< 0.005 – 0.001$) and higher percentage hepatoprotection for GGT (92%), AST (63%), ALT (103%), ALP (76%), TP (75%), ALB (110%), TBIL (131%) and CBIL (170%) compared to the diseases control group. The extract degree of hepatoprotection was higher than vinpocetine.

3.7. Effect on lipid profile

The effect of MCS on lipid profile following sub-acute valproic acid intoxication is presented in Table 6. The extract provoke significant elevation of TC and TG ($P <0.001$), LDL ($P < 0.01$) and VLDL ($P < 0.001$) and depression in HDL ($P <0.001$) in the SVPA intoxicated rats compared to the control group. Intoxication with SVPA of the diseases control rats steered hyperlipidemia by significant ($P < 0.01 - 0.001$) elevation in the levels of TC (60%), TG (154%), LDL (92%), VLDL (79%) and depression in HDL (70%). However oral gavage of the rats with MCS extract offer higher percentage protection against SVPA–induced hyperlipidemia. The Treatment with 50 mg/kg body weight MCS extract for 28 days reduced TC (87%), TG (121%), LDL (101%) and VLDL (108%) but elevated HDL (86%). Administration of MCS extract 100 mg/kg yield a higher protection by reducing TC (74%), TG (122%), LDL (133%), VLDL (151%) and elevated HDL (84%). Similarly, administration of MCS 200 mg/kg offer higher protection by depressing TC (103%), TG (103%), LDL (116%), VLDL (116%) and elevated HDL (94%) compared to the disease control group. The level of hepatoprotection was very significant for the lower dose of MCS extract that the higher dose. The reference drug, vinpocetine, treatment significantly offer less heptoprotection on lipid profile than the

MCS extract as the percentage deceases of each biomarker, TC, TG, LDL, VLDL are 93%, 93%, 95%, 127% and elevation of HDL by 80% which are in most parameters lower than the levels observed for the MCS extract.

3.8. Effect on electrolytes and kidney function

The subacute intoxication with SVPA on electrolytes Na^+, K^+, Cl^- and HCO_3^- and kidney profile, CR, UA; are presented in Table 7. There was statistical significant increase in Na^+ ($P < 0.001$) but a significant decrease in K^+ ($P < 0.001$), Cl^- ($P < 0.01$) and HCO_3^- ($P < 0.001$) compared to the normal control group. There was an increase in Na^+ (28%) and depression of K^+ (26%), Cl^- (13%) and HCO_3^- (20%) compared to the normal control group. Nevertheless sub-acute post treatment for 28 days with MCS extract (50 mg/kg) protected the rats against SVPA-induced hepatotoxicity as evidence of elevation of electrolyte biomarkers in the serum, K^+ (99%), Cl^- (137%), HCO_3^- but elevation of Na^+ (117%). For the 100 mg/kg the percentage increase in electrolytes are K^+ (101%), Cl^- (70%), HCO_3^- (169%) but an depression of Na^+ (59%). At the highest dose of MCS (200 mg/kg b.w.) the elevation in the levels of K^+(95%), Cl^- (63%), HCO_3^- (136%) and decrease of Na^+ (111%) were noted. The reference drug vinpocetine (25 mg/kg) demonstrated elevation of K^+ (98%), Cl^- (106%), HCO_3^- (161%) but decrease in Na^+ (70%). Likewise, SVPA intoxication of experimental rats induced kidney damage revealed by marked elevation of UA (25%, $P < 0.01$), CR (22% $P < 0.05$). Treatment with MCS 50, 100 and 200 mg/kg decreased UA (152%, 164%, 82%) and CR (140%, 113%, 102%) respectively; while the reference drug (25 mg/kg b.w.) reduced UA (27%) and CR (78%).

3.9. Effect on histopathology

The liver, kidney and lungs photomicrographs revealed gross microscopic features presented in Figure 1, Figure 2 and Figure 3 respectively. The liver group 1 reveal normal liver tissue with normal central vein, sinusoids and hepatocytes consistent with normal histology; group 2 display severe inflammatory response indicating hepatocellular damage or injury; group 3 indicate mild inflammatory response, group 4 shows acute depletion of inflammatory cells, group 5 present with features consistent with normal histology observed in group 1; while group 6 demonstrated similar pathology observed in group 2. The MCS extract at high concentration is hepatoprotective and SVPA induces hepatocellular injury but reference drug interact with SVPA to induced liver necrosis. The kidney (Fig 2) shows normal renal tissue with abundant tubules with normal epithelium; glomerulus with intact Bowman's capsule consistent with normal histology of the kidney is shown in group 1. Marked glomerular nephritis was observed in the nephrotoxic group 2. The features presented in group 3, 4 5 were consistent with normal histology of the kidney. Similar interaction between vinpocetine and SVPA observed in the liver was seen in the kidney with resultant atrophy of the tissue. The MCS extract demonstrated nephron-protective effect. The lungs (Fig 3) normal histology is revealed showing lung tissue with the respiratory alveoli with a normal interstitial tissue, alveolar sac and epithelium consistent with normal histology; group 2 display diffuse alveolar damage with numerous inflammatory cells; group 3 pathological features is similar with group 2; group 4,5 and 6 demonstrated histomorphological features consistent with normal alveoli. Both MCS extract and standard drug displayed pulmonary-protective potentials.

Table 2 Effect of MCS extract and vinpocetine subacute oral dosing on body weights parameters in SVPA –induced toxicity in rats

Groups	Initial weight	Week 1	Week 2	Week 3	Week 4	Final weight
Group 1	141.6 ±4.0	140.7± 3.1	143.7 ±2.9	151.7 ±2.9c,f	138.1 ±5.3	165.0 ± 3.7[a, f]
Group 2	133.6 ±2.5	130.8 ±2.7[a, d]	142.2 ±3.4[b, f]	37.9 ±3.7c,d	137.4 ±2.5	153.4 ±3.1[a, d, c ,f]
Group 3	111.1 ±2.5	154.4 ±8.3 [c, e, c, f]	139.9 ±3.2[c,f]	148.8 ±4.0 [b, e, c, f]	155.6 ±4.0[b, e, c, f]	164.5 ±4.2[c, f]
Group 4	145.7 ±10.5	136.2 ±2.7	139 ±1.9	140.9 ±7.0	141.6 ±14.3	141 ±16.7
Group 5	144.3 ±22.9	144.6 ±8.0[a, e]	157.3 ±7.5[c, e]	163.9 ±5.9[c, e]	178.0 ±3.9 [c, e, a, f]	195.3 ±4.2[c, e, c, f]
Group 6	137.7 ±25.9	134.2 ±4.3[a, f]	140.8 ±5.2	144.3 ±5.5[c, f]	175.9 ±10.2[c, e, c, f]	150.0 ±4.4 [b, f]

Group 1: Negative control receiving 10 ml/kg b.w. with 2% Tween 80; Group 2: Diseases control group receiving 10 ml/kg b.w. 2% Tween 80 + SVPA 500 ml/kg; Group 3: receiving MCS extract (50 mg / kg b.w.) + SVPA 500 ml/kg; Group 4: receiving MCS extract (100 mg / kg b.w.) + valproic acid 500 mg/kg; Group 5: receiving MCS extract (150 mg / kg b.w.) + SVPA 500 ml/kg, Group 6: Reference control receiving vinpocetine (25 mg/kg b.w.) + SVPA 500 ml/kg. MCS = *Musanga cecropioides* stem-bark; SVPA = sodium valproate. Values presented as mean ± standard deviation (n = 7); [a] P< 0.05, [b] P< 0.01, [c] P< 0.001 [d] Values compared with the Grp 1, [e] Values are compared with Grp 2, [f] values are compared with initial weight using one way ANOVA and Turkey Test .

Table 3 Effect of MCS extract and vinpocetine subacute oral dosing on relative organ weights in SVPA –induced toxicity in rats

Organs	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Liver	4.73 ±0.39	5.08 ±0.95	3.90 ±0.88	3.91 ±0.56	4.10 ±0.42	4.09 ±0.50
Kidney	0.64 ±0.07	0.76 ±0.12	0.71 ±0.09	0.79 ±0.23	0.72 ±0.09	0.74 ±0.03
Lungs	0.94 ±0.45	0.86 ±0.20	1.12 ±0.22	0.82 ±0.49	1.18 ±0.28	1.09 ±0.32
Testes	2.22 ±0.55	2.25 ±0.77	2.41 ±0.64	3.57 ±1.71	2.48 ±0.41	2.28 ±0.58
Heart	0.38 ±0.04	0.39 ±0.07	0.38 ±0.08	0.51 ±0.16	0.35 ±0.10	0.54 ±0.18
Brain	0.95 ±0.15	0.95 ±0.15	1.12 ±0.32	1.00 ±0.18	1.10 ±0.45	1.04 ±0.22
Stomach	2.65 ±1.13	1.77 ±0.50	1.54 ±0.17	0.99 ±0.11	1.53 ±0.23	2.03 ±0.42
Spleen	0.63 ±0.13	0.63 ±0.17	0.66 ±0.13	0.59 ±0.19	0.54 ±0.08	0.64 ±0.17

Group 1: Negative control receiving distil water 10 ml/kg b.w. with 2% Tween 80; Group 2: Diseases control group receiving 10 ml/kg b.w. 2% Tween 80 + SVPA 500 ml/kg; Group 3 to 5: receiving MCS extract (50, 100, 200 mg / kg b.w.) + SVPA 500 ml/kg each; Group 6: Reference control receiving vinpocetin (25 mg/kg b.w.) +SVPA 500 ml/kg. MCS = *Musanga cecropioides* stem-bark; SVPA = sodium valproate. Values presented as mean ± standard deviation (n = 7; P > 0.05, using one way ANOVA and Turkey Test. Relative organ weight was calculated as (organ weight (g)/ body weight of animal on sacrifice day (g) × 100.

Table 4 Effect of MCS extract and vinpocetine subacute oral dosing on hematological parameters in SVPA –induced toxicity in rats

Parameters	Units	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
WBC	10^9/L	20.11 ±11.62	15.13±2.99	21.9 ±9.42	12.1 ±3.95	10.70 ±2.18	16.84 ±7.19
LYM	(%)	64.40 ±8.12	70.55±6.87	73.92 ±5.69	58.05 ±15.64	72.25 ±4.29	68.94 ±10.71
MID	(%)	8.06 ±0.97	8.55±1.1	9.12 ±1.63	8.9 ±00	9.15 ±0.44	9.04 ±0.84
NEUT	(%)	27.54 ±7.73	20.9±5.82	16.97 ±4.69	28.55 ±10.9	20.68 ±2.01	22.02 ±9.99
RBC	10^{12}/L	5.59 ±1.25	5.47 ±0.47	5.17 ±0.96	5.73 ±0.54	4.48 ±1.01	5.92 ±0.45
HGB	g/dL	13.76 ±3.04	13.5 ±1.28	13.38 ±2.57	13.45 ±2.29	12.00 ±1.24	15.80 ±1.48
PCV	(%)	30.59 ±7.4	31.38 ±3.61	29.28 ±6.62	32.2 ±3.97	26.80 ±2.59	32.84 ±3.24
MCV	fL	54.50 ±1.73	57.4 ±3.43	56.32 ±3.54	55.15 ±3.51	55.75 ±1.81	55.52 ±2.25
MCH	pg	24.63 ±0.97	24.63 ±1.61	25.82 ±0.76	25.45 ±0.06	25.25 ±1.85	26.62 ±0.5
MCHC	g/dL	45.31 ±2.63	43.23 ±5.32	46.17 ±3.32	45.15 ±1.76	45.25 ±2.5	48.10 ±1.95
RDW-SD	fL	37.70 ±1.39	48.78 ±8.51	53.87 ±16.13	45.1 ±1.81	51.63 ±3.9	42.38 ±2.03
RDW-CV	(%)	17.30 ±0.44	21.13 ±5.49	20.12 ±1.90	19.9 ±0.12	21.05 ±0.99	19.08 ±0.99
PLT	10^9/L	274.9 ±95.29	306.5 ±91.3	225.2 ±108.2	160 ±38.3	140.5 ±11.39	183.8 ±95.23
MPV	fL	8.6 ±0.35	8.75 ±0.54	8.68 ±0.59	8.35 ±0.29	8.53 ±0.29	8.30 ±0.27
RDW	(%)	9.67 ±0.78	9.68 ±1.99	8.9 ±1.05	8.05 ±0.17	8.85 ±0.85	7.74 ±1.31
PCT	(%)	0.23 ±0.09	0.26 ±0.08	0.19 ±0.1	0.15 ±0.04	0.12 ±0.02	0.15 ±0.08
P-LCR	(%)	19.6 ±3.47	20.33 ±7.58	19.4 ±9.16	14.05 ±3.43	18.25 ±3.25	11.12 ±6.43

Group 1: Negative control receiving 10 ml/kg b.w. with 2% Tween 80; Group 2: Diseases control group receiving 10 ml/kg b.w. with 2% Tween 80 + SVPA 500 ml/kg; Group 3 receiving MCS extract (50 mg / kg b.w.) + SVPA 500 ml/kg; Group 4 receiving MCS extract (100 mg / kg b.w.) + SVPA 500 mg/kg; Group 5 receiving MCS extract (150 mg / kg b.w.) + SVPA 500 ml/kg, Group 6: Reference control receiving vinpocetine (25 mg/kg b.w.) + SVPA 500 ml/kg. PCV: packed cell volume; HGB: hemoglobin; WBC: total white blood cell; PLT: platelet; RBC: total red blood cell: MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; NEU: neutrophils; LYM: Lymphocytes; MEB: monocytes, eosinophils and basophils.MID: mid-range percent of monocytes, eosinophils, and basophils; MPV: mean platelet volume, RDW-SD: red cell distribution width- standard size, RDW- CV: red blood cell distribution width –coefficient of variation;, RDW: red cell distribution width, P-LCR; MCS = *Musanga cecropioides* stem-bark; SVPA=sodium valproate. Values presented as mean ± SD (n = 7).One -way Analysis of variance (ANOVA) followed by post hoc Turkey's multiple comparison Test .P > 0.05.

Table 5 Effect of MCS extract and vinpocetine sub acute oral dosing on biochemical parameters in SVPA –induced toxicity in rats

Parameters	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
GGT	1.85 ±0.40	4.4 ± 0.57[c,d] (138%)	3.92 ±0.43[c,e] (91%)	2.08 ±0.42[c,e] (107%)	2.4 ±0.46[c,e] (77%)	2.05 ±0.60[c,e] (92%)
AST	60 ±4.93	94.17 ±3.31[c,d] (57%)	59.5 ±7.69[c,e] (101%)	57.33 ±6.81[c,e] (108%)	61.9 ±9.54[c,e] (94%)	72.5 ±2.65[c,e] (63%)
ALT	33.43 ±3.9	54.29 ±2.06[c,d] (62%)	28.17 ±5.64[c,e] (125%)	31 ±5.00[c,e] (112%)	30.33 ±8.33[c,e] (115%)	32.75 ±4.79[c,e] (103%)
ALP	55.86 ±0.90	62.83 ±2.99[c,d] (12%)	44.67 ±3.08[C,e] (261%)	55 ±2.00[C,e] (112%)	53.33 ±1.53[C,e] (136%)	57.5 ±1.29[a,e] (76%)
T.P	74.86 ±3.08	63.33 ±2.42[c,d] (15%)	80.5 ±7.12[c,e] (30%)	73.78 ±1.00[a,e] (91%)	78 ±1.00[c,e] (127%)	72 ±2.12[a,e] (75%)
ALB	38.43 ±4.43	23 ±3.58[c,d] (40%)	39 ±5.06[c,e] (104%)	36.67 ±0.58[c,e] (89%)	43.67 ±1.53[c,e] (134%)	40 ±1.83[c,e] (110%)
TBIL	20.29 ±3.59	31 ±2.28[c,d] (53%)	17.17 ±4.02[c,e] (129%)	22.67 ±2.08[b,e] (78%)	20.67 ±1.53[c,e] (96%)	17 ±2.16[c,e] (131%)
CBIL	16.29 ±3.04	20.25 ±2.04[a,d] (24%)	8.52 ±1.77[c,e] (195%)	15 ±1.00[a,e] (133%)	13.33 ±3.22[b,e] (175%)	13.5 ±0.93[c,e] (170%)

Group 1: Negative control receiving 2% Tween 80 with distilled water 10 ml/kg b.w.; Group 2: Diseases control group receiving 2% Tween 80 with 10 ml/kg b.w + SVPA 500 mg/kg; Group 3 to 5 receiving MCS extract (50 , 100, 200 mg / kg b.w.) + SVPA 500 ml/kg each; Group 6: Reference control receiving vinpocetine (25 mg/kg b.w.) + SVPA 500 mg/kg. MCS = *Musanga cecropioides* stem-bark; SVPA= sodium valproate. Values presented as mean ± standard deviation (n = 7); [a] $P< 0.05$, [b] $P< 0.01$, [c] $P< 0.001$ [d] Values compared with the Grp 1, [e] Values are compared with Grp 2.

Table 6 Effect of MCS extract and vinpocetine subacute oral dosing on lipid profile in SVPA –induced toxicity in rats

Parameters	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
TC	2.52 ±0.39	4.03 ±0.42 [c, d] (60%)	2.72 ±0.61[c, e] (87%)	2.92 ±0.21[a, e] (74%)	2.48 ±0.17 [c, e] (103%)	2.63 ±0.63 [c, e] (93%)
TG	0.61 ±0.33	1.55 ±0.33 [c, d] (154%)	0.41 ±0.29 [c, e] (121%)	0.40 ±0.37 [c, e] (122%)	0.58 ±0.40 [b, e] (103%)	0.68 ±0.26 [b, e] (93%)
LDL	0.83 ±0.27	1.59 ±0.36 [b, d] (92%)	0.82 ±0.22 [b ,e] (101%)	0.58 ±0.40 [b, e] (133%)	0.71 ±0.54 [b, e] (116%)	0.87 ±0.17 [a, e] (95%)
HDL	1.54 ±0.33	0.46 ±0.28 [c, d] (70%)	1.39 ±0.29 [c, e] (86%)	1.37 ±0.48 [b, e] (84%)	1.47 ±0.34 [b, e] (94%)	1.32 ±0.32 [b, e] (80%)
VLDL	0.47 ±0.13	0.84 ±0.11[c, d] (79%)	0.44 ±0.18 [c, e] (108%)	0.28 ±0.12 [c, e] (151%)	0.41 ±0.09 [b, e] (116%)	0.37 ±0.04 [c, e] (127%)

Group 1: Negative control receiving 2% Tween 80 with distil water 10 ml/kg b.w.; Group 2: Diseases control group receiving 10 ml/kg b.w. with 2% Tween 80 + SVPA 500 mg/kg; Group 3 to 5 receiving MCS extract (50, 100, 200 mg / kg b.w.) + SVPA 500 ml/kg each; Group 6: Reference control receiving vinpocetine (25 mg/kg b.w.) + SVPA 500 mg/kg. MCS = *Musanga cecropioides* stem-bark; SVPA =sodium valproate; TC = Total cholesterol, TG =Total glycerol, LDL=Low density lipoprotein, HDL=High density lipoprotein, VLDL=Very low density lipoprotein. Values presented as mean ± standard deviation (n = 7); [a] P< 0.05, [b] P< 0.01, [c] P< 0.001 [d] Values compared with the Grp 1, [e] Values are compared with Grp 2.

Table 7 Effect of MCS extract and vinpocetine subacute oral dosing on electrolytes and kidney function parameters in SVPA –induced toxicity in rats

Parameters	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Na^+	117.6 ±4.20	150.2 ±5.31[c, d] (28%)	112.2 ±8.70 [c, e] (117%)	131 ±5.20 [b, e] (59%)	114 ±3.61[c, e] (111%)	127.5 ±5.26 [c, e] (70%)
K^+	5.61 ±0.92	4.13 ±0.74 [a, d] (26%)	5.60 ±0.69 (99%)	5.62 ±0.46 (101%)	5.53 ±1.15 (95%)	5.58 ±1.09 [c, e] (98%)
Cl^-	35 ±2.1	30.5 ±1.64 [b, d] (13%)	36.67 ±2.5 [c, e] (137%)	33.67 ±2.08 (70%)	33.33 ±1.53 (63%)	35.25 ±2.22 [a, e] (106%)
HCO_3^-	26.14 ±2.4	21 ±0.89 [b, d] (20%)	28.67 ±1.63 [c, e] (149%)	29.67 ±1.53 [c, e] (169%)	28 ±2.00 [c, e] (136%)	29.25 ±2.99 [c, e] (161%)
UA	5.2 ±0.98	6.5 ±0.86 [a, d] (25%)	4.53 ±0.40 [b, e] (152%)	4.37 ±0.67 [b, e] (164%)	5.43 ±0.47 [ns] (82%)	4.85 ±0.59 [a, e] (27%)
CR	135.4 ±14.3	164.3 ±10.33 [b, d] (22%)	123.2 ±4.59 [c, e] (140%)	131.3 ±21.01 [b ,e] (113%)	134.3 ±4.0 [b, e] (102%)	141.3 ±0.28 [ns] (78%)

Group 1: Negative control receiving 2% Tween 80 in 10 ml/kg b.w.; Group 2: Diseases control group receiving 2% Tween 80 in 10 ml/kg b.w. + SVPA 500 ml/kg; Group 3 to 5 receiving MCS extract (50, 100, 200 mg / kg b.w.) +SVPA 500 ml/kg;, Group 6: Reference control receiving vinpocetine (25 mg/kg b.w.) + SVPA 500 ml/kg. MCS= *Musanga cecropioides* stem-bark. Na^+ =Sodiun, K^+ =Potassium, Cl^- = Chloride, HCO_3^- =Bicarbonate, UA = Urea, CR= creatinine. (%) = Percentage intoxication by SVPA for Group 2 and also Percentage of protection by MCS extract for Groups 3 to 6. Values presented as mean ± standard deviation (n = 7); [a] P< 0.05, [b] P< 0.01, [c] P< 0.001,ns=not significant, [d] Values compared with the Grp 1, [e] Values are compared with Grp 2.

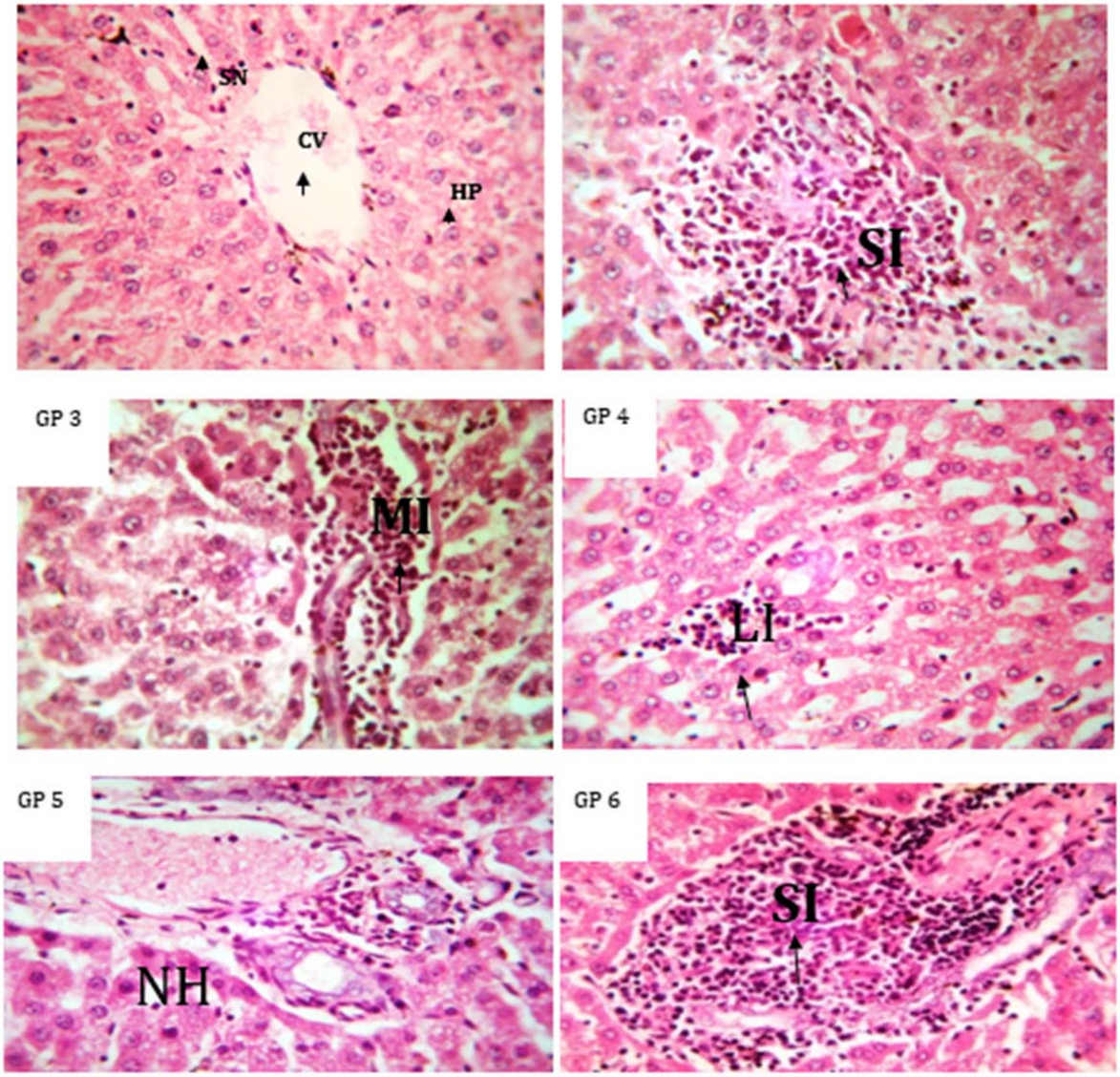

Figure 1 Photomicrograph of hematoxylin and eosin stained liver section (×400).

Group 1 shows a normal liver tissue with normal central vein, sinusoids and hepatocytes consistent with normal histology. Group 2 shows severe inflammatory response indicating hepatocellular damage or injury. Group 3 shows mild inflammatory response while group 4 revealed acute depletion of inflammatory cells. Group 5 presented with features consistent with normal histology, normal hepatocytes with nuclei cytoplasmic ratio, central vein and blood vessels. Group 6 exhibited the same pathology with group 2. The extract at high concentration is hepatoprotective and valproic acid induces hepatocellular injury. Key: NH= normal histology, SI= severe inflammatory response, MI= moderate inflammatory response, LI= low inflammatory response. CV= central vein, HP= hepatocytes, SN = sinusoid; GP=group.

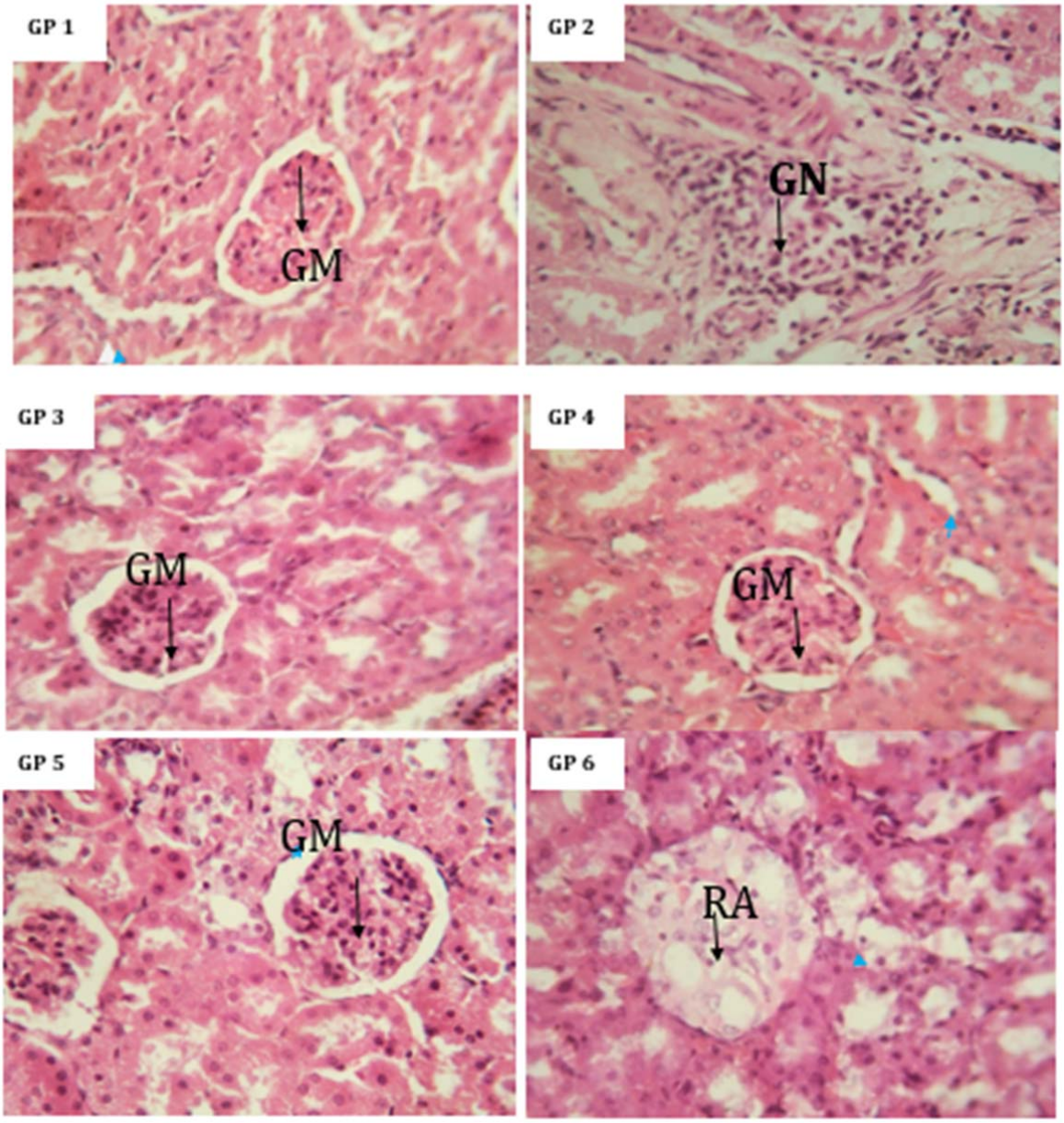

Figure 2 Photomicrograph of hematoxylin and eosin stained kidney tissues (×400)

Group 1 shows normal renal tissue with abundant tubules with normal epithelium. The glomerulus shows intact Bowman's capsule consistent with normal histology of the kidney. Group 2 show marked glomerular nephritis. Group 3, 4 5 presented features consistent with normal histology. Group 6 interaction between SVPA and vinpocetine resulted in atrophy. Extract is nephroprotective. Key: GM= glomerulus, RT= renal tubule, RA= tubular atrophy, GN= glomerular nephritis.

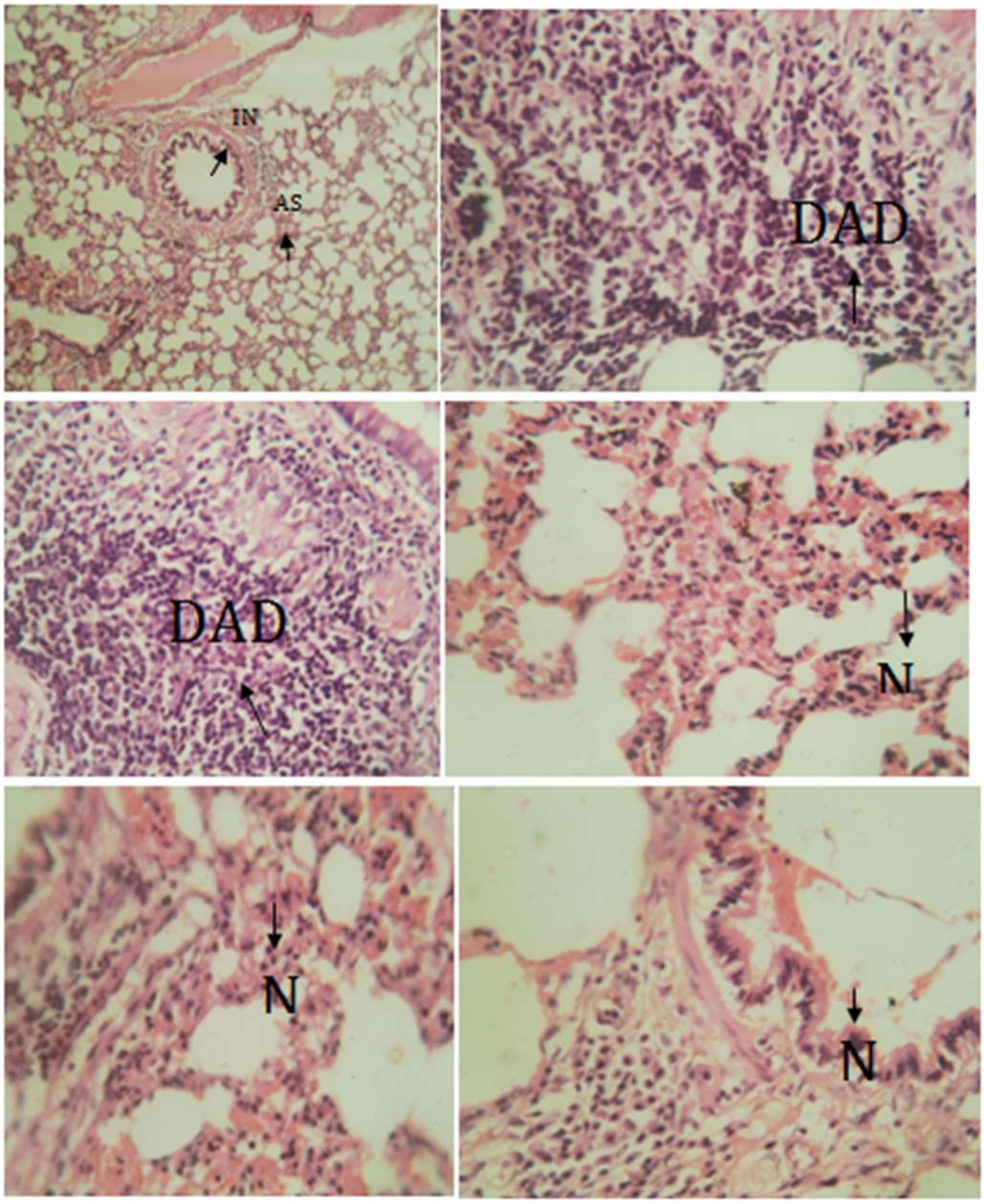

Figure 3 Photomicrograph of hematoxylin and eosin stained lung sections x400 magnification

Group 1 shows a lung tissue showing the respiratory portion, the alveoli with a normal interstitial tissue, alveolar sac and epithelium consistent with normal histology. Group 2 shows diffuse alveolar damage with numerous inflammatory cells. Group 3 share the same pathological features with group 2. Group 4, 5 and 6 exhibited features consistent with normal alveoli. Extract and standard drug shows protection. Key: DAD= diffuse alveolar damage, AC= alveolus sac, IN= Interstitial; GP=group.

4. Discussion

Sodium valproate is indicated worldwide for management generalized and partial seizures and numerous other neurological and psychiatric conditions [7-9]. Though it is a broad-spectrum antiepileptic drug it is usually well tolerated, but posit toxicities concerns [16-25]. As valproic acid is a branched chain carboxylic acid (2-propylpentanoic acid or di-*n*-propyl acetic acid) and very similar to short-chain fatty acids, making VPA a substrate for the fatty acid oxidation pathways [63, 64].

Valproic acid is well absorbed and has high ability to bind to albumin (87–95%), leading to insignificant part of valproic acid being excreted by the kidneys (6–20 ml/day/kg body weight) [64]. At therapeutic dosing the long-

term use plasma level is approximately 40–100 μg/ml or 280–700 μmol/L [64].Most of the valproic acid undergoes biotransformation endogenously via three main mechanisms: glucuronidation; β-oxidation in the mitochondria and P450 cytochrome-mediated oxidation [7]. There is increasing incidence of complications arising from acute SVPA overdose. Intoxication usually only results in mild central nervous system depression, but serious toxicity and death have been reported. However, there are limited data addressing the safety/toxicity of SVPA in the current literature. Although there are some data for VPA and its major metabolites, in rodents in the literature following repeated administration. To the best of our knowledge, there are no data on the ameliorative effects of MCS following repeated exposure to SVPA- induced pan-toxicity derangement in rodent. Therefore, this study is designed to address the data gap.

Long-term use of valproic acid induced metabolic derangement with resultant increase of body weight resulting from hyperinsulinemia, insulin resistance, hyperleptinemia and leptin resistance [66]. Our study confirmed marked elevation of body weights from week 1 to 4 and in the final weights evaluation ($P < 0.05$ - 0.001) compared with the initial weighs at the start of the experiment. Comparison of the disease control group with the normal control showed a significant reduction in body weight of the rats during the course of acute intoxication; the increase weights effect was countered by repeated supplementation of SVPA along with MCS extract; the reference drug also demonstrated significant elevation of weight, surprisingly the middle weight of the MCS extract (100 mg/kg b.w.) did not demonstrate any putative significant change in weights compared to the diseases control. Earlier report of the effect of MCS on weight indicated no significant effect on weight within the first month of therapy [67] suggesting that the significant subacute weight increase probably might be induced by SVPA repeated dosing. Sodium valproate long duration of therapy is associated with significant weight gain that continues after the first rapid increase in the first months of therapy. No correlations exist between the degree of weight gain and the daily valproic acid dosage and/or serum valproic acid concentration [68]. The mechanism of weight elevation might in part be through SVPA-induced activation of hypothalamic dysregulation mediated through elevation of gamma-aminobutyric acid (GABA) transmission in the hypothalamic axis activating the stimulation of increase appetite with a substantial increased intake of cholesterol and carbohydrate [68] and consequential weight gain. Egger and Brett [69] reported weight gain in 44 out of 100 children treated with SVPA. Increased appetite and excessive weight gain were also reported in 31 out of 66 patients with generalized epilepsy and 13 out of 34 with partial epilepsy treated with SVPA. However, the MCS extract did not demonstrate any significant concentration dependent effect on the relative organ weights and on the hematological profile. The observation is in line with previous reports on MCS extract [70].

The liver plays a significant role in detoxification and metabolic biosynthetic processes such as synthesis of plasma proteins and gluconeogenesis [71]. More than 1 in 37,000 subjects exposed to SVPA develop idiosyncratic liver injury. In young children, the proportion was higher, with the risk reaching 1 in 500 subjects [72]. This confirms the result of our investigation that SVPA intoxication in the experimental rats produced significant alteration and upregulation of the liver function enzymes dose-dependently. The percentage hepatotoxicity induced by SVPA for the liver enzymes are as follows: GGT (138%), AST (57%), ALT (62%) and ALP (12%). The mechanism of VPA induced hepatotoxicity is unclear but it is thought to be understood from its toxic metabolites.

The metabolism of SVPA by the liver is extensively achieved in three pathways: glucuronic acid conjugation, mitochondrial β-oxidation, and cytoplasmic ω–oxidation. Under normal conditions, mitochondrial β-oxidation prevails and produces relatively non-toxic metabolites. Only a small amount of SVPA is metabolized through cytoplasmic ω-oxidation, a pathway that produces toxic metabolites, especially 2-propyl-4-pentanoic acid, 4-en-VPA, and propionic acid metabolites, all incriminated in the origin of hepatotoxicity and hyperammonemia [30]. During long-term or high-dose VPA therapy, or after acute VPA overdose, a greater degree of ω-oxidation occurs, potentially increasing the risk of hepatotoxicity [73]. The concentrations of toxic SVPA metabolites, 4-ene-VPA and 2,4-diene-VPA was associated with CYP2A6 polymorphism and CYP2A6 and CYP2C9 was associated with SVPA hepatotoxicity [74]. From our study it appears that the MCS extract counteract these potential mechanistic hepatotoxicity pathways to abrogate SVPA - induced toxicity and offering hepatoprotection. These mechanism might in part producing metabolites (4-en-VPA and 2,4-dien-VPA) which have been reported as potent inducers of microvesicular steatosis in rats [75]; sequestration of CoA-SH and direct inhibition of specific enzymes in the β-oxidation sequence by CoA esters (especially 4-en-VPA-CoA) are other mechanisms of hepatotoxicity suggested in rat studies [76].Some data suggest that hepatotoxicity and encephalopathy may be stimulated either by a pre-existing carnitine deficiency or by a deficiency induced by VPA *per se*[73].The potential mechanism regulating the metabolism of SVPA and metabolism of fatty acids is linked to carnitine, a 3-hydroxy-4-trimethylamino-butyric acid or β-hydroxy-gamma-*N*-trimethylamino-butyrate biosynthesized endogenously from dietary amino acids (trimethyllysine), especially in the liver and in the kidneys [77, 78, 79]. For example

carnitine depletion impairs the transport of long-chain fatty acids into the mitochondrial matrix, with subsequent decrease in β-oxidation, acetyl-CoA, and ATP production. Such impairment in mitochondrial β-oxidation also shifts the metabolism of SVPA toward predominantly peroxisomal ω-oxidation, resulting in excessive production and accumulation of toxic products [30]. The metabolism of VPA linked to carnitine might be modulating carnitine depletion [80], biotransformation to valproylcarnitine and excretion in urine [81], interfere or reduce tubular reabsorption of carnitine and acylcarnitine [82], reduction of endogenous synthesis of carnitine by blockade of the enzyme υ-butyrobetaine hydroxylase [83]; valproylcarnitine inhibits the membrane carnitine transporter, thereby decreasing the transport of extracellular carnitine into the cell and the mitochondria [73], VPA metabolites combine with mitochondrial CoA-SH thereby depleting the pool of free CoA-SH, so that free mitochondrial carnitine stores cannot be restored from acylcarnitine (including valproylcarnitine) under the action of carnitine palmitoyl transferase II (CPT II). The mitochondrial depletion of CoA-SH impairs β-oxidation of fatty acids (and VPA) and ATP production, which further impairs the function of the ATP-dependent membrane carnitine transporter [73]. The MCS bioactive agents might in part be interacting with these or yet unraveled potential mechanisms mediating observed hepatoprotection reported.

On lipid profile, the sub-acute SVPA intoxication result in significant elevation of TC and TG ($P < 0.001$), LDL ($P < 0.01$) and VLDL ($P < 0.001$) and depression in HDL ($P < 0.001$) in the SVPA intoxicated rats compared to the normal control rat. The percentage increases in biomarkers of lipid profile are: TC (60%), TG (154%), LDL (92%), VLDL (79%) and depression in HDL (70%). But post treatment of rats with MCS extract offers higher percentage hepatoprotection against SVPA –induced hyperlipidemia. The SVPA induced hyperlipidemia was significantly reduced by treatment of the various doses of MCS extract. The level of hepatoprotection was very significant for the lower dose of MCS extract that the higher dose. The reference drug vinpocetine treatment significantly offer less heptoprotection on lipid profile than the MCS extract.

The mechanism of lipid profile changes due to valproic acid is still unclear. A possible mechanism may be through its mediation in insulin resistance and hyperinsulinemia and by pharmacological modulation in several organs or tissues, such as adipose tissue, hypothalamus, pituitary and pancreatic beta cells [84] resulting in impaired lipid transport and lipogenesis [85]. The upregulated insulin inhibits lipolysisin the adipocytes by activating the phosphoinositol-3-kinase signal which stimulates catecholamine inhibitory effects on lipolysis, causing depressed levels of free fatty acids and glycerol in the circulation [84]. Insulin plays a role in the process of triglyceride clearance through lipoprotein lipase (LPL) activation and triglyceride output through its effect on synthesis and secretion of very low-density lipoprotein (VLDL) in the liver [66]. On the pancreatic beta cells, SVPA interact directly with it to provide inappropriate surge of insulin release or increases its oxidative stress states resulting in beta cells dysfunction. Beta cells are very sensitive to reactive oxygen and nitrogen species (ROS and RNS) due to low level of antioxidants (free radicals quenchers). Oxidative stress in the beta cells has the ability to damage mitochondria, which impair the impaired mitochondrial processes involved in glucose-mediated insulin secretion [86].

Our study demonstrated significant effect on electrolytes (Na^+, K^+, Cl^- and HCO_3^-) and kidney function (CR, UA). The subacute intoxication of the rats with SVPA induces the elevation of sodium ($P < 0.001$) and depression of K^+ ($P < 0.001$), Cl^- ($P < 0.01$) and HCO_3^- ($P < 0.001$) compared to the normal control group. The percentages increase in Na^+ (28%) and decreases of K^+ (26%), Cl^- (13%) and HCO_3^- (20%) are not profound. But the increased in Na^+ and depression of Cl^- might in part mediate the diuretic effects of SVPA in experimental animals [87, 88, 89].

With the sub-acute post-treatment of MCS extract (50 mg/kg), the nephroprotective percentages were K+ (99%), Cl^- (137%), HCO_3^- (149%) with elevation of Na^+ (117%); at 100 mg/kg the nephroprotection percentages are K^+ (101%), Cl^- (70%), HCO_3^- (169%) but depression of Na^+ (59%); at MCS 200 mg/kg b.w. the percentages nephroprotection were K^+ (95%), Cl^- (63%), HCO_3^- (136%) and decrease of Na^+ (111%). The percentage nephroprotection of reference drug vinpocetine (25 mg/kg) are K^+ (98%), Cl^- (106%), HCO_3^- (161%) but a decrease in Na^+ (70%). The SVPA intoxication of experimental rats induced kidney damage revealed moderate nephrotoxicity percentage damage and significant elevation for UA (25%, $P < 0.01$) and CR (22% $P < 0.05$); but treatment with MCS 50, 100 and 200 mg/kg decreased UA (152%, 164%, 82%) and CR (140%, 113%, 102%) respectively, while the reference drug (25 mg/kg b.w.) reduced UA (27%) and CR (78%). The result corroborates down-regulation of UA in the urine in experimental animal exposed to SVPA [90].

On the histopathological investigation, the liver, kidney and lungs histological reports corroborate the biochemical findings. In the liver, intoxication of the hepatocytes with SVPA revealed severe inflammatory response indicating hepatocellular damage or injury which was alleviated with increasing dose of the MCS

extract produced alteration in the histomorphology of the rat but the reference drug was unresponsive to VPA-induced damage.

The kidney intoxicated with SVPA demonstrated marked glomerulus nephritis which was reversed with MCS extract to al normal renal tissue with abundant tubules and with normal epithelium. Like in the liver, vinpocetine was unresponsive peradventure due to poor bioavailability of the drug or limited excretion through the kidney or there exist possibility of drug – drug interaction. Thus the extract was nephroprotective but the reference drug was insensitive.

On the lungs SVPA treatment elicited diffuse alveolar damage with numerous inflammatory cells which was reversed with MCS extract to display lung tissue with normal respiratory portion, the alveoli with a normal interstitial tissue, alveolar sac and epithelium consistent with normal lung histology. The MCS extract and the reference drug present features consistent with normal alveoli indicative that both are mediating pulmonary-protective effect.

The MCS extract phytochemical screening is inundated with armamentariums of bioactive agents such as saponins, alkaloids, flavonoids, tannins, phlobatanins and cardiac glycosides implicated with putative pharmacological effects on several targets [91, 92], in addition to mediating putative bio-enhancing effects [93].

5. Conclusion

The valproic acid induced-hepatotoxicity, nephrotoxicity, hyperlipidemia, alteration in electrolytes profiles and histomorphological insults on liver, kidney and lungs all of which were significantly reversed following repeated subacute oral dosing of MCS extract in rats indicative of presence of bioactive agents with potentials of development as an alternative adjunctive therapy to abrogate SVPA – induced pan-toxicity and adverse drug reaction in man.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest declared.

Statement of ethical approval

'The present research work does contain studies performed on animals by the authors'. The animal study was approved by the Institutional Animal Care and Use Committee with approval code (No. UPHAEC / 2018 / 089) in February 2018. The animal procedures were in accordance with the "Guide and Care and Use of Laboratory Animals" National Research Council, 2011) and study conducted with strict compliance with Food and Drug Administration Good Laboratory Practice Regulation, 1987).

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