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Methanol Leaf Extract of *Clerodendrum violaceum Grüke* modulates some haematological indices of mice

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Abstract

Clerodendrum violaceum is an indigenous antimalarial remedy; its antimalarial efficacy has been previously authenticated. Haematological indices are usually affected in several disease conditions and can be affected by ingestion of drugs and medicinal plants. This study evaluates the effects of methanol leaf extract of Clerodendrum violaceum on haematological indices of mice. Six groups (A-F) of ten mice each were used. Groups B, C, D, E and F were administered 31.25, 62.5, 125, 250 and 500 mg/kg body weight methanol leaf extract of Clerodendrum violaceum respectively. Group A received 5% DMSO and served as control. After fourteen days of administration, five animals from each group were sacrificed and blood collected for analysis of haematological indices. Extract administration continued for another fourteen days after which the remaining animals were sacrificed and treated similarly. After 14 days of administration, there was a significant increase ($p<0.05$) in packed cell volume, haemoglobin concentration and red blood cell count, at all doses (except 500 mg/kg body weight) compared to control. However, extract administration significantly reduced ($p<0.05$) white blood cell count at 500 mg/kg body weight only; and significantly ($p<0.05$) increased lymphocytes at all doses compared to control. After twenty-eight days, there was no significant alteration ($p>0.05$) in all red blood cell indices except red blood cell count and haemoglobin which were significantly reduced ($p<0.05$) at 500 mg/kg body weight while mean corpuscular volume significantly increased ($p<0.05$) at the same dose. White blood cell indices were not altered significantly ($p>0.05$) except lymphocytes which significantly increased ($p<0.05$) at all doses compared to control. The methanol leaf extract of Clerodendrum violaceum increased red blood cells which may be beneficial in counteracting conditions that predispose to anaemia and hypoxia and increased lymphocytes which can strengthen immunity.

Keywords: ***Clerodendrum violaceum,*** **haematological indices, haemoglobin, lymphocytes, erythrocytes.**

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INTRODUCTION

Blood is a specialized fluid responsible for gaseous exchange, transportation of nutrients and metabolites and is also a route of entry for several foreign bodies (Guyton and Hall, 2015). It is composed of red blood cells (erythrocytes), white blood cells (leucocytes) and platelets (thrombocytes) suspended in plasma and these components are usually exposed to drugs, chemicals/toxic compounds thereby exposing them to possible adverse effects (Olayode *et al.,* 2020; Enenebeaku *et al.,* 2021). These possible exposures thus make the assay for haematological parameters important, and any abnormal changes observed in numbers or morphology of these cells and their indices can give valuable information in diagnosis, recovery, and monitoring of many medical conditions (Sexena *et al.,* 2011; Obakiro *et al.,* 2021). Usually, most of the chemical components suspended in blood plasma originate from various organs and tissues, therefore, any changes in haematological parameters may be regarded as indicators of biochemical, physiological and pathological status of the tissues and organs from which they are transported to the blood stream and can serve as good indicators of the overall physiological status (Etim *et al.,* 2014; Porwal *et al.,* 2017).

Although several medicinal plants are the sources and precursors of conventional drugs, ingestion of compounds contained in medicinal plants have also been shown to elicit organ and haematoxicity (Odeghe *et al.,* 2012; Razack *et al.,* 2017). Despite this, the use of medicinal plants and their related products continue to gain popularity mainly because of availability, affordability and supposed safety (Olayode *et al.,* 2020). *Clerodendrum violaceum* Gürke is one of such medicinal plants. It is commonly called Clerodendrum in English and `Ewe isedun´ in Yoruba (Nigeria). It is a straggling, semi-woody, climbing shrub with glabrous leaves and conspicuous violet and white or greenish flowers to up to 2½ cm across. The genus *Clerodendrum* is widely distributed in the tropics and subtropics, with a few species extending into the temperate regions. It has been found in Ghana, Guinea, Zimbabwe, Zambia, Congo, Cameroon and Nigeria (Burkill, 1995). In Southwestern Nigeria, it is found in Lagos, Oyo and Kishi (Balogun *et al.,* 2009). A decoction of its leaves is used in the traditional treatment of fever/malaria, and it is also taken as a prophylactic. Phytochemical evaluation of the leaf extract of *Clerodendrum violaceum* and its antimalarial efficacy has been previously reported. Its antioxidant activity has also been reported and shown to augment its antimalarial actvivity (Balogun *et al.,* 2014; Adebayo *et al.,* 2022). However, its effect on haematological indices of normal animals have not been evaluated thus far. Since changes in haematological indices is characteristic of several conditions including malaria (Momoh *et al.,* 2014; Mooney *et al.,* 2022), it is of interest to investigate the effect of this leaf extract on the haematological indices. This study, therefore, evaluates the effects of the methanol leaf extract of *Clerodendrum violaceum* on haematological parameters of Swiss laboratory mice.

MATERIALS AND METHODS

Chemicals and reagents

Methanol was obtained from BDH Laboratory Supplies, Poole Dorset BH15 UK. All other reagents used were of analar grade and were prepared in all glass distilled water.

Animals

Adult Swiss laboratory mice with an average weight of 20±2.0 g were obtained from the animal breeding unit of the Department of Biochemistry, University of Jos, Plateau State. The mice were housed in plastic cages and maintained under standard laboratory conditions with free access to rat pellets and tap water *ad libitum*.

Plant material
Fresh leaf samples of *Clerodendrum violaceum* were collected in Oyo town, Oyo State, Nigeria and botanically authenticated at Forestry Research Institute of Nigeria (FRIN), Ibadan, Oyo State, Nigeria. A specimen with voucher number FHI 109857 was deposited.

Plant extract preparation
Fresh leaf samples of the plant were dried in the shade at room temperature for a week and pulverized to powder using an electric blender (Mazeda Mill, MT 4100, Japan). Four hundred and fifty gram (450 g) of the powder was exhaustively macerated in 4 L n-hexane, 4 L ethyl acetate and 4 L absolute methanol for 72 h each successively. The extracts were filtered using Whatman filter paper No 1 and concentrated under pressure after each extraction period using a rotary evaporator. The concentrates were then exposed to air and allowed to evaporate at room temperature to dryness (Adebayo *et al.,* 2003). Only the methanol extract was used in this study because it was found to have the highest antioxidant activity (Balogun *et al.,* 2014) and the best antimalarial activity (Adebayo *et al.,* 2022).

Experimental Design
Sixty Swiss laboratory mice were randomly divided into six groups (A-F) of ten mice each and given the methanol leaf extract of *Clerodendrum violaceum* orally as follows:
Animals in group A received 5% DMSO and served as control; those in groups B, C, D, E and F received 31.25, 62.5, 125, 250 and 500 mg/kg body weight of the methanol leaf extract of *Clerodendrum violaceum* respectively. After fourteen days of administration, five animals from each group were sacrificed and blood was collected for analysis. Extract administration continued for another fourteen days after which the remaining animals in all the groups were sacrificed and treated like the first half.

Collection of blood samples
The mice were sacrificed after they were anesthetized with diethyl ether. Blood was collected by cardiac puncture from the unconscious mice into bottles containing EDTA anticoagulant and used for haematological analyses.

Analysis of haematological parameters
Heamatological parameters consisting of Packed Cell Volume (PCV), Haemoglobin concentration (Hb), Red Blood Cell (RBC), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), White Blood Cell (WBC), platelet count, neutrophils (NEU) and lymphocytes (LYM) were determined using the automated haematological analyzer SYSMEX KX21, (SYSMEX corporation, Japan).

Statistical analysis
The group means ± SD for each parameter was calculated and significant differences were determined by Analysis of Variance (ANOVA) and Duncan's Multiple Range Test (DMRT) at 95% confidence level using SPSS-PC programme package (Version 24.0, SPSS Inc. Chicago).

RESULTS

Red Blood Cell Indices
After 14 days of administration, there was a significant increase ($p<0.05$) in packed cell volume (PCV), haemoglobin concentration (Hb) and Red blood cell counts (RBC) at all doses (except at 500 mg/kg body weight) compared to controls (Table 1). After 28 days of administration, there was no significant alteration ($p>0.05$) in PCV, MCH and MCHC at the doses

administered compared to controls (Table 2). There was no significant alteration ($p>0.05$) in Hb and RBC at all doses administered except at the dose of 500 mg/kg body weight which reduced them significantly ($p<0.05$) compared to controls (Table 2). MCV was significantly increased ($p<0.05$) only at the dose of 500 mg/kg body weight while other doses did not significantly ($p>0.05$) alter it compared to control (Table 2).

White Blood Cell Indices

On day 14, extract administration significantly reduced ($p<0.05$) WBC only at the dose of 500 mg/kg body weight compared to control (Table 3). However, there was significant increase ($p<0.05$) in the platelet count at doses higher than 31.25 mg/kg body weight and a significant increase ($p<0.05$) in lymphocytes at all doses compared to control (Table 3).

After 28 days of administration, only percentage lymphocyte was increased significantly ($p<0.05$) at all doses compared to control (Table 4).

Table 1: Effects of Methanol Leaf Extract of *Clerodendrum violaceum* on Red Blood Cell Indices of Mice after 14 Days of Administration

Treatment	PCV (%)	Hb (g/L)	RBC ($x10^{12}$/L)	MCV (fl)	MCH (pg)	MCHC (g/dL)
Control	35.84±1.62^{a}	14.03±1.15^{a}	7.43±0.25^{a}	45.63±2.56^{a}	18.45±0.55^{a}	39.90±1.22^{a}
31.25 mg/kg b.wt	39.37±1.54^{b}	15.45±0.60^{b}	8.16±0.23^{b}	45.99±2.78^{a}	18.59±1.18^{a}	40.37±1.62^{a}
62.5 mg/kg b.wt	39.46±1.10^{b}	14.49±0.74^{b}	8.58±0.83^{b}	46.13±1.92^{a}	18.69±0.53^{a}	39.96±0.71^{a}
125 mg/kg b.wt	39.91±1.63^{b}	15.25±1.12^{b}	8.60±0.74^{b}	45.57±2.14^{a}	18.55±0.43^{a}	40.82±1.23^{a}
250 mg/kg b.wt	38.74±1.48^{b}	15.73±0.53^{b}	8.86±0.33^{b}	45.63±3.08^{a}	18.49±0.41^{a}	39.30±2.14^{a}
500 mg/kg b.wt	33.57±1.16 ^{a}	12.69±1.06 ^{a}	6.07±0.84 ^{a}	46.35±2.79 ^{a}	17.38±0.69 ^{a}	37.88±2.34 ^{a}

Values are means of 5 replicates ±SD. Means for each parameter in the same column with different superscripts are significantly different compared to control ($p<0.05$).

Table 2: Effects of Methanol Leaf Extract of *Clerodendrum violaceum* on Red Blood Cell Indices after 28 Days of Administration

Treatment	PCV (%)	Hb (g/L)	RBC ($x\ 10^{12}$/L)	MCV (fl)	MCH (pg)	MCHC (g/dL)
Control	37.49±2.83^{ab}	13.83±0.92^{a}	7.85±0.74^{a}	48.13±2.97^{a}	18.89±0.77^{a}	38.87±1.79^{a}
31.25mg/Kg b.wt	40.21±2.46^{b}	14.55±1.66^{a}	8.47±0.52^{a}	49.72±1.08^{a}	18.46±0.47^{a}	38.01±2.19^{a}
62.5 mg/Kg b.wt	41.30±2.49^{b}	14.92±1.00^{a}	8.51±0.62^{a}	49.33±0.60^{a}	18.56±1.22^{a}	38.33±2.68^{a}
125 mg/Kg b.wt	40.81±2.05^{b}	15.69±0.44^{a}	8.37±0.62^{a}	49.18±0.62^{a}	18.41±0.29^{a}	38.27±2.37^{a}
250 mg/Kg b.wt	41.25±2.04^{b}	15.06±0.98^{a}	8.19±0.24^{a}	49.27±0.51^{a}	18.52±0.42^{a}	38.05±2.41^{a}
500 mg/Kg b.wt	33.33±2.33^{a}	11.99±1.47^{b}	5.96±1.04^{b}	58.48±2.55^{b}	19.11±0.55^{a}	28.14±2.61^{b}

Values are means of 5 replicates ±SD. Means for each parameter in the same column with different superscripts are significantly different compared to control ($p<0.05$).

Table 3: Effects of Methanol Leaf Extract of *Clerodendrum violaceum* on White Blood Cell Indices and Platelet count of Mice after 14 Days of Administration

Treatment	WBC (x10⁹/L)	Platelet count (x10⁹/L)	Neutrophils (%)	Lymphocytes (%)
Control	19.97±1.06[a]	561.75±2.24[a]	34.90±1.12[a]	51.26±1.44[a]
31.25mg/kg b.wt	18.92±3.33[a]	544.25±3.13[a]	33.34±6.34[a]	67.98±5.17[b]
62.5 mg/kg b.wt	18.35±1.25[a]	669.75±2.04[b]	33.75±3.75[a]	68.93±4.28[b]
125 mg/kg b.wt	18.50±2.39[a]	666.25±2.95[b]	34.62±6.27[a]	68.04±2.78[b]
250 mg/kg b.wt	18.76±2.82[a]	662.81±2.99[b]	33.42±7.53[a]	69.47±7.10[b]
500 mg/kg b.wt	9.53±1.89[b]	644.11±1.95[b]	33.98±6.91[a]	69.16±3.22[b]

Values are means of 5 replicates ±SD. Means for each parameter in the same column with different superscripts are significantly different compared to control ($p<0.05$).

Table 4: Effects of Methanol Leaf Extract of *Clerodendrum violaceum* on White Blood Cell Indices and Platelet count of Mice after 28 Days of Administration

Treatment	WBC (x10⁹/L)	Platelet count (x10⁹/L)	Neutrophils (%)	Lymphocytes (%)
Control	18.89±1.34[a]	552.25±9.49[a]	34.03±2.98[a]	63.00±2.70[a]
31.25mg/kg b.wt	18.19±1.18[a]	581.75±5.78[a]	33.51±2.77[a]	73.93±2.16[b]
62.5 mg/kg b.wt	19.00±1.84[a]	597.21±6.25[a]	33.09±4.81[a]	73.61±2.84[b]
125 mg/kg b.wt	18.14±2.05[a]	640.00±3.58[a]	33.49±4.07[a]	73.74±2.56[b]
250 mg/kg b.wt	19.05±2.17[a]	645.52±8.51[a]	32.47±1.02[a]	74.49±2.11[b]
500 mg/kg b.wt	17.00±2.58[a]	669.50±6.78[a]	33.18±1.74[a]	74.31±3.44[b]

Values are means of 5 replicates ±SD. Means for each parameter in the same column with different superscripts are significantly different compared to control ($p<0.05$).

DISCUSSION

Evaluation of blood parameters is key in determining the effect of foreign compounds including medicinal plants on the blood and any change observed can be used to explain their effects on the functions of blood and its various components (Christian *et al.,* 2017; Nalimu *et al.,* 2022). Medicinal plants typically contain phytochemicals (secondary metabolites) which usually confer different pharmacological properties on the plant in addition to other functions. Since *Clerodendrum violaceum* leaf extract has been reported to contain tannins, saponins, steroids, phlobatannins, triterpenes, glycosides, and anthraquinones and appreciable quantities of phenolics, flavonoids and alkaloids (Adebayo *et al.,* 2022); the significant increase in PCV, Hb and RBC observed after 14 days (Table 1) suggests that these active secondary metabolites in the extract may have stimulated an increase in the rate of production of red blood cells (erythropoiesis) possibly by stimulating erythropoietin release since erythropoietin is the humoral regulator of red blood cell production in the kidney (Malomo *et al.,* 2007; Cheng *et al.,* 2018). These secondary metabolites have previously been reported to have the ability to protect the erythrocytes from oxidative damage as well as possess erythropoietin stimulatory, immune stimulatory and thrombopoietic stimulatory activities which can be useful in the management of hematological disorders (Jorum *et al.,* 2016; Muhammed *et al.,* 2022). Kasim *et al.* (2013) also reported marked increases in packed cell volume, haemoglobin concentration, coupled with raised red blood cell count from herbal preparations containing similar phytochemicals. They attributed this to a direct effect of the

extract components on the haematopoietic system. Flavonoid and phenolic compounds have also been reported to have antioxidant and hematinic properties (Gheith & El-Mahmoudy, 2018). An accelerated activation of hemopoietic precursors due to the direct action of alkaloids have also been reported (Zyuz'kov *et al.*, 2013). Similar phytochemicals were also reported to be responsible for improving the levels of red blood cells, white blood cells (WBCs), and hemoglobin with an increase in hematocrit (Pandey *et al.*, 2016; Putra & Rifa'i, 2019). Thus, the phytochemicals contained in the extract acting singly or synergistically could be responsible for this effect. Since red blood cells and haemoglobin are crucial in transferring respiratory gases, this increase in their levels implies that there will be an enhancement in the oxygen-carrying capacity of the blood and the amount of oxygen delivered to the tissues following extract administration (Adebayo *et al.,* 2005; Zivot *et al.,* 2018). The fact that the extract was able to stimulate increase in PCV, Hb and RBC could be of great importance in the management of diseases that predispose to anaemia like malaria, where anaemia results from repeated immune and non-immune lysis of infected and uninfected red blood cells, increased splenic clearance and dyserythropoiesis (Hermansyah *et al.,* 2017; Nsiah *et al.,* 2020).

The reduction in the level of PCV, Hb and RBCs at 500 mg/kg body weight compared to other doses (though not significantly different from control) (Table 1) suggests that the extract components may exert this beneficial effect better at lower doses. A similar pattern was observed for PCV, Hb and RBC after 28 days of extract administration; this shows that the beneficial effect of the extract components reduced in intensity with the duration of the study (28 days). However, the fact that Hb and RBC significantly reduced at 500 mg/kg body weight (Table 2) suggests that higher doses and longer period of exposure of animals to the extract could reduce red blood cell production (Adebayo *et al.,* 2005; Akintimehin *et al.,* 2021). The non-significant alteration in MCV, MCH and MCHC at all doses on day 14 suggests that the extract components may neither affect the oxygen carrying capacity of RBC's nor the size of RBC's produced (Adebayo *et al.,* 2005). The significant reduction in MCHC at 500 mg/kg body weight after 28 days of extract administration compared to control (Table 2) further suggests that higher doses of the extract for longer periods could elicit selective toxicity (Ashafa *et al.,* 2009; Clemen-Pascual *et al.,* 2022).

White blood cells are usually deployed to fight infection and defend against foreign body invasion by phagocytosis and production of antibodies in the immune response. There was no significant alteration in WBC on day 14 compared to control except at 500 mg/kg body weight which significantly reduced it (Table 3). This suggests that the extract at high doses may cause immunosuppression. However, after 28 days of extract administration, there was no significant alteration in WBC at all doses compared to controls (Table 4). This suggests that the reduction in the level of WBC on day 14 may have been a response to the initial consumption of the extract and the animals may have adapted after a while.

The significant increase in platelets at all doses (except 31.25 mg/kg body weight) after 14 days (Table 3) suggests stimulation of the bone marrow where the cells are produced. This increase could be beneficial in the treatment of conditions that cause decrease in the platelet count like malaria which causes thrombocytopenia because of sequestration of the platelets in the spleen (Chandra and Chandra, 2013; Jiero *et al.,* 2021). However, in normal subjects it may enhance formation of clots in blood vessels and trigger systemic embolism. The increase declined after 28 days suggesting an acute response to the active components of the extract.
Lymphocytes are the main effector cells of the immune system. The increased level of lymphocytes at all doses throughout the study period (Tables 3 and 4) indicates stimulation of the adaptive immune system. This could be beneficial in counteracting infections.

CONCLUSION

The methanol leaf extract of *Clerodendrum violaceum* is a rich source of phytochemicals that are responsible for demonstrating haematopoietic effects. This may be beneficial in counteracting anaemia and hypoxia. The increased level of lymphocytes indicates stimulation of the adaptive immune system which could be beneficial during an infection. However, this effect is better at lower doses for shorter durations.

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