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Haematological Modulation Associated with Sub-Chronic Oral Administration of Extracts of *Simarouba glauca* (Paradise tree) in Male Wister Rats: A Comparative Study

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Abstract

Simarouba glauca has been reported to possess various bioactive compounds with therapeutic potentials; with paucity of data on safety; hence, the study aimed to evaluate the effects of aqueous, ethanol and methanol leaf extracts of *Simarouba glauca* on hematological indices of male *Wistar* rats. The study was conducted according to the guidelines of organization for economic co-operation and development (OECD), No. 425; with a total of thirty male *Wistar* rats; divided into ten groups of n ≥ 3. Experimental rats were administered *Simarouba glauca* Leaf extracts at 500, 1000 and 2000 $mgkg^{-1}$ body weight, respectively; while the control group received feed and water only *ad libitum* daily for 30 days. Selected hematological indices were evaluated. Groups administered respective doses of ethanol and methanol leaf extracts demonstrated significant ($p < 0.05$) dose-dependent elevation of red blood cell; significant ($p< 0.05$) rise in the white blood cell count of groups administered aqueous, ethanol and methanol extracts respectively at high doses; whereas, at 500 $mgkg^{-1}$ of respective extracts, there were no differences ($p > 0.05$) in white blood cell count. Monocytes increased ($p < 0.05$) in groups administered respective doses of the extracts; while lymphocytes increased in groups administered respective doses of ethanol extract. Although, the extracts elicited alterations in white blood cells at higher doses; extract(s) did not induce anemia. Interestingly, extracts stimulated marked increases in red blood cell counts; an indication of the seemingly erythropoietic potentials of the extracts.

Keywords: Haematology; Erythropoiesis; Leukocytosis; Toxicity; Simarouba glauca.

INTRODUCTION

Haematopoietic system is one of the most susceptible targets of toxic compounds, especially in the bone marrow where the synthesis of red blood cell occurs (Kifayatullah *et al*., 2015). Adverse effects of plant compounds of medicinal importance often elicit inflammatory responses associated with toxicity of these biological compounds. However, herbal preparations which are assumed to be safe may contain contaminants such as heavy metals (Okaiyeto and Oguntibeju, 2021), aflatoxins and pathogenic microbes due to the manner in which they are prepared or as a result of acquisition of metals (e.g. cadmium) from the soil (Chandra *et al*., 2019; Victor Jeyaraj *et al*., 2022). There is also the notion amongst the large population of herbal remedy users that these herbal medicines are not toxic because they are derived from natural sources (Welz *et al*., 2018).

Pluripotent stem cell of the bone marrow is the source of red blood cell, white blood cells and the platelets; as such, toxicological events associated with drugs like chloramphenicol and its depressant effect on the bone marrow has been reported (Wilson and Trump, 2006). Similarly, phytochemicals from plants may also affect the bone marrow; thus, interfering with the production of blood cells (Beack *et al*., 2020). Furthermore, the activities of numerous enzymes involved in the synthesis of blood components in the bone marrow are also possibly affected by phytochemical constituents of medicinal plants (Alshibly, 2014). This suggests that any substance which affects the enzyme activities of bone marrow may adversely compromise the synthesis of blood cells.

The haematopoietic physiology is very sensitive to toxins, hence data obtained after exposure of an animal to certain compounds may be used to evaluate the pathological or physiological status of the test animal (Abubakar *et al.,* 2015). Also, Obode *et al.* (2020), reported decrease in the white blood cell count (WBC) due to the presence of some phytochemicals such as saponins and cardiac glycosides.

Like erythrocytes, leukocytes are constitutively produced throughout adult life from haematopoietic stem cells in the red bone marrow; they are released into the circulation where they perform defense tasks; then

removed from the blood by the liver and spleen (Thiagarajan *et al*., 2021). Unlike erythrocytes, these large, nucleated, and translucent cells undertake significant protective functions. They are often capable of phagocytosis and are highly specialized to defend the body against various microorganisms and others like, tumor cells or foreign substances (Thiagarajan *et al*., 2021). In general, leukocytes are motile and very flexible; most of these cells are found in body tissues, as opposed to the bloodstream (Arika *et al.*, 2016). Some specific molecules that are released by damaged, abnormal, and dead cells, or by foreign invaders, attract leukocytes by chemotaxis to the sites of injury, infection, and inflammation (Arika *et al.*, 2016). Although all five types of leukocytes contribute to the same general function; each type of these cells undertake a specific function in the defense system. For example, neutrophils and monocytes are capable of the process of phagocytosis of various pathogens. While neutrophils are the more abundant phagocytic cells which are short-lived, monocytes are significantly more efficient as they differentiate into macrophages which can perform phagocytosis of damaged, abnormal or dead cells and tissues at the sites of injury or inflammation (Arika et al., 2016). During infectious responses, neutrophils are produced more rapidly, and the immature forms of these cells, called band cells (or stab cells), may appear in significantly greater numbers in the peripheral blood (Thiagarajan *et al*., 2021; Arika *et al*., 2016).

The increase in application of medicinal plants cannot be overemphasized; toxicity and safety of herbal products remains a mainstay in evaluation and development of herbal medicine for treatment and (or) management of various diseases in humans (Ekor, 2014). *Simarouba glauca*, (paradise tree) or "Laxmitaru" has a long history of herbal medicine application considering documented evidence of pharmacological potentials in literatures (Patil and Gaikwad, 2011). The stem-bark and leaf extracts of *S. glauca* contain triterpenes, useful in curing amoebiasis, diarrhea and malaria (Jose *et al*., 2018). Chemicals present in leaf, fruit, pulp and seed of *S. glauca* have been reported to possess analgesic, anticancer, antimicrobial, antiviral, astringent, cardio-protective, emmenagogue, stomachic, tonic, vermifuge properties (Jose *et al*., 2018; Biba *et al.*, 2021; Hussain *et al*., 2021; Osagie-Eweka *et al*, 2023). This study focused on the toxicological evaluation of leaf extracts of *S. glauca* on some selected hematological indices of male *Wistar* rat

MATERIALS AND METHODS

Collection of S. glauca leaves and preparation of Extracts

Leaves of *S. glauca* were collected from *Cercobela* Farms®, Ubiaja, Esan South East Local Government Area of Edo State, Nigeria. The plant was authenticated and at the Department of Plant Biology and Biotechnology, University of Benin with an herbarium voucher specimen N0. UBH_S382. The leaves were rinsed with tap water and air-dried at room temperature for twenty-eight (28) days. Leaves were pulverized and sieved to obtain a fine powder. A 500 g sample of the leaf powder was soaked in 2.5 L of distilled water, ethanol or methanol solvent (99 % purity w/v) respectively; stirred at intervals for 24 h, and filtered. The residue was re-extracted using the same procedure. Filtrate portions were decanted separately; freeze-dried in line with the modified method previously reported by Osagie-Eweka *et al.* (2016). The percentage yield of extraction was calculated by multiplying the weight of freeze-dried sample by 100 % and dividing by weight of macerated sample w/w. Figure 1 below shows a section of the paradise tree (*S. glauca*) with fruits in its natural habitat.

Plate 1. *S. glauca* Plant in its Natural Habitat (Cercobela Farms®, Ubiaja).

Experimental animals

A total of 24 male *Wistar* rats divided into four groups of six rats weighing between 184 and 200 g were used for the study. The animals were housed in metabolic cages, fed with normal commercial pellets (Livestock Feeds®) and drank water *ad libitum.* They were maintained under laboratory conditions of 12 h light/ 12 h dark cycle and were acclimatized for two weeks prior to commencement of studies. All experiments were conducted in accordance with the internationally accepted guidelines for laboratory animal use. The protocols were approved by the Faculty of Pharmacy, University of Benin Ethics Committee with reference number EC/FP/021/11.

Oral administration of Leaf Extracts of S. glauca

The study was conducted as prescribed in the OECD No. 425 test guidelines (OECD, 2008), as described by (Rout *et al*., 2014; Oliveira *et al*., 2016). The rats were randomly allotted into ten (10) groups ($n \geq 3$). Test animals received oral doses of 500, 1000, and 2000 mg/kg body weight respectively of leaf extracts reconstituted in distilled water, feed and water *ad libitum* daily for thirty (30) days while the control group received only feed and water *ad libitum*.

Collection of samples and specimens
On day 30, the rats were fasted overnight; the following day, each group of rats were weighed, anesthetized with 1.5g/kg boy weight urethane i.p and sacrificed. Blood sample was withdrawn from the thoracic aorta into an ethylenediaminetetraacetic (EDTA) acid specimen bottle.

Hematological Analyses
The Erma hematology analyzer and Automated/Electronic cell counters was utilized to analyze the whole blood collected from *Wistar* rats as previously reported by Clark *et al*. (2007). The hematological parameters include measurement of red blood cell (RBC) count, haemoglobin (Hb), haematocrit (HCT), white blood cell (WBC) count and differential WBC count (lymphocytes and monocytes count).

Statistical Analyses
Data are expressed as mean ± SD. Differences between means of test groups were evaluated by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. Differences were considered significant at $p < 0.05$. All statistical analyses were conducted using *GraphPad prism*®, version 9.0.

RESULTS

Effects of S. glauca Leaf Extracts on Red Blood Cell Count, Platelet Count, Haemoglobin Concentration and Haematocrit Level of Male Wistar Rats
The data presented in Figure 1 indicate marked increases ($p < 0.05$) in Red Blood Cell (RBC) count of experimental rats administered EESG and MESG at 500, 1000 and 2000 mg/kg body weight, respectively when compared with the control rats whereas there were no observed differences in the RBC of rats administered AESG at respective doses when compared with the control rats administered feed and water *ad libitum* only. The data presented in Figure 2 indicate observed reduction ($p < 0.05$) in haemoglobin concentrations (Hb) across all groups of rats administered all respective extracts at 500 $mgkg^{-1}$ b.wt.. However, groups administered AESG and MESG indicated marked ($p < 0.05$) decrease in Hb concentration at 500 mg/kg b.wt.; whereas, in rat administered EESG 500 mg/kg b. wt., the reduction in Hb concentration was not significant ($p > 0.05$) when compared with the control. Furthermore, figure 2 reveals a significant reduction ($p < 0.05$) in Hb concentrations of experimental rats administered 1000 mg/kg b.wt. across all extracts; whereas only rats administered EESG 2000 mg/kg b. wt. indicated observed reduction ($p < 0.05$) in haemoglobin concentration; compared to the control group. Figure 3 reveals that doses administered at 500 or 1000 $mgkg^{-1}$ b.wt. across respective extracts did not indicate any significant differences in the HCT when compared with the haematocrit level of the control group. Albeit, there was marked increase in the haematocrit level of the experimental animal administered AESG 2000 $mgkg^{-1}$, compared with the control group. The data presented in Figure 4 indicate significant increase ($p < 0.05$) in platelet count at MESG 500 $mgkg^{-1}$ b. wt., significant decrease ($p < 0.05$) at AESG 1000 $mgkg^{-1}$ b. wt. and EESG 2000 $mgkg^{-1}$ b.wt., compared to the platelets count of the control group; whereas, there was no significant ($p > 0.05$) differences in platelet count at other doses across different extracts when compared with the control group.

Effects of S. glauca Leaf Extracts on White Blood Cell Count and Differentials of Male Wistar Rat
The data presented in figure 5 indicate significant increase ($p < 0.05$) in the white blood cell (WBC) count of experimental rats administered AESG and EESG 1000 $mgkg^{-1}$ respectively, when compared with the control group. The data further reveal that rats administered EESG and MESG 2000 $mgkg^{-1}$ respectively likewise indicate significant increase ($p < 0.05$) in WBC count; whereas, there were no significant differences in WBC count of rats administered the extracts at 500 $mgkg^{-1}$ compare to the control. Figure 6 show increased ($P < 0.05$) lymphocyte count in experimental rats administered EESG 500, 1000 & 2000 $mgkg^{-1}$ respectively; AESG 2000 $mgkg^{-1}$. Whereas, there were no significant differences ($p > 0.05$) in the lymphocyte count of other extracts; at varying doses, when compared to the control. The data presented in Figure 7 indicate significant ($p < 0.05$) increase in the monocytes count of experimental rat administered AESG or EESG 1000 $mgkg^{-1}$ respectively; whereas at MESG 1000 $mgkg^{-1}$b.wt., there was no significant difference in monocytes count; compared to the control. The data further indicated significant ($p < 0.05$) in monocytes count of rats administered AESG, EESG or MESG at 500 & 2000 $mgkg^{-1}$ bwt. respectively; when compared to the monocytes counts of the control.

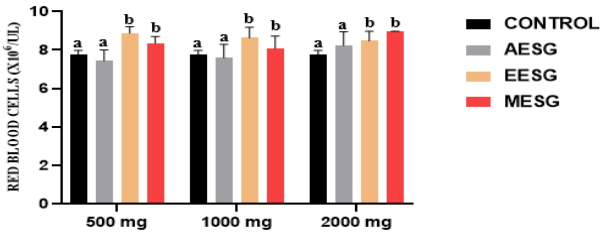

Figure 1. Effect of Varying Doses of Aqueous (AESG), Ethanol (EESG) or Methanol (MESG) Leaf Extracts of *S. glauca* on Red Blood Cells Counts (RBC) of Male *Wistar* Rats after 30b Days.
Data with different lower-case alphabets are significantly different ($p < 0.05$). Data are presented as Mean ± SD.

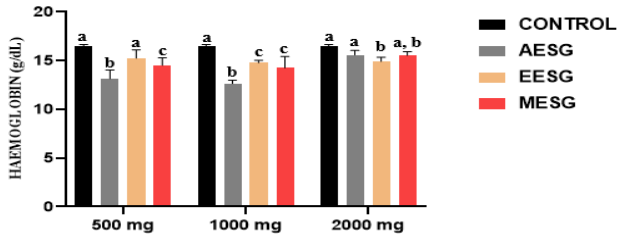

Figure .2. Effect of Varying Doses of Aqueous (AESG), Ethanol (EESG) or Methanol (MESG) Leaf Extracts of *S. glauca* on Haemoglobin (Hb) Concentration of Male *Wistar* Rats after 30 days.
Data with different lower-case alphabets are significantly different ($p < 0.05$). Data are presented as Mean ± SD.

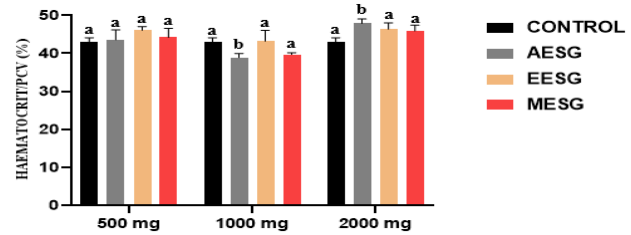

Figure 3. Effect of varying doses of Aqueous (AESG), Ethanol (EESG) or Methanol (MESG) Leaf Extracts of *S. glauca* on Haematocrit (HCT) Concentration of Male *Wistar* Rats after 30 days.
Data with different lower-case alphabets are significantly different ($p < 0.05$). Data are presented as Mean ± SD.

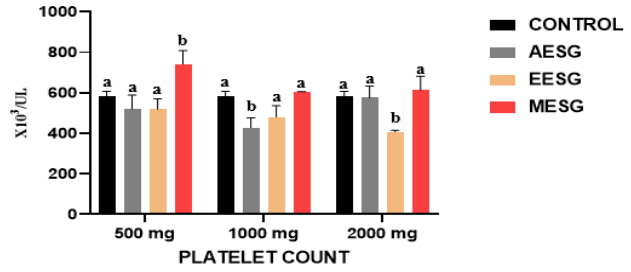

Figure 4. Effect of Varying Doses of Aqueous (AESG), Ethanol (EESG) or Methanol (MESG) Leaf Extracts of *S. glauca* on Platelets Count of Male *Wistar* Rats After 30 days.
Data with different lower-case alphabets are significantly different ($p < 0.05$). Data are presented as Mean ± SD.

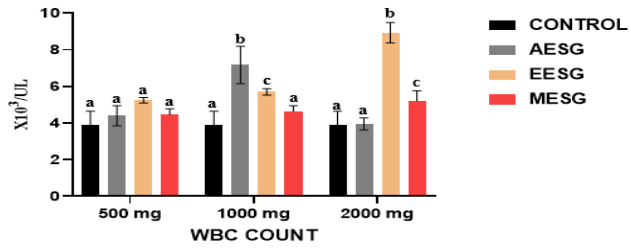

Figure 5. Effect of varying doses of Aqueous (AESG), Ethanol (EESG) or Methanol (MESG) Leaf Extracts of *S. glauca* on White Blood Cell (WBC) Count of Male *Wistar* Rats After 30 days.
Data with different lower-case alphabets are significantly different ($p < 0.05$). Data are presented as Mean ± SD.

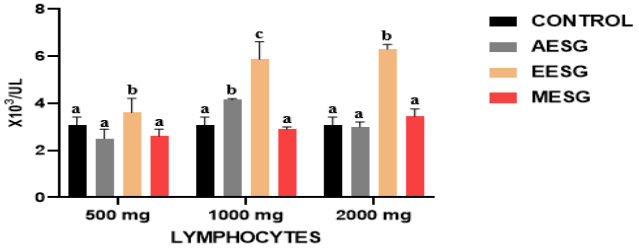

Figure 6. Effect of varying doses of Aqueous (AESG), Ethanol (EESG) or Methanol (MESG) Leaf Extracts of *S. glauca* on Lymphocyte Count of Male *Wistar* Rats After 30 days.
Data with different lower-case alphabets are significantly different ($p < 0.05$). Data are presented as Mean ± SD.

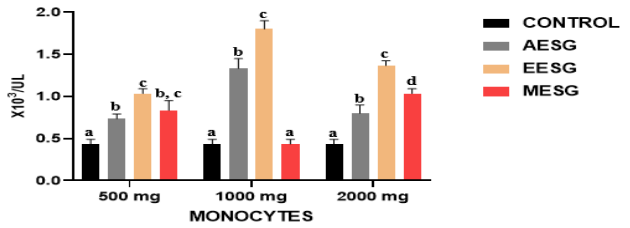

Figure 7. Effect of varying doses of Aqueous (AESG), Ethanol (EESG) or Methanol (MESG) Leaf Extracts of *S. glauca* on Monocyte Count of Male *Wistar* Rats after 30 days.
Data with different lower-case alphabets are significantly different ($p < 0.05$). Data are presented as Mean ± SD.

DISCUSSION

Safety of medicinal plants remains a focus in alternative medicine application; in the management of various diseases in human life. Regardless of the general perception that medicinal plants are without adverse effects, it is indeed of scientific importance to evaluate the safety and (or) potential toxic effect(s) of these medicinal plant(s) compounds on relevant organs and tissues (Kharchoufa *et al*., 2018; Abraham and Ahmad, 2021). Studies have reported experimental designs directed at evaluating the bioactive compounds inherent in medicinal plants for safety purposes (Christapher *et al*., 2017; Erhire and Moke, 2022).

The haematopoeitic system is susceptible to inflammatory conditions often linked to foreign compounds, be it medicinal, anthropogenic and (or) allopathic drugs. Alterations in red blood cell (RBC) counts, haemoglobin concentrations (Hb), and haematocrit (HCT) are prominent indicators of anaemic conditions; whereas alterations in white blood cell (WBC) count and its agranulocyte differentials (lymphocyte and monocyte counts) are indicators of infections, inflammatory conditions; as well as tissue and organ damage. There are several reports in the literatures detailing the effects of the application of medicinal plants. Olaniyan *et al.* (2016) reported that aqueous and methanol extracts of *N. campestris* did not result to significant changes ($p > 0.05$) in the haematological

profile of rats that received the entire test doses; whereas, Musila *et al.*, (2017) reported that administration of *C. volkensii* to test animals indicated observed changes in the RBC counts.

In this study, the marked increase in RBC counts of experimental animals administered ethanol and methanol leaf extracts of *S. glauca* at the respective doses indicates erythropoietic potential; perhaps attributable to inherent phytocompounds and abundant co-factors in the leaf extract of *S. glauca* such as Fe^{2+} and vitamin B complex required for synthesis of erythrocytes. The findings are consistent with the earlier reports stressing the roles of phytocompounds and vitamins in synthesis of erythrocytes (Ikewuchi, 2013; Osagie-Eweka *et al.*, 2016; Gurupriya *et al*., 2017; Nagaraj *et al*., 2021). Polycythemia may be avoided at relatively low doses as may be required.

The data also agrees with the findings of Muriithi *et al.*, (2015) who reported significant increase in RBC counts speculatively relying on the possible stimulating effect of erythropoietin by inherent phytochemicals in leaf extract of *S. Incanum*. Although, the increased Hb concentration reported by Muriithi *et al*. (2015) is at variance with the outcome of this study; perhaps due to difference in isoforms of similar phytocompounds of interests. The significant reduction in Hb concentrations, particularly at 500 and 1000 $mgkg^{-1}$ doses indicate that extracts interfered with the oxygen binding capacity of the RBC, although, by a yet to be identified phytocompound.

Administration of leaf extracts of *S. glauca* at respective doses did not indicate significant alteration to the percentage by volume of the red cells in the total blood test rats, although, there was observed significant reduction in haematocrit level at AESG 1000 $mgkg^{-1}$; which further suggest that extract may not have resulted to hemorrhagic bleeding or heavy loss of blood. The significantly low platelet counts recorded in test animals administered AESG 1000 $mgkg^{-1}$ and EESG 2000 $mgkg^{-1}$ may be attributed to the adverse effect of a yet to be identified phytocompound inherent in the leaf extract, as similarly observed in reduced haemoglobin.

The thrombocytopenic state observed at AESG 1000 $mgkg^{-1}$ may raise concerns for suspected bleeding of no deleterious effect; which may be reversed at lower doses or withdrawal of extract. It is important to note that the haematocrit level was similarly significantly affected at AESG 1000 $mgkg^{-1}$. Contrariwise, it may be considered that the extract demonstrated some noticeable degree of anti-platelets activity, being a considerable mechanism in the management of agglutination associated with complicated cardiovascular conditions.

White blood cells (WBC) function to fight infections; are mobilized when the body system encounters foreign elements. Studies have reported the immune-stimulatory effects of certain herbal extracts (Nguenang *et al*., 2020; Abraham and Ahmad, 2021). In the present study, it is strongly suggested that the markedly elevated WBC counts, lymphocytes and monocytes differentials observed at varied doses may not be unconnected with cellular inflammatory responses elicited by inherent phytochemicals of the leaf extracts of *S. glauca* (Nguenang *et al*., 2020; Biba *et al*., 2021; Abraham and Ahmad, 2021), which may have signaled, stimulated and activated the release of T-helper cells, macrophage colony stimulating factor, interleukins IL-2 IL-4 and IL-5, proliferation, differentiation and maturation of committed stem cells responsible for the production of white blood cells and differentials (Guyton and Hall 2000; Barret *et al*., 2012).

CONCLUSION

The present study has revealed that oral administration of the considered extracts of *S. glauca* did not elicit anaemia; rather stimulated marked increases in red blood cell counts, an indication of a promising erythropoietic potential of the extracts. The extract also exhibited some sort of anti-platelets activity. The alterations recorded in the white blood cell (WBC) and differential counts suggests obvious immune-stimulatory responses elicited by yet to be identified phytocompounds of the leaf extract(s) of *S. glauca.* Future studies shall focus on isolating and identifying the phytocompound inherent in the leaf extracts of *S. glauca* responsible for the elicited responses characterized by marked alterations in WBC counts and agranulocytes differentials, the interference with the oxygen-binding capacity of the blood, as well as the disturbances observed in platelets counts.

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Ethical approval: All protocols were approved by the Faculty of Pharmacy, University of Benin Ethics Committee with reference number **EC/FP/021/11**.

Conflict of Interest: I make the solemn statement believing same to be true that there is no competing or conflict of interests.

Data Availability: Author(s) declares that supplementary data or raw data that may be required for clarity are available on request from the corresponding author

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Author Contributions: SDE and KAI contributed to the concept of the study; SDE carried out the formal analysis and investigation; including interpretation of the analyzed data. SDE and KA contributed to writing of the

original manuscript. All authors read and approved the final version of the manuscript.

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