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# Changes in Haematological Parameters and Possible Adverse Reactions of Terminalia Catappa Leaves Extract in Wistar Rats.

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***Abstract:*** *The study of changes in haematologic parameters and possible adverse reactions following the administration of aqueous leaf extract of Terminalia catappa was carried out on male albino Wistar rats The experimental animals were randomly distributed into three (3) groups of five (n=5) rats per group. Group 1 served as control and was administered normal deionized water orally at a dose of 5ml/kg body weight. Group 2 and 3 animals were administered with aqueous extract of Terminalia catappa at a dose of 40mg/kg body weight as low dose and 120mg/kg body weight as high dose by oral gavaging. The body weight of the animals were taken daily and the study lasted for 17 days. The results showed that aqueous extract of Terminalia catappa has no significant change in the mean value of red blood cell count when compared with control, but a significant decrease ($p<0.05$) in the white blood cell and platelets when compared to control was obtained. Agranulocytosis and thrombocytopenia were observed as the possible adverse reactions associated with the extract. Therefore, aqueous crude extract of Terminalia catappa might possess some adverse reactions capable of disturbing the body defence system and haemostasis*

***Keywords:*** *Red Blood Cell count, White Blood Cell count, Platelets count, haematological indices, Terminalia catappa, adverse drug reaction*

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## I. Introduction

Blood is an important component of homeostatic mechanism and it is regulated at a normal range in order to carry out its functions. Changes in some blood parameters serve as important indicators of the harmful effect of substances like drugs, chemicals as well as disease conditions (Coffey *et al*., 2017). Hematologic disorders have long been a potential risk of modern pharmacotherapy (Rao, 2014). Some agent causes predictable hematologic disease, but others induce idiosyncratic reactions not directly related to the drugs' pharmacology. The most common drug-induced hematologic disorders include aplastic anemia, agranulocytosis, megaloblastic anemia, hemolytic anemia, and thrombocytopenia (Hine, 1990; Rao, 2014). Several drugs have been studied and reported to have variable hematologic effects, drugs such as antibiotics (Chen *et al.,* 2012), anti-cancer drugs (Muravyova, *et al.,* 2016) anti-inflammatory drugs (Trnkova *et al*., 2007), sulfonamides (Heimpel and Raghavachar, 1987) among many others have been reported to induce varying degrees of effect on blood. Although drug-induced hematologic disorders are less common than other types of adverse reactions, they are associated with significant morbidity and mortality (Rao, 2004). Studies have shown that death due to hematologic disorders is mainly caused by aplastic anemia followed by thrombocytopenia, agranulocytosis, and hemolytic anemia (Hine *et al.,* 1990). On the other hand, incidence of idiosyncratic drug-induced hematologic disorders varies depending on the condition and the associated drug (Rao, 2014). Few epidemiologic studies have evaluated the actual incidence of these adverse reactions, but these reactions appear to be rare (Rao, 2014). Adverse effects of drugs may be produced through toxicity, by an immunological process, by inhibiting the action of important enzymes, by decreasing the absorption of substances essential for normal hematopoiesis, or by as yet unknown mechanisms (Yunis, *et al*., 1980; Young and Maciejewski, 1997, Lichtman, 2010). Similar to most other adverse drug reactions, drug-induced hematologic disorders are more common in elderly adults than in the young and the risk of death also appears to be greater with increasing age (Cahir *et al*., 2014). However, women are generally more susceptible than men to the hematologic effects of drugs and the incidence also varies based on geography, which suggests that genetic differences may be important determinants of susceptibility (Rao, 2004).

Besides the use of conventional medicine, reliance on medicinal plants for therapeutic purposes have been on the rise globally (Ekor, 2013) and different plant parts are in use and they contain several active compounds which posses therapeutic potentials useful for both traditional medicine and as source for orthodox medicine (Gregory, 2004). These active ingredients elicit their therapeutic effect in mechanisms similar to that of conventional drugs (Tapsell *et al*., 2006). Some secondary metabolites domicile in medicinal plant had shown

robust biological effect (De-Fatima *et al*., 2006). In various locations in Nigeria, a wide range of plant species are put to use in the treatment of diseases (Nwaeze, *et al*., 1986). One of the medicinal plants with huge therapeutic claims is *Terminalia catappa* (Indian almond) and it is extensively used throughout the tropical areas of Africa, Asia and Australia (Venkatalakshmi *et al*., 2016). The leaf extract of *Terminalia catappa* has been reported to have therapeutic effect in the treatment of liver disease (Chiu and Chang, 1986), dermatitis and hepatitis (Lin *et al*., 1997), inflammation (Pawar *et al*., 1997; Fan *et al*., 2004) diabetic mellitus (Ahmed *et al*., 2005, Koffi *et al*., 2011), headache and colic (Morton, 1985). Following the extensive use of medicinal plants which is supported by WHO, appropriate survey for adverse effects of these medicinal plants is also recommended by WHO (WHO Dept. of Essential Drugs and medicine policy, 2004). Therefore, though the therapeutic uses of the leave extract of *Terminalia catappa* have been supported by many scientific researches, it becomes necessary to assess the haematological parameters in relation to the possible adverse reactions associated with this extract.

## II. Materials And Methods

***Preparation of plant extract***

Fresh leaves of *Terminalia catappa* were collected at the premises of the University of Uyo and the area was free of pesticides and other contaminants. The leaves were authenticated by a botanist at the Department of Botany and Ecological studies, University of Uyo. The leaves were then washed with clean water to remove debris. The water was blotted out and kept over night at room temperature to dry up. The clean leaves were pulverized and 5000g of the pulverized leaves was soaked in 5 litres of deionised water for 18 hours. The mixture was filtered using muslin cloth and evaporated to dryness using thermostatic water bath at $45^{o}$C until a semi solid paste was obtained. 204.18g of the extract was obtained after evaporation which represent a percentage yield of 4.08% and the extract was stored in refrigerator for later use.

***Preparation of experimental animal***

Fifteen (15) healthy male albino Wistar rats weighting between 150-200g were used for the study. The animals were procured from the animal house, Faculty of Basic Medical Sciences, University of Uyo and were housed in a well ventilated cage in the animal house. They were allowed to acclimatize for two weeks and maintained in a 24 hours dark and light cycle. The animals were fed with standard pellets (from Guinea Feeds, Plc Nigeria) and have access to water *ad libitum*.

***Experimental design***

The experimental animals were randomly distributed into three (3) groups of five (n=5) rats per group. Group 1 served as control and was administered normal deionized water orally at a dose of 5ml/kg body weight. Group 2 and 3 animals were administered with aqueous extract of Terminalia Catappa at a dose of 40mg/kg body weight as low dose and 120mg/kg body weight as high dose respectively by oral gavaging. The body weight of the animals were taken daily and the feed were measured before and after feeding daily. The study lasted for 17 days.

***Collection of blood samples***

At the end of the experiment, blood samples were obtained from the experimental animal 24 hours after the last extract administration. The animals were sedated with chloroform vapour and blood was collected by cardiac puncture. Blood sample from each animal was emptied into EDTA sample sequestered bottle. The bottles were gently turned to mix adequately with the anticoagulant in preparation for analysis of various parameters.

***Determination of haematological parameters***

Sample blood from each of the bottle was used for the analysis of haematological parameters. Standard laboratory procedures for auto-heamatological analysis were employed using Midray haematological auto-analyser (model BC5300, serial number OA-101505, Germany). The result for each parameter was obtained in a print out from the analyser.

***Statistical analysis***

Data were analysed via Statistical Package for Social Science (SPSS) software version 20.0 (SPSS Inc. Chicago, IL) and Microsoft excel. Results were represented using tables and discrete variables are represented in percentages. Descriptive analysis i.e. comparison of mean was via analysis of variance (ANOVA). The results were presented as mean ± standard error of mean (SEM) and the values of $p<0.05$ were considered significant.

## III. Results

***Red blood cell count (RBC)***

The result of the effect of *Terminalia catappa* extract on the red blood cell count is shown in figure 1. The mean value for red blood cell (RBC) count in control group was 7.48 ± 0.14 (× $10^{12}$/L), the red blood cell count for extract treated groups were 7.08 ± 0.14 (× $10^{12}$/L) and 7.86 ± 0.31 (×$10^{12}$/L), for group 2 and group 3 respectively. A comparison of the result of the test group with that of control group showed some marginal changes which were reduction in low dose group and increase in high dose group but these differences were not statistically significant.

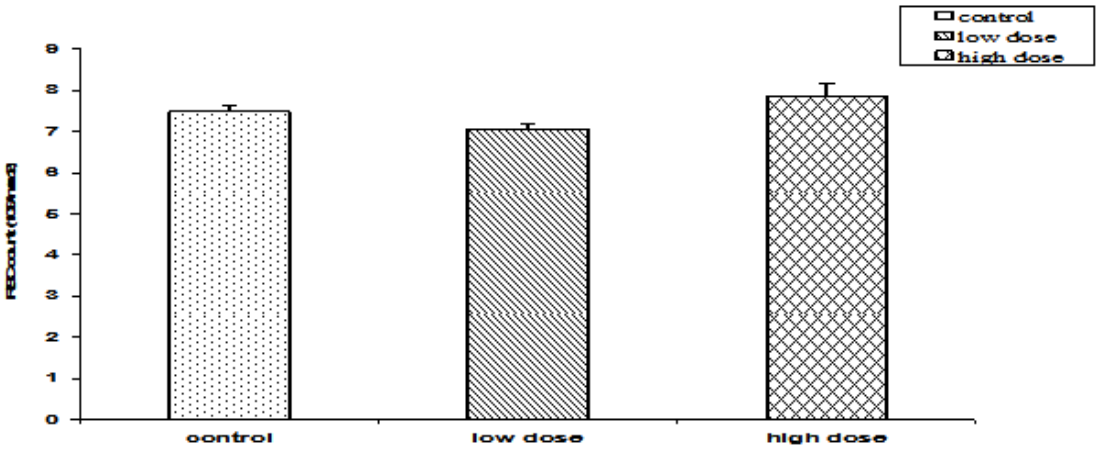


Figure 1. Red blood cell count in extract treated rats compared with control. Values are mean SEM. P < 0.05

***White blood cell count (WBC)***

In figure 2 the results of the effect of the extract on the white blood cell (WBC) count is represented. The low dose (group 2) result was 8.42 ± 0.52 (×$10^9$/L) and this was a significant ($p<0.05$) reduction when compared to the mean value of 15.7 ± 0.91 (×$10^9$/L) in the control group. Also there was a significant reduction ($p<0.05$) in group 3 (higher dose) to mean value of 12.04 ± 0.07 (×$10^9$/L) when compared with control.

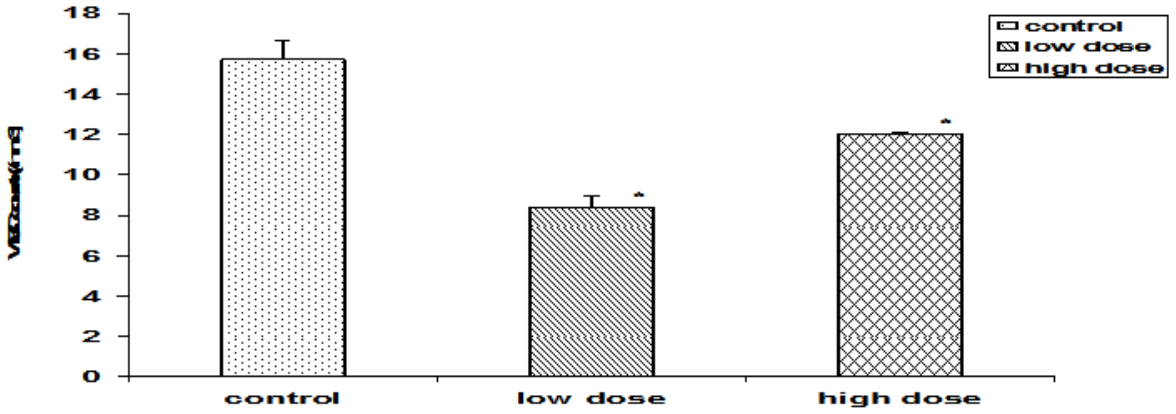


Figure 2. White blood cell count in extract treated rats compared with control. Values are mean ± SEM. ** p< 0.01, * p < 0.05

***Changes on platelet count (PLT)***

The platelet count following the administration of *Terminalia catappa* extract is shown in figure 3. The platelet (PLT) count of the control group was 838±19.89 (× $10^9$/L) and in comparison with the mean value of the low dose group 414.6±18.34 (× $10^9$/L) there was significantly ($p<0.001$) decreased in the extract treated group. Also, the mean value of group 3 (high dose extract treated) was 736.6±16.22 (× $10^9$/L) and this was also significantly reduced at $p<0.001$. However, the level of reduction in group 3 was not as much as that of group 2

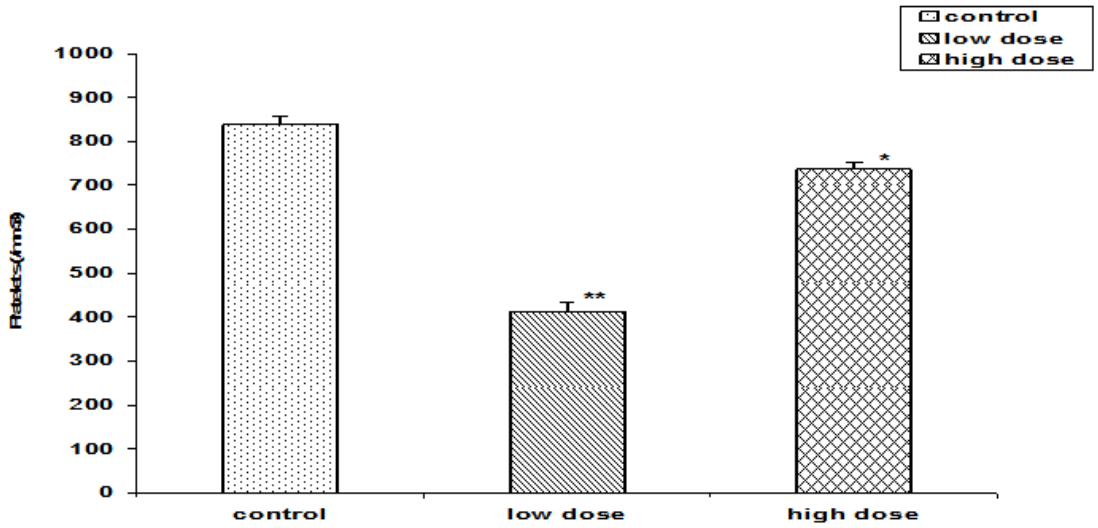


**Figure 3. Platelet count in extract treated rats ompared with control. Values are mean ± SEM. ** p < 0.01, * p< 0.05**

***Changes in haemoglobin (HB) concentration***

The result of the haemoglobin concentration after the administration of aqueous extract of *T. catappa* is shown in **table 1**. The mean value of haemoglobin in the control group was 14.38 ± 0.22 g/dl. Comparing this with the results of group 2 and 3, which have mean values of 13.41 ± 0.40 g/dl and 15.34 ± 0.47 g/dl respectively showed slight changes which were not statistically significant.

***Table1. Haematological indices in rats treated with extract compared with control.***

| Indices | Control | Low dose | High dose |
|---|---|---|---|
| Haemoglobin (g/dl) | 14.38 ± 0.22 | 13.41 ± 0.40 | 15. 34 + 0.47 |
| Packed Cell Volume (%) | 43.0 +0.94 | 40.2 +0.87 | 45.8 + 1.5 |
| Mean Corpuscular Volume (fL) | 57.6 +0.61 | 56.6 + 0.73 | 58.2 + 1.24 |
| Mean Corpuscular Haemoglobin (pg) | 19.4 + 0.22 | 18.8 + 0.44 | 19.6 + 0.46 |
| Mean Corpuscular Haemoglobin Concentration (g/dl) | 33.4 + 0.36 | 33.8 + 0.18 | 33.6 + 0.22 |

Values are mean ± SEM, p< 0.05

***Changes in packed cell volume (PCV)***

The data obtained for packed cell volume is presented in table 1. A mean value for low dose and high dose groups were 40.2 ± 0.87 % and 45.8 ± 1.5%. These in comparism with the mean value of the control group, 43.0 ± 0.94% showed that there was a reduction in the packed cell volume of group 2 but this was not significant statistically.

***Changes on haematological Indices***

Changes observed in the haematological indices are shown in table 1. Starting with the Mean Corpuscular Volume (MCV), the mean value for group 1 was 57.6 ± 0.61(fL) while that of group 2 and 3 were 56.6 ± 0.73 (fL) and 58.2 ± 1.24 (fL) respectively.

The results of the extract treated groups were not statistically significant when compared with the control group. On the mean Corpuscular haemoglobin (MCH), the result showed that group 2 (lower dose) has a mean value of 18.8 ± 0.44 pg. and group 3 (higher dose) has a mean value 19.6 ± 0.46 pg. Comparing theses values with 19.4 ±0.22 pg from control group showed no significant difference.

The mean corpuscular haemoglobin Concentration (MCHC) of the control group was 33.4 ± 0.36 (g/dl). The extract treated groups MCHC values were 33.8 ± 0.18 (g/dl) and 33.6 ± 0.22 (g/dl) for group 2 and group 3 respectively. The result when tested statistically did not show any significant difference.

## IV. Discussion

The study of changes in haematologic parameters and possible adverse reactions following the administration of aqueous leaf extract of *Terminalia catappa* was carried out on male albino Wistar rats. The results of the study on the red blood cell (RBC) count showed no significant difference between the test groups and the control group. However, marginal changes were observed in the red blood cell count in the test groups but the changes were not significant. This suggest that the extract therefore does not have significant effect on erythropoiesis and cannot be used in treatment of anemia. The results also showed that there were no significant changes in the packed cell volume (PCV), haemoglobin level (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH) and Mean Corpuscular Haemoglobin Concentration (MCHC). These results collaborated with the non-significant changes in MCV reported by Schecter *et al*., (1987), Contran *et al*., (1999) and the study of Ibegbulem *et al*, (2011) who reported that there were no significant changes in the packed cell volume (PCV), but is contrary to the findings of Aimola *et al*., (2011) who reported elevation of packed cell volume and enhancement of intracellular haemoglobin content in Balb mice. The difference may however be due to the method of extraction as this was a methanolic extract of *Terminalia catappa* leaves while the present work is with aqueous extract.

Adverse reactions of drugs associated with Red blood cell includes drug-induced immune hemolytic anemia, drug-induced oxidative hemolytic anemia, or drug-induced megaloblastic anemia (Rao, 2014), while drugs used as hematinics increases the RBC count and other red cell parameters (Seeber,and Shander. 2012). Thus the extract may neither cause adverse reactions in relation to various types of anemia nor become useful in the treatment of anemic condition since none of the red blood cell parameters was either positively or negatively affected.

In consideration of the effect of the extract on the white blood cell (WBC) count, it was observed that there was a significant reduction in WBC both in the low dose and the high dose groups. This result disagrees with the work of Ibegbulem *et al.,* (2011) who reported that there was no significant change in the white blood cell counts in albino Wistar rats given *Terminila catappa* leaves decoction in place of water. But there was agreement with a similar work carried out by Muhammad and Oloyede (2009) who reported a significant reduction in the white blood cell count in broiler chicks fed with raw *Terminalia catappa* seed meal-based diet and Aspergillus niger fermented *Terminalia catappa* seed meal-based diet. The result also agrees with the findings of Aster and Kumar (1999), Nelson and Cox (2000) who reported a significant decrease in the white blood cell count in rats. A decrease in white blood cell count following a drug therapy leads to agranulocytosis which is an adverse reaction.

The cause of drug-induced agranulocytosis is not fully understood, but two mechanisms namely direct toxicity and immune-mediated toxicity have been proposed (Pea and Cojutti, 2015). Direct toxicity to myeloid cells has been shown with medications such as chlorpromazine, procainamide, clozapine, and diclofenac (Rao, 2014). The toxicity may be due to either the parent drug or a toxic metabolite or by-product.

Agranulocytosis due to direct toxicity is usually associated with a slower decline in neutrophils (Youg, 2000; Tesfa *et al*., 2009; Pontikoglou and Papadaki 2010) while the immune-mediated subset of agranulocytosis, can use hapten mechanisms of toxicity (Rao, 2014). The hapten mechanism involves the drug or its metabolite binding to the membrane of neutrophils or myeloid precursors (Rao, 2014). After binding, antibodies are induced that destroy the cell. Although the mechanism by which the extract might affect the white blood cells is not yet understood, it is possible for one or more of the active constituent to employ the direct or hapten mechanisms of toxicity to induce a significant reduction of White blood cell. Therefore, extract induced reduction in WBC count at normal condition implies a serious risk to the body defence system in a healthy state but this may be beneficial in abnormal health conditions associated with raised White blood cell count.

Moreover, the platelet count result showed a significant reduction in both low dose and high dose groups with the effect more marked in low dose group. This result collaborated with the work of Muhammad and Oloyede (2009) who reported a platelet count reduction in Terminalia catappa seed meal-based diet administration. Decreased platelet count is one of the haemolytic disorders of modern pharmacology (Hine 1990; Kamakshi 2004). Drug-induced thrombocytopenia can result from immune-mediated and non immune-mediated mechanism (George *et al.,* 1998). Non immune-mediated mechanisms, such as direct toxicity- type reactions, cause bone marrow suppression leading to suppressed thrombopoiesis and a decreased number of megakaryocytes (Rao,2014). But in immune-mediated drug-induced thrombocytopenia, hapten type reactions which involves covalent binding of the offending drug to certain platelet G-proteins. Then antibodies are generated that bind to the platelet surface and lysis occurs through complement activation or through clearance from the circulation by macrophages (Aster, 1999; Aster and Bougie, 2007; Aster *et al*., 2009). Hapten-mediated immune thrombocytopenia usually occurs at least 7 days after the initiation of the drug, although it can occur much sooner if the exposure is actually a re-exposure to a previously administered drug (Reese *et al.,* 2010). The recovery period, after the suspected drug is discontinued, is often short in duration with a median recovery time within 1 week (Reese *et al.,* 2010). The duration of the extract administration is observed to be

within the range of time for hapten type reaction. This is suggestive of involvement of hapten type of mechanism for adverse reaction by *Teminalia catappa* although this is not yet ascertaining. Thus the result suggests an extract induced thrombocytopenia and might be detrimental to the body haemostasis haemostasis.

In conclusion, the aqueous extract of *Terminalia catappa* has no effect on red blood cell count but decreases the white blood cell and platelets counts in healthy rats. These suggest a state of agranulocytosis and thrombocytopenia as the possible haemolytic adverse reactions associated with the extract as observed in normal rats. Thus the medicinal use of aqueous crude extract *Terminalia catappa* could have some adverse reactions which affects the body defence system and haemostasis.

## V. Conclusion

A severe reduction in the number of white blood cells and abnormally low thrombocytes are the observed possible adverse effects associated with the use of the extract. Therefore, aqueous crude extract of *Terminalia catappa* leaf extract may possess some adverse effect capable of altering the immune status of the individual hence caution should be taken in the use of this extract for any therapeutic or prophylactic benefit.

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