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# Effect of *Citrullus lanatus* Seeds Extract on Haematological Parameters After Administration with Medroxyprogesterone Acetate on Female Wistar Rats

**Michael Chuks Nnumolu*, Onyeso Godspower**
Department of Physiology, Faculty of Basic Medical Sciences, Madonna University, Elele, Nigeria.

**Corresponding author***
michaelnnumolu@gmail.com

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**Abstract**

This study was carried out to investigate the effect of *Citrullus lanatus* seeds extract on the haematological parameters after administration with medroxyprogesterone acetate on female Wistar rats. Twenty-five rats weighing 170-230 g were divided into five groups containing five rats each. Group I served as control and received only rat chow and water; Group II received rat chow, water and a high dose of MPA only; Group III received rat chow, water, a high dose of MPA and a high dose of extract; group IV received rat chow, water, high dose of MPA and a low dose of extract, and group V received rat chow, water and high dose of extract only. The administration lasted for twenty-eight days after two weeks of acclimatisation. On the twenty-ninth day, the animals were anaesthetised using chloroform, sacrificed and their blood samples obtained via cardiac puncture for haematology analysis. The results showed that the level of haematological parameters significantly increased ($p<0.05$) in the rats that received a high dose of MPA and a high dose of *Citrullus lanatus* seed extract compared to the control group. This suggests that MPA affects bone marrow, which produces blood cells, significantly decreasing platelet count, white blood cell count, red blood cell count, haemoglobin count, packed cell volume, mean corpuscular volume, and mean corpuscular haemoglobin concentration. This study also shows that an aqueous extract of *Citrullus lanatus* seed is potent in increasing the level of haematological parameters when co-administered with MPA.

**Keywords:** Medroxyprogesterone acetate; *Citrullus lanatus* seeds; Haematology; Blood Physiology.

## INTRODUCTION

There has been a notable increase in the utilisation of contraceptives among women of reproductive age in recent years (Abdel-Salam et al., 2020). A growing inclination towards methods such as oral contraceptive pills, female sterilisation, and condoms characterises this trend (Jain et al., 2021). Simultaneously, the advent of novel contraceptive alternatives has resulted in a heightened utilisation of injectable methods, most notably Depo-Provera, which encompasses medroxyprogesterone acetate (MPA). Medroxyprogesterone acetate, also known as 17α-hydroxy-6α-methylprogesterone acetate, is a steroidal progestin, a synthetic variant of the steroid hormone progesterone. It is used as a contraceptive, in hormone replacement therapy, and for the treatment of endometriosis as well as several other indications (Gompel, 2020). The contraceptive effectiveness of MPA has been well-established; however, its impact on different physiological processes, specifically in haematology, has attracted significant interest among researchers.

The haematological parameters are of utmost importance in preserving general health and welfare. Any changes in these parameters can substantially affect individuals utilising contraceptives such as MPA. Prior studies have provided evidence suggesting that using MPA may lead to alterations in blood coagulation, fibrinolytic systems, and plasma levels (Abe et al., 1995). This underscores the significance of comprehending the impact of this contraceptive on haematological parameters.

*Citrullus lanatus*, commonly called watermelon, has garnered considerable interest in medicinal plants due to its perceived health-promoting properties. Watermelon seeds possess a rich composition of diverse nutrients and minerals, with a notable emphasis on magnesium, a vital element for the proper functioning of the heart and blood pressure regulation (Benmeziane and Derradji, 2023). Research shows that the LD50 of *Citrullus lanatus* seed extract is >5000 mg/kg (Ihejieto et al., 2022). Traditional healthcare practices have utilised natural sources, rendering them deserving of scrutiny in contemporary scientific research.

This study investigated the effects of *Citrullus lanatus* seed extract on haematological parameters in female Wistar rats administered with high doses of MPA. The goal was to explore potential plant-based interventions that could mitigate the negative effects associated with using MPA. By assessing the correlation between MPA and *Citrullus lanatus* seed extract concerning blood parameters, this research contributes significant insights to contraceptive research. The study's significance lies in its potential to shed light on the impact of MPA on haematological parameters and its investigation of natural interventions like watermelon seed extract. Ultimately, this research aims to bridge the gap between conventional plant medicine and contemporary healthcare, thereby presenting novel and all-encompassing strategies for enhancing the safety and efficacy of contraceptive alternatives pertaining to women's reproductive well-being.

## MATERIALS AND METHODS

### Experimental Animals

Twenty-five female Wistar rats weighing 170 – 230 grams were used for the sub-chronic study. The rats were purchased from the animal house of the Department of Medical Physiology, Delta State University, Abraka campus Delta state. The animals were housed in the experimental animal house of the Department of Medical Physiology, Madonna University, Elele campus, Rivers State. The animals were kept under normal room conditions of 25 ± 2$^{o}$c, 50 ± 5% humidity, and 12 hours of light and day cycles. The rats were randomised into a control group and four experimental groups with five rats in each compartment (n=5), according to their weight range and housed in a sanitised wooden cage containing sawdust as bedding. Feeding was provided twice a day during the acclimatisation period and then reduced to once daily as the rats increased their body weight. All animal experiments were in compliance with the National Institute of Health Guide for Care and for Laboratory Animals (pub. No. 85-23, revised 1985).

### Plant Collection and Identification

The seeds were extracted from the pods after it was allowed to rot manually by washing. Only healthy-looking seeds (brown, not floating on water, without mechanical damage or sign of infection) were collected. The collected seeds were oven-dried at 35°C until a constant weight was obtained. The dried seeds were reduced into a fine powder using a laboratory grinding hand mill. The powder was weighed and kept away from light before extraction. It was then soaked in water and refrigerated.

### Preparation of Extract

The extraction process was conducted on 255.19 grams of ground *Citrullus lanatus* seeds using an aqueous water solution. On four occasions, 1000 mL of water was sequentially added to ground *Citrullus lanatus* seeds. The extracts were kept in a bucket, left for 24 hours, and then manually squeezed out of the mixture using clean handkerchiefs to obtain the extracts. The filtrate (chocolate in colour) was collected in beakers and then placed in a water bath at about 45$^{0}$C for seven days. The extracts were kept in the refrigerator to prevent loss of potency. The aqueous extract was then dissolved and stored in a container for administration.

### Experimental Design

Twenty-five adult female Wistar rats weighing 170 – 230 g were randomly distributed into five groups of five rats each. The animals were acclimatised on regular feed (Grower mash- Guinea feed) and water for two weeks. Group I served as control and received only rat chow and water; Group II received rat chow, water and a high dose of MPA only; Group III received rat chow, water, a high dose of MPA and a high dose of extract; group IV received rat chow, water, high dose of MPA and a low dose of extract, and group V received rat chow, water and high dose of extract only (Table 1).

Medroxyprogesterone acetate was administered only once because the drug is administered once every three months. The rat groups administered with the drug were monitored for seven days before treatment with *Citrullus lanatus* seed extract for 28 days based on varying individual body weights.

**Table 1.** Experimental design for the administration of *Citrullus lanatus* seed extract and MPA on Wistar rats.

| Groups | Agent | Dosage (mg/kg/day) |
|---|---|---|
| I | Nil | Nil |
| II | MPA only | 25 |
| III | MPA + high dose of *C. lanatus* seed extract | 25 mg/kg + 200 mg/kg/day |
| IV | MPA + low dose of *C. lanatus* seed extract | 25 mg/kg + 100 mg/kg/day |
| VIII | High dose of *C. lanatus* seed extract only | 200 |

**Source:** Field data (2022)

### Collection of Blood Samples

The rat groups received their respective doses of *Citrullus lanatus* seed extract orally, once daily before feeding (10 am), for 28 days. After this, the animals were sacrificed by cardiac puncture and blood samples were collected in EDTA bottles and centrifuged for further testing.

### Haematological Analysis

The haematology profile, which covers white blood cell (WBC), red blood cell (RBC), haemoglobin level (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and

platelets (PLT) were determined using an automated Haematology analyser (Sysmex Haematology – Coagulation system, Model MO-1000 I, Trans Asia, Japan).

### Statistical Analysis and Data Evaluation

The results were analysed using the statistical software package for social sciences (SPSS) version 16.0 for Windows. Analysis of variance (ANOVA) was used to compare means ($p<0.05$) and post hoc multiple comparisons used LSD. All results are presented as Mean ± SEM Graphs were created in Microsoft Excel 2007.

## RESULTS AND DISCUSSION

### Results

***Effect of Citrullus Lanatus Seeds Extract on some Hematological Parameters After Administration of Medroxyprogesterone Acetate on Female Wistar Rats***

The results of the haematology analysis of the blood samples of rats that received medroxyprogesterone acetate and different doses of the extract are shown in Table 2.

**Table 2.** Results of the haematological analysis of the aqueous extract of *Citrullus Lanatus* seeds after administration of MPA on female Wistar rats.

| GROUPS | WBC ($X10^9$/L) | RBC ($X10^{12}$/L) | Hb (g/dL) | Hct (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) | PLT ($X10^9$/L) |
|---|---|---|---|---|---|---|---|---|
| **I** | 7.45 ± 0.38 | 7.81 ± 0.27 | 14.84 ± 0.45 | 41.65 ± 0.96 | 53.22 ± 0.66 | 20.14 ± 0.92 | 34.11 ± 0.66 | 171.55 ± 3.06 |
| **II** | $4.35 \pm 0.35^{a}$ | $4.90 \pm 0.40^{a}$ | $8.74 \pm 0.54^{a}$ | $24.30 \pm 1.63^{a}$ | $31.08 \pm 3.36^{a}$ | $10.54 \pm 1.07^{a}$ | $23.64 \pm 1.14^{a}$ | $98.56 \pm 4.45^{a}$ |
| **III** | $11.59 \pm 0.35^{a,b}$ | $7.93 \pm 0.35^{b,c}$ | $16.50 \pm 0.37^{a,b}$ | $47.25 \pm 1.02^{a,b}$ | $54.33 \pm 1.14^{b,c}$ | $24.49 \pm 0.55^{a,b}$ | $41.06 \pm 1.17^{a,b}$ | $226.61 \pm 12.16^{a,b}$ |
| **IV** | $8.23 \pm 0.42^{b,c}$ | $6.43 \pm 0.23^{a,b}$ | $11.83 \pm 0.38^{a,b}$ | $31.18 \pm 1.13^{a,b}$ | $40.81 \pm 1.25^{a,b}$ | $16.27 \pm 0.35^{a,b}$ | $27.84 \pm 1.23^{a,b}$ | $124.43 \pm 4.65^{a,b}$ |
| **V** | $11.25 \pm 0.34^{a,b}$ | $9.41 \pm 0.36^{a,b}$ | $14.63 \pm 0.42^{b,c}$ | $43.02 \pm 0.46^{b,c}$ | $51.88 \pm 0.43^{b,c}$ | $22.02 \pm 0.42^{b,c}$ | $38.28 \pm 0.42^{a,b}$ | $182.54 \pm 5.64^{b,c}$ |

Data represented as Mean ± SEM; n=5, ($^{a}$) $p<0.05$ significantly different in comparison with Negative control group, ($^{b}$) $p<0.05$ significantly different in comparison with Positive control group, ($^{c}$) $p>0.05$ not significantly different in comparison with Negative control group, I=Negative control, II=Positive control (MPA), III= MPA + 200mg/kg CL, IV= MPA + 100mg/kg CL, V=200mg/kg CL

### *Effect on White Blood Cells*

The result of the study (Figure 1) revealed a significant decrease ($P<0.05$) in WBC count (4.35 ± 0.35) for rats treated with MPA only (Group II) compared to Group I, which neither received MPA nor *C. lanatus* seed extract (7.45 ± 0.38). Conversely, rats treated with MPA + 200mg/kg of *C. lanatus* seed extract (Group III) exhibited a significant increase ($P<0.05$) in mean WBC count (11.59±0.35) compared to both Group I (7.45±0.38) and Group II (4.35 ± 0.35) that received MPA alone.

Group IV, treated with MPA + 100mg/kg of *C. lanatus* seed extract, demonstrated a significant decrease ($P<0.05$) in mean WBC count (8.23 ± 0.42) compared to Group II receiving MPA only (4.35 ± 0.35). However, there was no significant difference ($P>0.05$) in the mean WBC count compared to Group I, which received neither MPA nor *C. lanatus* seed extract (7.45 ± 0.38). Furthermore, Group V exhibited a significant increase ($P<0.05$) in WBC count (11.25 ± 0.34) compared to both Group I, not given MPA or *C. lanatus* seed extract (7.45 ± 0.38), and Group II, given MPA only (4.35±0.35).

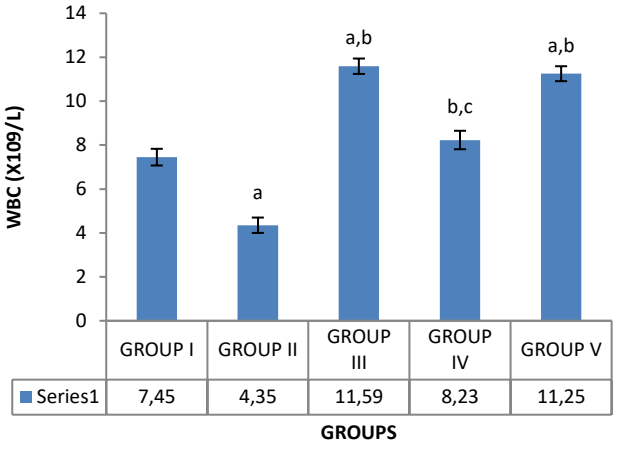


**Figure 1.** A chart showing the effect of *C. lanatus* on WBC count after administration of MPA on female Wistar rats.

### *Effects on Red Blood Cells*

The result of the study (Figure 2) showed that the rats treated with MPA only (Group II) had a significant decrease (P<0.05) in the RBC count (4.90 ± 0.40) in comparison to Group I not given either MPA or *C. lanatus* seed extract (7.81± 0.27).

Additionally, the rats treated with MPA + 200mg/kg of *C. lanatus* seed extract (Group III) had a significant increase (P<0.05) in the mean RBC count (7.93±0.35) as compared to Group II given MPA only (4.90 ± 0.40). However, there was no significant difference (P>0.05) in the mean RBC count as compared to Group I, which was neither given MPA nor *C. lanatus* seed extract (7.81 ± 0.27).

Furthermore, the results obtained from Group IV & V showed a significant difference (P<0.05) in RBC count, (6.43± 0.23) and (9.41 ± 0.36), respectively, as compared to Group I (7.81 ± 0.27) & Group II (4.90 ± 0.40).

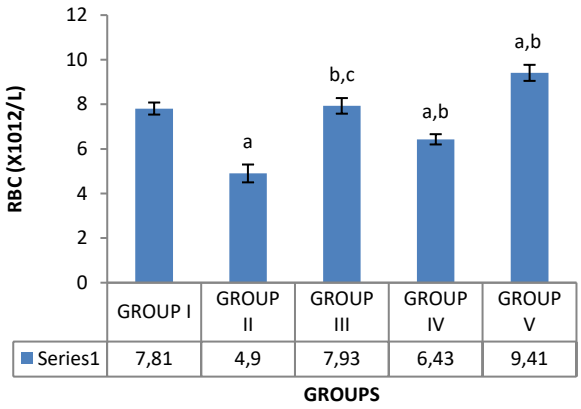


**Figure 2.** A chart showing the effect of *C. lanatus* on RBC count after administration of MPA on female Wistar rats.

### *Effects on Haemoglobin Count*

The result of the study (Figure 3) revealed that the rats treated with MPA only (Group II) experienced a significant decrease (P<0.05) (8.74 ± 0.54) compared to Group I, which was neither given MPA nor C. lanatus seed extract (14.84 ± 0.45).

Both Group III, treated with MPA + 200mg/kg of *C. lanatus* seed extract, and Group IV, treated with MPA + 100mg/kg *C. lanatus* seed extract, showed a significant difference (P<0.05) in the haemoglobin count (16.50 ± 0.37) and (11.83 ± 0.38) respectively, as compared to Group I, which was neither given MPA nor *C. lanatus* seed extract (14.84 ± 0.45), and Group II, given only MPA (8.74 ± 0.54).

Results obtained from Group V, treated with 200mg/kg *C. lanatus* seed extract, demonstrated a significant increase (P<0.05) in haemoglobin count (14.63 ± 0.42) in comparison with Group II, treated with MPA only (8.74 ± 0.54). However, there was no significant difference (P>0.05) compared to Group I (14.84 ± 0.45).

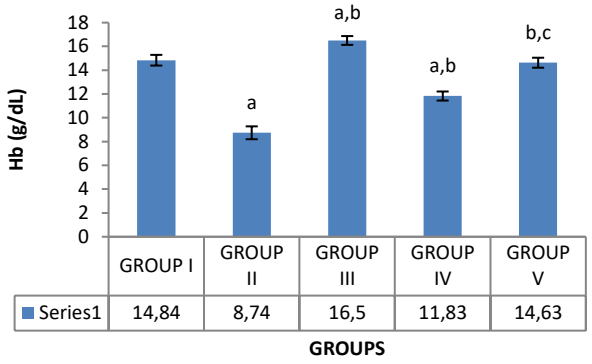


**Figure 3.** A chart showing the effect of *C. lanatus* on haemoglobin count after administration of MPA on female Wistar rats.

### *Effects on Hematocrit Levels*

The result of the study (Figure 4) showed that the rats treated with MPA only (Group II) had a significant decrease (P<0.05) in the Hct value (24.30 ± 1.63) in comparison to Group I that neither MPA nor *C. lanatus* seed extract (41.65 ± 0.96).

Both Group III, treated with MPA + 200mg/kg of *C. lanatus* seed extract, and Group IV, treated with MPA + 100mg/kg *C. lanatus* seed extract, showed a significant difference (P<0.05) in the Hct value (47.25 ± 1.02) and (31.18 ± 1.13) as compared to Group I neither given MPA nor *C. lanatus* seed extract (41.65 ± 0.96) and those in Group II given only MPA (24.30 ± 1.63).

Furthermore, results obtained from Group V treated with 200mg/kg *C. lanatus* seed extract showed a significant increase (P<0.05) in Hct value (43.02± 0.46) in comparison with Group II treated with MPA only (24.30± 1.63). However, there was no significant difference (P>0.05) as compared to Group I (41.65± 0.96).

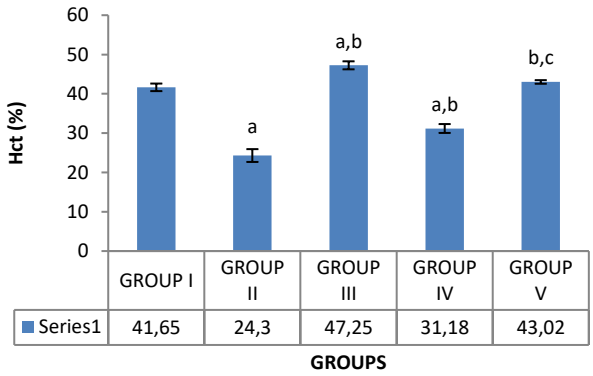


**Figure 4.** A chart showing the effect of *C. lanatus* on HCT after administration of MPA on female Wistar rats.

### *Effects on Mean Corpuscular Volume*

The result of the study (Figure 5) showed that the rats treated with MPA only (Group II) indicated a significant decrease (P<0.05) in the MCV (31.08 ± 3.36) in comparison to Group I that was not given MPA and still not given *C. lanatus* seed extract (53.22 ± 0.66).

Furthermore, the rats treated with MPA + 200mg/kg of *C. lanatus* seed extract (Group III) and those given only 200mg/kg *C. lanatus* seed extract (Group V) had a significant difference (P<0.05) in the MCV (54.33 ± 1.14) and (51.88 ± 0.43) as compared to Group II given MPA only (31.08±3.36). However, there was no significant difference (P>0.05) in the MCV of both groups as compared to Group I, which was neither given MPA nor *C. lanatus* seed extract (53.22± 0.66).

Moreover, results obtained from Group IV treated with MPA + 100mg/kg of *C. lanatus* seed extract had a significant decrease (P<0.05) in MCV, (40.81± 1.25) as compared to Group I neither given MPA nor *C. lanatus* seed extract (53.22± 0.66) as well as a significant increase those in Group II given MPA only (31.08 ± 3.36).

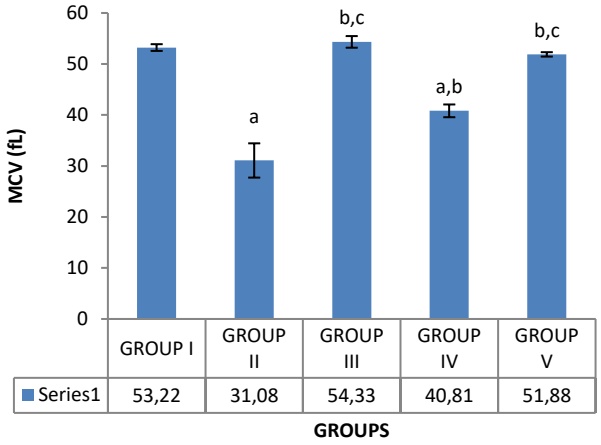


**Figure 5.** A chart showing the effect of *C. lanatus* on MCV after administration of MPA on female Wistar rats.

### *Effects on Mean Corpuscular Haemoglobin*

The result of the study (Figure 6) showed that the rats treated with MPA only (Group II) had a significant decrease (P<0.05) in the MCH value (10.54 ± 1.07) compared to Group I, which neither received MPA nor *C. lanatus* seed extract (20.14 ± 0.92).

Moreover, the rats treated with MPA + 200mg/kg of *C. lanatus* seed extract (Group III) and Group IV given MPA + 100mg/kg of extract had a significant difference (P<0.05) in the MCH value (24.49 ± 0.55) and (16.27 ± 0.35), respectively, as compared to Group I (20.14 ± 0.92) and Group II (10.54 ± 1.07).

Furthermore, results obtained from Group V treated with 200mg/kg of extract showed a significant increase (P<0.05) in the MCH value (22.02 ± 0.42) compared to Group II (10.54 ± 1.07). However, there was no significant difference (P>0.05) when compared to Group I (20.14 ± 0.92).

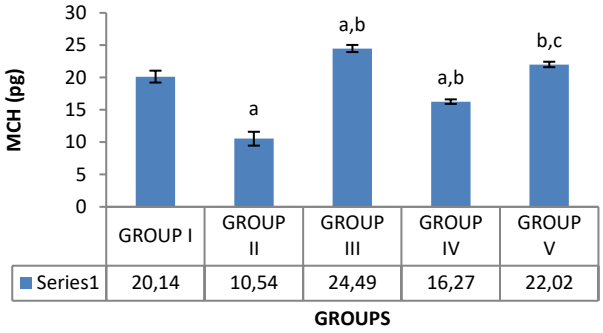


**Figure 6.** A chart showing the effect of *C. lanatus* on MCH after administration of MPA on female Wistar rats.

### *Effects on Mean Corpuscular Haemoglobin Concentration*

The result of the study (Figure 7) showed that the rats treated with MPA only (Group II) had a significant decrease (P<0.05) in the MCHC value (23.64 ± 1.14) as compared to Group I that neither received MPA nor *C. lanatus* seed extract (34.11 ± 0.66).

Furthermore, the rats treated with MPA + 200mg/kg of extract (Group III), Group IV given MPA + 100mg/kg of extract and Group V given 200mg/kg of extract only, had a significant difference (P<0.05) in the MCHC value (41.06±1.17), (27.84 ± 1.23) and (38.28 ± 0.42) respectively, as compared to Group I that was not given the drug and extract (34.11 ± 0.66) and Group II that was given only the drug (23.64 ± 1.14).

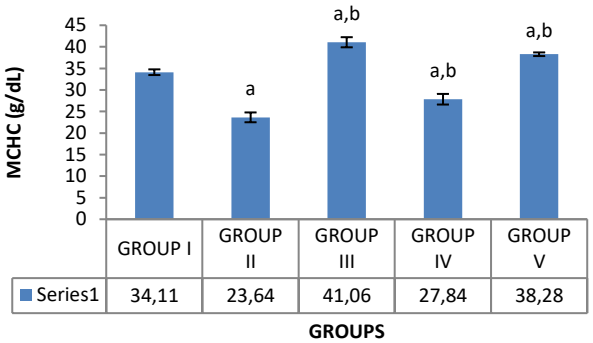


**Figure 7.** A chart showing the effect of *C. lanatus* on MCHC after administration of MPA on female Wistar rats.

### *Effects on Platelet Count*

The result of the study (Figure 8) showed that the rats treated with MPA only (Group II) had a significant decrease (P<0.05) in the platelet count (98.56 ± 4.45) compared to Group I, which was not given MPA or C. lanatus extract (171.55 ± 3.06).

Furthermore, the rats treated with MPA + 200mg/kg of C. lanatus (Group III) and Group IV given MPA +

100mg/kg C. lanatus had a significant difference (P<0.05) in the platelet count (226.61 ± 12.16) and (124.43 ± 4.65), respectively, compared to Group I, which was not given MPA or C. lanatus (171.55 ± 3.06) and those in Group II administered MPA only (98.56 ± 4.45).

Additionally, results obtained from Group V treated with 200mg/kg C. lanatus showed a significant increase (P<0.05) in platelet count (182.54± 5.64) compared to Group II given MPA alone (98.56± 4.45). However, there was no significant difference (P>0.05) when compared to Group I (98.56± 4.45).

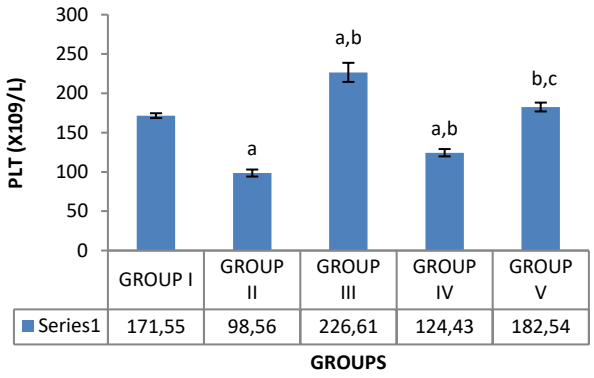


**Figure 8.** A chart showing the effect of *C. lanatus* on PLT after administration of MPA on female Wistar rats.

## Discussion

The administration of MPA resulted in a significant reduction in WBC count. However, the *C. lanatus* seeds extract exhibited a dose-dependent enhancement in WBC production. The administration of MPA suppressed the formation of white blood cells, thereby increasing the susceptibility of rats to opportunistic infections. The extract effectively counteracted the inhibitory effect of MPA on white blood cells. The extract induced a modest elevation in the white blood cell count in non-infected rats, suggesting its immunostimulatory effect. Based on the results, it can be inferred that the extract has the potential to enhance immune function.

No synergism was observed between MPA and the *C. lanatus* seed extract on RBC count. The extract suppressed the inhibitory effects of MPA on RBC production. Thus, the administration of *C. lanatus* seed extract increased RBC production. The results in groups III, IV, and V show that the extract's ability to suppress the effect of MPA on erythropoiesis and further increase RBC production is dose-dependent. Group V signifies that the extract alone significantly improves RBC count, showing that the extract can improve RBC production independently. This also implies that the lower values obtained on simultaneous administration of MPA and the extract are partly due to the unit used to overcome the MPA inhibition.

Group II animals experienced a significant decrease in Hb count, PCV, MCV, and MCH levels, suggesting they became anaemic. When the extract was administered in low doses after MPA administration, the level of decline in the Hb count and hematocrit level was reduced, and when administered in high doses, it suppressed the effects of MPA, thus raising the haemoglobin and hematocrit levels. Interestingly, concomitant administration of the extract with MPA significantly increased Hb count and HCT level, signifying a synergetic action between the extract and the drug.

The findings indicate minimal impact on MCHC by the extract. However, it effectively mitigated MPA-induced adverse effects on MCHC levels, demonstrating inhibitory effects on microcytic anaemia associated with MPA. Administering a high dosage of extract after MPA significantly suppressed the adverse effects and increased MCHC levels.

The results imply that after MPA administration, there was a significant decrease in platelet count, which could cause blood-clotting problems. There were remarkable Improvements in the platelet count when the extract was administered alone. The synergetic action of MPA and the extract resulted in a significant increase in PLT count.

## CONCLUSION

This study investigated the impact of an aqueous extract of *Citrullus lanatus* seeds on haematological parameters following the administration of medroxyprogesterone acetate (MPA) in female Wistar rats. The results revealed a significant decrease in platelet count, white blood cell count, and other blood cell parameters, indicating MPA's influence on bone marrow, which is responsible for blood cell production. Although the daily administration of the extract alone did not elevate blood cell parameters beyond the normal range, it increased them compared to their initial state before drug administration. Notably, when co-administered with MPA, the extract prevented the decrease in blood parameters and improved their values from the average levels. These effects were dose-dependent, suggesting the potential of the extract to counter the adverse effects of MPA on blood parameters.

These findings suggest that the C. lanatus seed extract possesses immunostimulatory properties, counters the adverse effects of MPA on blood cell counts, and demonstrates the potential to enhance immune function and ameliorate anaemia-related parameters. The extract's dose-dependent effects further highlight its therapeutic potential in the context of MPA treatment.

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***Competing Interests*:** The author declares that there is no conflict of interest concerning this manuscript.

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