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ARTICLE

Effect of methanol extract of *Citrullus lanatus* seed on hematological profile and tissue histology of normal Wistar rats

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Abstract

Background: *Citrullus lanatus* seeds are known to be highly nutritious, and rich sources of phenolic compounds. They are usually milled into flour and used for making sauces, snacks, and cooking oil.

Aim: The present study investigated the effect of methanol extract of *C. lanatus* seed on hematological profile and tissue histology of normal Wistar rats.

Methods: Adult male Wistar rats (n = 35) weighing 130 to 170 g (mean weight = 150 ± 20 g) were randomly assigned to 7 groups (5 rats/group): normal control, Tween 80 control, and five treatment groups. Rats in the treatment groups received graded doses of the extract (10 - 5000 mg/kg body weight, bwt) orally for 35 days. Hematological profile and rat tissue histology were assessed.

Results: Treatment of normal rats with graded doses of methanol extract of *C. lanatus* seed did not significantly affect the levels of hematological parameters, as well as absolute and relative weights of liver and kidneys ($p > 0.05$). Results of histopathological examinations showed that methanol extract of *C. lanatus* seed did not significantly alter the histology of rat liver, kidney and heart ($p > 0.05$). Graded doses of the extract induced progressive vasodilatation and mild congestion in the selected organs, thereby favoring increased blood flow in the tissues.

Conclusion: These results indicate that *Citrullus lanatus* seeds have beneficial effect on hematological indices and may not be toxic to rat tissues/organs.

Keywords: Blood, Citrullus lanatus, Hematology, Liver, Tissue histology.

1 | INTRODUCTION

Histology, also known as microscopic anatomy or microanatomy, is the branch of Biology which studies the microscopic anatomy of biological tissues. It is the microscopic version of gross anatomy which looks at larger structures visible without a microscope. Although microscopic anatomy may be divided into organology, the study of organs, histology, the study of tissues, and cytology, the study of cells, modern usage places these topics under the field of histology. In medicine, histopathology is the branch of histology that includes the microscopic identification and study of diseased tissue[1]. There are four basic types of animal tissues: muscle, nervous, connective, and epithelial tissue . All animal tissues are considered to be subtypes of these four principal tissue types. For example, blood is classified as connective tissue since blood cells are suspended in an extracellular matrix, the plasma[2,3].Hematology refers to the study of the numbers and morphology of cellular elements of the blood – red cells (erythrocytes), white cells (leucocytes), and platelets (thrombocytes), and their use in the diagnosis and monitoring of diseases. Hematological studies are useful in the diagnosis of many diseases as well as investigation of the extent of damage to blood (Togun *et al.,* 2007). Hematological studies are of environmental and physiological importance helping to unravel the relationship of blood characteristics to the environment (Ovuru and Ekweozor, 2004) and so could be useful in the selection of animals that are genetically resistant to certain diseases and environmental conditions (Isaac, 2013; Mmereole, 2008). Hematological indices are parameters that are related to the blood and blood-forming organs (Bamishaiye *et al.,* 2009; Waugh *et al.,* 2001). Blood serves as a pathological reflector of the status of exposed animals to toxicants and other conditions (Olafedehan *et al.,* 2010). Animals with good blood composition are likely to show good performance (Isaac *et al*., 2013). Blood examination provides the opportunity to investigate the presence of several metabolites and other constituents in the body of animals and it plays a vital role in the physiological, nutrition and pathological status of an organism (Aderemi, 2004; Doyle, 2006). Blood constituents change in response to the physiological conditions of animals (Togun *et al.,* 2007). These changes are of immense importance in the assessment of response of animals to various physiological situations (Khan and Zafar, 2005). Changes in hematological parameters are often used to ascertain various status of the body and to determine stresses due to environmental, nutritional and/or pathological factors (Afolabi *et al.,* 2010).

Hematological parameters such as haematocrit, hemoglobin, erythrocytes and white blood cells (WBCs) are used as indicators of toxicity. They have broad applications in environmental and occupational monitoring. The normal ranges of these parameters are altered by the ingestion of some toxic substances. It has been reported that alterations in hematological parameters by medicinal compounds could either be positive or negative (Afolabi *et al.,* 2010). This study investigated the effect of methanol extract of *C. lanatus* seed on hematological profile and tissue histology of normal Wistar rats.

2 | MATERIALS AND METHODS

2.1 | Study Area

The present study was carried out at the Department of Biochemistry, Faculty of Life Sciences, University of Benin, Benin City, Nigeria from July 2019 to December 2019.

2.2 | Materials

All reagents/chemicals used in this study were of analytical grade and were obtained from British Drug House (BDH, England), Merck (Germany) and

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Sigma-Aldrich Chemical Company (USA). Hematology analyzer (Horiba ABX 80) was a product of ABX pentra Montpellier Ltd. (France).

2.3 | Plant Sample Collection

Citrullus lanatus seeds were obtained from a major market in Benin City, Edo State, Nigeria, and authenticated at the herbarium of the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria.

2.4 | Plant Preparation and Extraction

Citrullus lanatus seeds were washed and shade-dried at room temperature for a period of two weeks and thereafter pulverized using a mechanical blender. Methanol extract of the seeds was obtained using cold maceration method. Exactly 2 kg of powdered seeds was extracted with 5 L of absolute methanol for 96 h with intermittent stirring. The extract was concentrated using rotary evaporator and freeze-dried via lyophilization (Abu *et al.,* 2020).

2.5 | Experimental Rats

Adult male Wistar rats (n = 35) weighing 130 – 170 g (mean weight = 150 ± 20 g) were obtained from the Department of Anatomy, University of Benin, Benin City, Nigeria. The rats were housed in metal cages under standard laboratory conditions: average temperature of 25 ^{o}C, 55 – 65 % humidity and 12-h light/12-h dark cycles. They were allowed access to rat feed (pelletized growers mash) and clean drinking water. Prior to commencement of the study, the rats were acclimatized to the laboratory environment for one week. The study protocol was approved by the Faculty of Life Sciences, University of Benin, Ethical Committee on Animal Use.

2.6 | Experimental Design

The rats were randomly assigned to 7 groups (5 rats/group): normal control, Tween 80

control, and five treatment groups. Tween 80 was used to solubilize the extract before administration. Rats in the treatment groups received graded doses of the extract (10 - 5000 mg/kg bwt) orally for 35 days.

2.7 | Collection of Blood and Tissue Samples

At the end of the treatment period, the rats were anaesthetized with chloroform vapor. Blood samples were drawn from each rat heart via cardiac puncture into EDTA containers. The liver, kidney and heart were excised, weighed and subjected to histopathological examination.

2.8 | Hematology

Horiba ABX 80 hematology analyzer was used for the determination of hematological parameters following the manufacturer's instructions. These included hemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RCDW). White blood cell (WBC) count, neutrophils, monocytes, lymphocytes, eosinophils, basophils and platelet were also analyzed.

2.9 | Histological Examination of the Tissues

Portions of the liver, kidney and heart were serially sectioned and fixed in 10 % formalin for 48 h. The specimen was then dehydrated with graded concentrations of alcohol and cleared in three changes of xylene before embedment in paraffin. Serial sections (4 μm thick) were made and stained with hematoxylin and eosin (H & E) according to standard method. Histological assessment was performed under light microscopy. In every H & E section a minimum of 25 circular tubules were measured in two axes drawn perpendicular to each other using an image analyzer (Image Proplus, Version 3.0).

2.10 | Statistical Analysis

Count data are presented as mean ± SEM. Statistical analysis was performed using GraphPad Prism Demo (6.07). Values of $p < 0.05$ were considered statistically significant.

3 | RESULTS

Effect of Methanol Extract of *C. lanatus* Seed on Body and Organ Weights of Rats

The absolute and relative weights of liver and kidneys of rats in each group were not significantly affected by extract treatment ($p > 0.05$). These results are shown in Tables 1 and 2.

Table 1: *Weights of Liver and Kidney of Rats Administered Methanol Extract of C. lanatus Seed*

Group	Liver Weight (g)	Kidney Weight (g)	Final Body Weight (g)
Normal control	5.20 ± 0.20	0.53 ± 0.03	167.20 ± 6.37
Tween 80 control	8.40 ± 0.25[a]	0.64 ± 0.03	228.60 ± 5.51[a]
10 mg extract/kg bwt	7.00 ± 0.32[a]	0.65 ± 0.04	221.40 ± 8.76[a]
100 mg extract/kg bwt	7.60 ± 0.32[a]	0.68 ± 0.07	210.00 ± 10.04[a]
1000 mg extract/kg bwt	7.60 ± 0.51[a]	0.61 ± 0.06	231.40 ± 9.34[a]
2000 mg extract/kg bwt	8.20 ± 0.58[a]	0.63 ± 0.02	235.20 ± 10.73[a]
5000 mg extract/kg bwt	8.20 ± 0.58[a]	0.65 ± 0.47	225.40 ± 11.41[a]

Data are expressed as mean ± SEM (n = 5). Values with superscript ([a]) differ significantly from the normal control value ($p < 0.05$).

Table 2: *Relative Organ Weight of Rats Administered Methanol Extract of C. lanatus Seed*

Group	Liver Weight/ Body Weight	Kidney Weight/Body Weight x 10^{-3}
Normal control	0.03 ± 0.00	3.20 ± 0.23
Tween 80 control	0.04 ± 0.00	2.80 ± 0.19
10 mg extract/kg bwt	0.04 ± 0.00	3.50 ± 0.73
100 mg extract/kg bwt	0.03 ± 0.00	3.30 ± 0.45
1000 mg extract/kg bwt	0.03 ± 0.00	2.60 ± 0.12
2000 mg extract/kg bwt	0.04 ± 0.00[a]	2.70 ± 0.16
5000 mg extract/kg bwt	0.04 ± 0.00	2.90 ± 0.34

Data are expressed as mean ± SEM (n = 5). Values with superscript ([a]) differ significantly from the normal control value ($p < 0.05$).

Effect of *Citrullus lanatus* Seed Extract on Different Hematological Parameters

Treatment of normal rats with graded doses of methanol extract of *C. lanatus* seed did not significantly alter the levels of hematological parameters ($p > 0.05$; Tables 3 and 4).

Table 3: *Effect of C. lanatus Seed Extract on Some Hematological Parameters*

Group	Parameter					
	RBC (x 10^6/µL)	Hgb (g/dL)	HCT (%)	MCV (fL)	PLT (x 10^5/µL)	PCT (%)
Normal control	8.69 ± 0.22	15.43 ± 0.57	46.30 ± 1.71	53.20 ± 0.62	7.59 ± 0.26	0.54 ± 0.05
Tween 80 control	8.12 ± 0.28	14.55 ± 0.38	43.63 ± 1.15	53.77 ± 0.52	8.07 ± 0.76	0.57 ± 0.05
10 mg extract/kg bwt	8.17 ± 0.11	14.22 ± 0.16	42.67 ± 0.48	52.17 ± 0.59	9.20 ± 0.79	0.68 ± 0.07
100 mg extract/kg bwt	8.77 ± 0.19	14.88 ± 0.38	44.63 ± 1.12	50.90 ± 1.81	6.58 ± 0.56	0.44 ± 0.06
1000 mg extract/kg bwt	8.76 ± 0.31	15.91 ± 0.30	47.73 ± 0.88	54.57 ± 1.85	11.41 ± 0.26	0.88 ± 0.03
2000 mg extract/kg bwt	8.11 ± 0.13	14.79 ± 0.65	44.37 ± 1.96	54.60 ± 1.61	8.26 ± 1.22	0.62 ± 0.11
5000 mg extract/kg bwt	7.91 ± 0.28	15.79 ± 0.85	47.37 ± 2.54	59.87 ± 2.92	7.60 ± 0.88	0.59 ± 0.09

Data are hematological parameters and are expressed as mean ± SEM (n = 5). RBC = red blood cell; Hgb = hemoglobin; HCT = hematocrit; MCV = mean corpuscular volume; PLT = platelet; PCT = plateletcrit.

Table 4: *Effect of C. lanatus Seed Extract on Some Blood Components*

Group	Parameter					
	WBC (x 10^3/µL)	LYMPH (x 10^3/µL)	MO (x 10^2/µL)	GR (x 10^2/µL)	RDW (%)	MPV (fL)
Normal control	6.17 ± 0.98	5.60 ± 0.94	2.00 ± 0.60	3.70 ± 0.90	17.27 ± 0.18	7.03 ± 0.38
Tween 80 control	5.73 ± 0.72	5.23 ± 0.68	2.00 ± 0.00	3.00 ± 0.60	17.57 ± 0.12	7.10 ± 0.21
10 mg extract/kg bwt	9.10 ± 1.25	8.13 ± 1.04	3.70 ± 0.90	5.70 ± 1.20	16.83 ± 0.28	7.40 ± 0.32
100 mg extract/kg bwt	9.27 ± 0.93	8.30 ± 0.66	4.00 ± 0.10	5.30 ± 1.30	17.10 ± 0.46	6.70 ± 0.30
1000 mg extract/kg bwt	6.63 ± 0.73	5.97 ± 0.66	3.00 ± 0.60	3.70 ± 0.70	17.40 ± 0.60	7.73 ± 0.14
2000 mg extract/kg bwt	7.97 ± 2.52	6.00 ± 1.08	3.70 ± 0.50	3.10 ± 0.51	17.20 ± 0.52	7.40 ± 0.45
5000 mg extract/kg bwt	8.57 ± 1.11	7.60 ± 0.90	4.00 ± 0.60	5.70 ± 1.20	18.70 ± 0.64	7.77 ± 0.27

Data are hematological parameters and are expressed as mean ± SEM (n = 5). WBC = white blood cell; LYMPH = lymphocytes; MO = monocles; GR = granulates; RDW = red blood cell distribution width; MPV = mean platelet volume.

Effect of *C. lanatus* Seed Extract on Rat Tissue Histology

Results of histopathological examinations showed that methanol extract of *C. lanatus* seed did not significantly alter the histology of rat liver, kidney and heart ($p > 0.05$). Graded doses of the extract induced progressive vasodilatation and mild congestion in the selected organs, thereby favoring increased blood flow in the tissues. These results are shown in Figures 1 – 7.

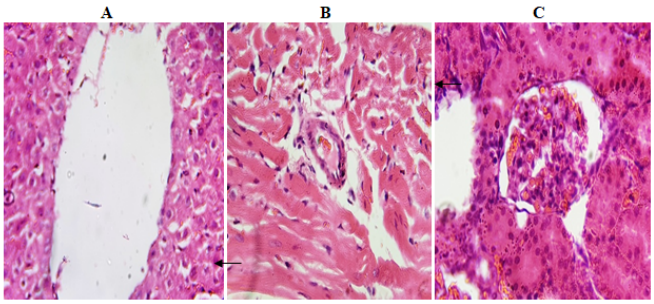

FIGURE 1:

Effect of C. lanatus Seed Extract on Normal Control Rat Tissue Histology. (A): Photomicrograph of control rat liver showing distinct centimole with hepatocytes and well penetrated sinusoidal space with mild mono nuclear cells; **(B):** Photomicrograph of control rat heart composed of bundles of myocardial fibres, interstitial space and coronary artery; and **(C):** Photomicrograph of control rat kidney showing visible renal corpuscle, interstitial space, and tubules.

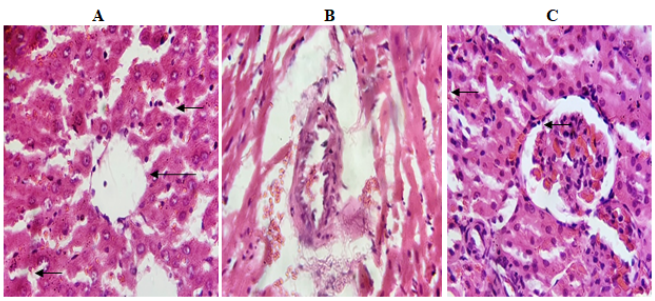

FIGURE 2:

Effect of *C. lanatus* Seed Extract on Tween 80 Control Rat Tissue Histology. **(A):** Photomicrograph of Tween 80 control rat liver showing visible centriole with hepatocytes nuclei appearing vacuolated. The tissue is characterized by mild fatty changes and mononuclear cells; **(B):** Photomicrograph of Tween 80 control rat heart composed of bundles of myocardial fibres, interstitial space and large coronary artery; and **(C):** Photomicrograph of Tween 80 control rat kidney showing visible renal corpuscle, interstitial space, and tubules with mild mononuclear infiltrate.

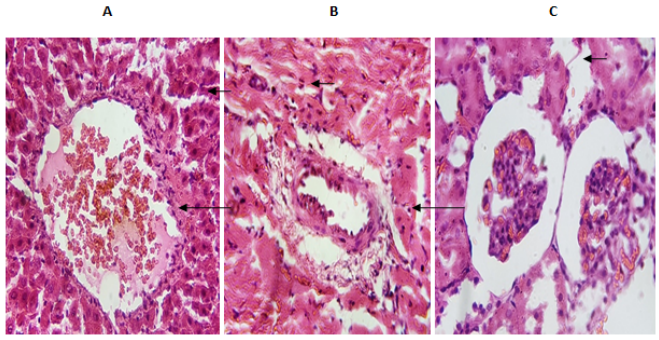

FIGURE 3:

Effect of *C. lanatus* Seed Extract on Tissue Histology of Rats Administered 10 mg extract/kg bwt . (A): Photomicrograph of rat liver showing congested centriole with thickened wall surrounded by mononuclear cells. The hepatocytes have pyknotic nuclei; **(B):** Photomicrograph of rat heart with normal histology; and **(C):** Photomicrograph of rat kidney showing atrophied renal corpuscle and interstitial space not appearing distinct

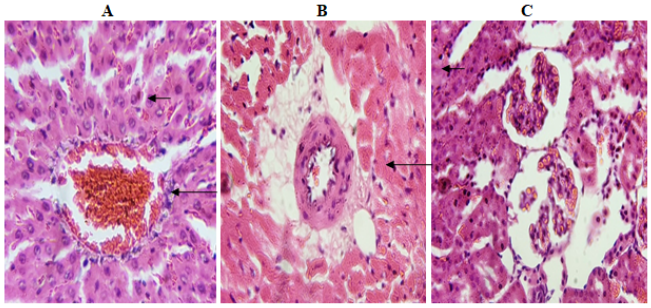

FIGURE 4:

Effect of *C. lanatus* Seed Extract on Tissue Histology of Rats Administered 100 mg extract/kg bwt . (A): Photomicrograph of rat liver showing congested centriole with fairly pyknotic hepatocytes nuclei and well fenestrated sinusoidal space with mild mononuclear cells; **(B):** Photomicrograph of rat heart with normal histology; and **(C):** Photomicrograph of rat kidney showing atrophied renal corpuscle with distorted glomerulus and interstitial space and tubules appearing not so distinct.

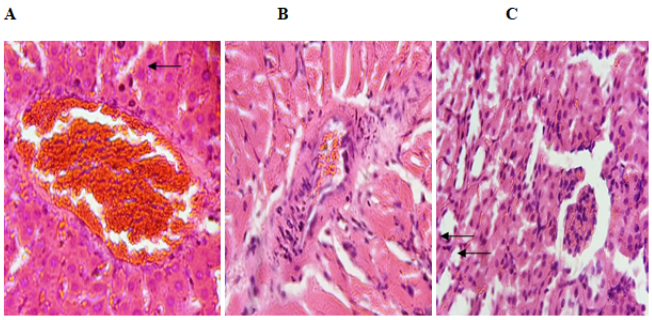

FIGURE 5:

Effect of C. lanatus Seed Extract on Tissue Histology of Rats Administered 1000 mg extract/kg bwt. (A): Photomicrograph of rat liver showing congested centriole with thickened wall surrounded by mild mononuclear cells with hepatocytes and well fenestrated sinusoidal space; (B): Photomicrograph of rat heart composed of bundles of myocardial fibres, interstitial space and congested coronary artery; and (C): Photomicrograph of rat kidney showing atrophied renal corpuscle and interstitial space and tubules with diffused mononuclear infiltrate.

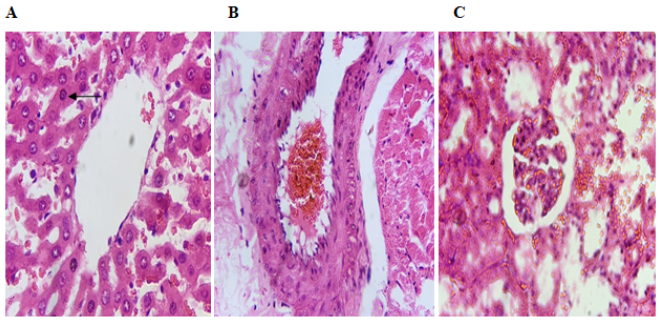

FIGURE 6:

Effect of *C. lanatus* Seed Extract on Tissue Histology of Rats Administered 2000 mg extract/kg bwt . (A): Photomicrograph of rat liver showing visible centriole with hepatocytes nuclei appearing vacuolated. There is prominent fatty changes and visible mononuclear cells; **(B):** Photomicrograph of rat heart composed of bundles of myocardial fibres, interstitial space and large dilated coronary artery; and **(C):** Photomicrograph of rat kidney showing visible renal corpuscle and interstitial space and tubular necrosis.

Effect of *C. lanatus* Seed Extract on Tissue Histology of Rats Administered 5000 mg extract/kg bwt

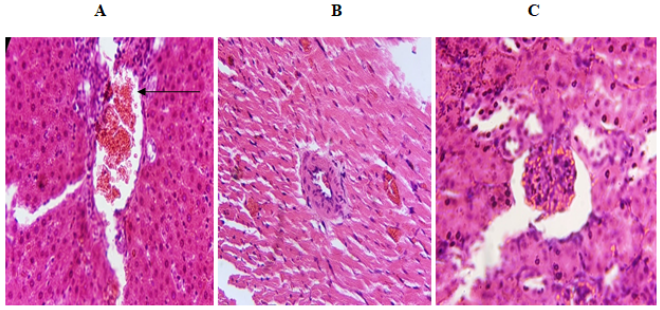

FIGURE 7:

. (A): Photomicrograph of rat liver showing centriole with thickened wall and surrounded by foci clusters of mononuclear cells with hepatocytes having pyknotic nuclei; **(B):** Photomicrograph of rat heart composed of bundles of closely packed myocardial fibres, interstitial space and coronary artery; and **(C):** Photomicrograph of rat kidney showing mildly atrophied renal corpuscle and interstitial space and tubules with diffused mononuclear infiltrate and appearing not so prominent.

4 | DISCUSSION

As a vital special circulatory tissue blood is composed of cells suspended in a fluid intercellular substance (plasma) with the major function of maintaining homeostasis (Isaac *et al.,* 2013). Hematological parameters such as red blood cells (RBCs), WBCs, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) are valuable in monitoring feed toxicity (Oyawoye and Ogunkunle, 2004). Red blood cells (erythrocytes) serve as carrier of hemoglobin. Hemoglobin reacts with oxygen carried in the blood to form oxyhemoglobin during respiration (Chineke *et al*., 2006; Johnston and Morris, 1996). A reduced red blood cell count implies reduction in the level of oxygen that would be carried to the tissues, as well as the level of carbon dioxide returned to the lungs (Soetan *et al*., 2013; Ugwuene, 2011). The major functions of WBC and its differentials are to fight infections, defend the body against invasion by foreign organisms, and to produce or at least transport and distribute antibodies in immune response. Thus, animals with low WBCs are exposed

to high risk of disease infection, while those with high counts are capable of generating antibodies in the process of phagocytosis and have high degree of resistance to diseases and enhanced adaptability to local environmental and disease prevalent conditions (Iwuji and Herbert, 2012; Kabir *et al*., 2011; Okunlola *et al.,* 2012). Blood platelets are implicated in blood clotting. Low platelet concentration suggests that the process of clot-formation will be prolonged resulting in excessive loss of blood in the case of injury. Packed Cell Volume (PCV) which is also known as hematocrit (HCT) or erythrocyte volume fraction (EVF), is the percentage of RBCs in blood (Purves *et al*., 2003). Packed Cell Volume is involved in the transport of oxygen and absorbed nutrients (Isaac *et al.,* 2013). Increased PCV means better transportation and thus results in an increased primary and secondary polycythemia. Hemoglobin is the iron-containing oxygen-transport metalloprotein in RBCs of all vertebrates with the exception of the fish family, channichthyldae, as well as tissues of invertebrates (Maton *et al*., 1993; Sidell and O'Brien, 2006). Hemoglobin has the physiological function of transporting oxygen to tissues of animals for oxidation of ingested food to release energy for other body functions, as well as transportation of carbon dioxide out of the body of animals (Ugwuene, 2011). Packed Cell Volume, hemoglobin and MCH are major indices for evaluating circulatory erythrocytes, and are significant in the diagnosis of anaemia and also serve as useful indices of bone marrow capacity to produce RBCs in mammals (Awodi *et al.,* 2005; Peters *et al.,* 2011). High PCV reading indicates either an increase in number of RBCs or reduction in circulating plasma volume (Chineke *et al.,* 2006). Mean corpuscular hemoglobin (MCH) and MCHC indicate blood level conditions. A low level is an indication of anaemia (Aster, 2004). Histopathological studies provided supportive evidence for hematological analysis. Administration of graded doses of methanol extract of *C. lanatus* seed induced progressive vasodilatation and mild vascular congestion in an otherwise normal hepatic, renal, and myocardial architecture. It did not significantly alter the levels of hematological parameters measured.

5 | CONCLUSION

The results obtained in this study indicate that *Citrullus lanatus* seeds have beneficial effect on hematological indices and may not be toxic to rat tissues/organs. It is a potential candidate for formulation into drug.

SIGNIFICANCE STATEMENT

This study has successfully provided an insight into the therapeutic properties of methanol extract of *Citrullus lanatus* seed. The data presented showed that the crude drug has no deleterious effect on Wis tar rats.

Conflict of Interest

No conflict of interest is associated with this work.

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