

Antidiarrheal and Hematological Effects of Aqueous and Ethanol Leaf Extracts of *Psidium guajava* L. in Castor Oil-Induced Diarrhea in Male Wistar Rats

Nanmar Chakfa, Isaac John Umaru, Yakubu Ojechenemi Eji

Federal University Wukari, Taraba State, Nigeria

umaruisaac@gmail.com

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Abstract

Although *Psidium guajava* (guava) leaves are traditionally used to manage diarrhoea, comparative evidence on aqueous and ethanol extracts remains limited. This study evaluated their antidiarrhoeal potential and haematological effects in male Wistar rats with castor oil-induced diarrhoea. Thirty-five rats weighing 150–200 g were randomly assigned to seven groups (n = 5): normal control, diarrhoeal control, loperamide control (2 mg/kg), and four treatment groups receiving aqueous or ethanol extracts at 100 or 200 mg/kg. Diarrhoea was induced by oral administration of castor oil (1 mL/kg). After 14 days of treatment, blood samples underwent haematological analysis, and small-intestinal tissues were examined histopathologically. Castor oil administration significantly increased white blood cell counts from 4.96 ± 0.66 to $7.03 \pm 2.65 \times 10^9/L$ and reduced platelet counts from 696.00 ± 344.34 to $522.66 \pm 148.04 \times 10^9/L$ ($p < .05$), alongside reductions in red blood cell counts and haematocrit. Both extracts significantly reversed these changes in a dose-dependent manner ($p < .05$). At 200 mg/kg, the ethanol extract produced the greatest increases in red blood cell count and haemoglobin, reaching $8.57 \pm 0.52 \times 10^{12}/L$ and 12.50 ± 0.52 g/dL, respectively, whereas the aqueous extract produced the highest platelet count ($1014.66 \pm 187.83 \times 10^9/L$). Intestinal histopathology showed near-normal restoration of villi, crypts of Lieberkühn, and goblet cells in the high-dose ethanol group. These findings provide preclinical evidence of haematological improvement and intestinal recovery, supporting further investigation of the antidiarrhoeal and

haematoprotective potential of *P. guajava* leaf extracts, particularly the ethanol extract at 200 mg/kg.

Keywords: *Psidium guajava*; Castor Oil-Induced Diarrhoea; Haematological Parameters; Intestinal Histopathology; Wistar Rats

INTRODUCTION

Diarrheal disease is defined as the passage of three or more loose or watery stools within a 24-hour period, or bowel movements more frequent than an individual's usual pattern (World Health Organization, 2023). It remains one of the leading causes of morbidity and mortality worldwide, accounting for an estimated 2.2 million deaths annually and disproportionately affecting children under five years of age in low- and middle-income countries (Troeger *et al.*, 2017; United Nations Children's Fund, 2022). Clinically, diarrhea is characterized by increased stool frequency, volume and fluidity, often accompanied by abdominal discomfort and excessive intestinal fluid secretion with impaired water and electrolyte absorption, which can result in significant dehydration if not promptly managed (Camilleri *et al.*, 2017; Spiller, 2022).

Because conventional antimotility agents can present undesirable side effects, there is growing interest in plant-based alternatives with established ethnomedicinal use (Naseer *et al.*, 2018; Dange *et al.*, 2020). The World Health Organization has supported the appropriate integration of evidence-based traditional herbal medicine into diarrheal disease control strategies, particularly where access to conventional healthcare is limited (WHO, 2017). *Psidium guajava* (guava) leaves are among the most widely used traditional remedies for gastrointestinal disturbances, and their antidiarrheal activity has been attributed principally to flavonoids such as quercetin and quercetin-3-arabinoside (guaijaverin), which exert a spasmolytic effect on intestinal smooth muscle via modulation of calcium-dependent contractile mechanisms, together with tannins, saponins and alkaloids that reduce intestinal fluid secretion and motility (Cziple *et al.*, 2022; Al Saiqali *et al.*, 2025; Chan, 2008). Experimental studies have shown that both aqueous and ethanolic guava leaf extracts can inhibit intestinal motility and fluid secretion (Díaz-de-Cerio *et al.*, 2017; Garrido *et al.*, 2024), including efficacy against diarrhea associated with enteropathogenic *Escherichia coli* toxins, through inhibition of intestinal fluid secretion, suppression of nitric oxide production, and downregulation of pro-inflammatory cytokine expression (Hirudkar *et al.*, 2020).

The castor oil-induced diarrhea model is a well-established experimental method for evaluating antidiarrheal activity, in which ricinoleic acid, the active metabolite of castor oil, provokes intestinal mucosal injury, increased motility, and fluid hypersecretion (Mascolo *et al.*, 1994). This intestinal insult is frequently accompanied by systemic haematological disturbances, including leukocytosis reflecting an inflammatory response and thrombocytopenia reflecting platelet consumption or sequestration (Nnadiukwu *et al.*, 2024; Okoye *et al.*, 2025; Lu *et al.*, 2005). Despite the traditional use of guava leaves for diarrhea, comparative data on how the extraction solvent (aqueous versus ethanol) influences antidiarrheal efficacy and the associated haematological and intestinal histopathological outcomes remain limited. This study therefore evaluated the antidiarrheal and haematological effects of aqueous and ethanol leaf extracts of *P. guajava* in castor oil-induced diarrhea in male Wistar rats, with corroborating intestinal histopathology.

MATERIALS AND METHODS

Experimental Animals

Thirty-five healthy young male Wistar rats weighing 150–200 g were obtained from a certified breeder and housed in clean polypropylene cages (five rats per cage) under standard conditions (temperature 25 ± 2 °C, relative humidity 55–65%, 12-hour light/dark cycle) with free access to standard rodent pellets and water. Animals were acclimatized for 14 days before the study, and all procedures were conducted in accordance with internationally recognized guidelines for the ethical care and use of laboratory animals.

Preparation of Plant Extracts

Psidium guajava leaves were collected from Wukari Local Government Area, Taraba State, Nigeria, shade-dried, powdered, and extracted separately by 72-hour maceration in 95% ethanol and in distilled water, as detailed in the companion phytochemical study. Ethanol extracts were concentrated by rotary evaporation (40–45 °C); aqueous extracts were concentrated by freeze-drying or evaporation at 60 °C. Both extracts were stored in a desiccator at 4 °C until use.

Animal Grouping and Experimental Design

35 Rats were randomly assigned to seven groups of five animals each: Group 1, normal control (distilled water, no diarrhea induction); Group 2, negative (diarrheal)

control (castor oil 1 mL/kg, no treatment); Group 3, standard (positive) control (castor oil + loperamide 2 mg/kg); Group 4, aqueous extract low dose (castor oil + 100 mg/kg); Group 5, ethanol extract low dose (castor oil + 100 mg/kg); Group 6, aqueous extract high dose (castor oil + 200 mg/kg); Group 7, ethanol extract high dose (castor oil + 200 mg/kg). All extracts and drugs were administered orally via orogastric cannula 30 minutes before castor oil induction, except for the normal control group.

Induction of Diarrhea

Diarrhea was induced by oral administration of castor oil (1 mL/kg body weight) to all groups except the normal control. All animals were fasted for 24 hours before induction. After castor oil administration, each rat was housed individually in a metabolic cage lined with clean, pre-weighed absorbent white paper, replaced every 2 hours over a 4-hour observation period.

Animal Sacrifice and Sample Collection

At the end of the 14-day treatment period, rats were anaesthetized with chloroform vapour, and blood was collected by cardiac puncture into EDTA tubes for haematological analysis and into plain tubes for serum analyses reported elsewhere. The small intestine was harvested and preserved in 10% formalin for histopathological examination.

Haematological Analysis

Whole blood samples were analyzed using an Agile S30 Hematology Autoanalyzer V2.0 to determine red blood cell (RBC) count, haemoglobin (Hb) concentration, packed cell volume (PCV/haematocrit), total white blood cell (WBC) count, and platelet (PLT) count.

Histological Examination

Formalin-fixed intestinal tissue was processed routinely, embedded, sectioned, and stained with haematoxylin and eosin (H&E) for light microscopic examination.

Data Analysis

Results are presented as mean $\pm$ standard deviation (SD) for each group ($n = 5$). Group means were compared statistically, with $p < 0.05$ considered significant; mean values sharing no common superscript letter differ significantly.

RESULTS

Effect on Haematological Parameters

Castor oil administration caused a significant ($p < 0.05$) increase in WBC count from $4.96 \pm 0.66 \times 10^9/\text{L}$ (normal control) to $7.03 \pm 2.65 \times 10^9/\text{L}$ (negative control), together with significant decreases in RBC count (7.51 ± 0.67 to $7.11 \pm 0.50 \times 10^{12}/\text{L}$), haematocrit ($39.13 \pm 3.17\%$ to $36.26 \pm 4.05\%$), and platelet count (696.00 ± 344.34 to $522.66 \pm 148.04 \times 10^9/\text{L}$). Treatment with aqueous and ethanol leaf extracts produced a significant ($p < 0.05$), dose-dependent decrease in WBC count and a corresponding increase in RBC, haemoglobin, haematocrit, and platelet values (Table 1). The 200 mg/kg ethanol extract produced the greatest increase in RBC ($8.57 \pm 0.52 \times 10^{12}/\text{L}$) and haemoglobin ($12.50 \pm 0.52 \text{ g/dL}$), while the 200 mg/kg aqueous extract produced the greatest increase in platelet count ($1014.66 \pm 187.83 \times 10^9/\text{L}$); these values were comparable to those of the standard control group.

Table 1. Haematological parameters of male Wistar rats with castor oil-induced diarrhea following treatment with aqueous and ethanol leaf extracts of *Psidium guajava*

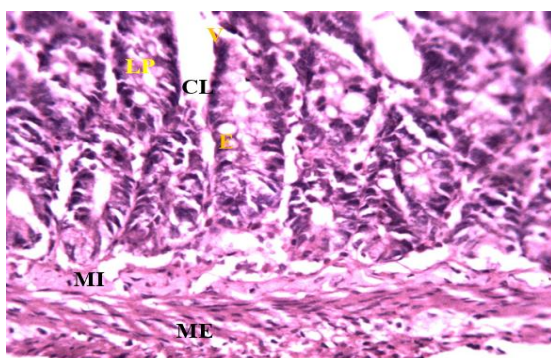
Groups	WBC ($\times 10^9/\text{L}$)	RBC ($\times 10^{12}/\text{L}$)	Hb (g/dL)	HCT (%)	PLT ($\times 10^9/\text{L}$)
Normal control	4.96 ± 0.66	7.51 ± 0.67	10.00 ± 2.25	39.13 ± 3.17	696.00 ± 344.34
Negative control	7.03 ± 2.65	7.11 ± 0.50	10.10 ± 1.11	36.26 ± 4.05	522.66 ± 148.04
Standard control	6.16 ± 3.19	7.64 ± 0.26	11.23 ± 0.15	40.53 ± 1.49	697.33 ± 265.36
Aqueous extract (LD)	3.70 ± 1.47	7.57 ± 0.77	10.63 ± 1.20	38.13 ± 4.67	837.66 ± 89.20
Ethanol extract (LD)	11.50 ± 1.77	8.46 ± 0.63	12.03 ± 1.09	43.86 ± 2.30	941.66 ± 54.07
Aqueous extract (HD)	6.90 ± 3.08	8.48 ± 0.83	12.16 ± 0.96	43.70 ± 4.48	1014.66 ± 187.83
Ethanol extract (HD)	10.06 ± 1.23	8.57 ± 0.52	12.50 ± 0.52	43.60 ± 0.55	649.66 ± 57.18

Results are mean $\pm$ SD ($n = 5$). LD = low dose (100 mg/kg); HD = high dose (200 mg/kg). Mean values in the same column carrying different superscript letters differ significantly ($p < 0.05$); superscript letters are omitted here for clarity and should be reinstated from the original dataset before submission.

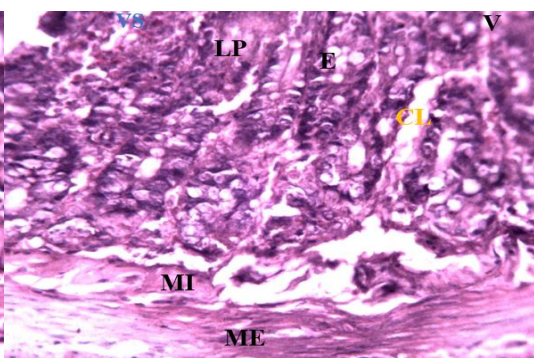
Intestinal Histopathology

The normal control group (Group 1) showed well-formed intestinal architecture with an intact epithelial lining, enterocytes, villi, and crypts of Lieberkühn. The diarrheal control group (Group 2) showed mild exfoliation of the epithelial lining, consistent with

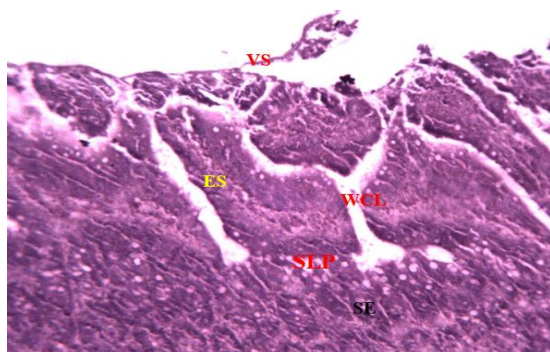
castor oil-induced mucosal injury. Treatment with the low-dose aqueous extract (Group 4) showed marked exfoliation and submucosal oedema, while the low-dose ethanol extract (Group 5) showed moderate restoration of epithelial cells. The high-dose ethanol extract (Group 7) showed near-normal restoration of intestinal epithelial tissue, with well-preserved villi, crypts, and goblet cells (Figure below).



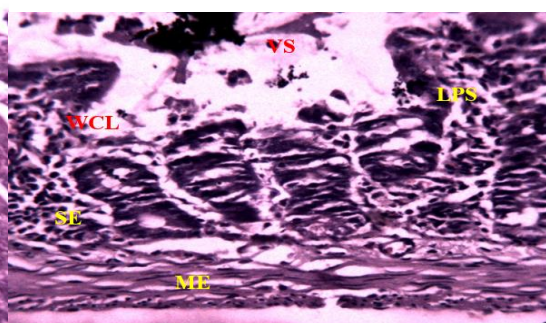
Group1: Photomicrograph of intestine section of male Wistar rat in Group 1 (Normal Control) showing well-formed and intact epithelial lining: Enterocytes (E), Villi (V), Lamina Propria (LP), Crypt of Lieberkühn (CL), and muscular architectures: Muscularis Interna (MI) and Muscularis Externa (ME). (HandE $\times$ 250)



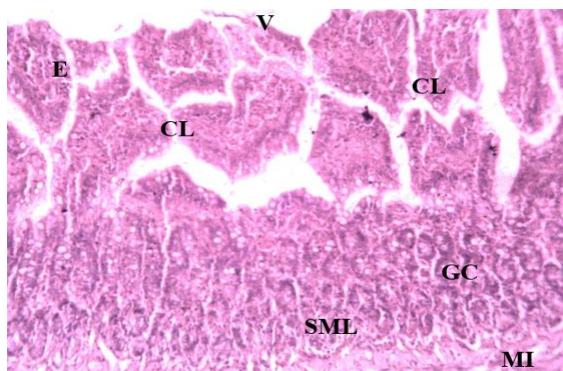
Group 2: Photomicrograph of intestine section of male Wistar rat in Group 2 (Diarrhea Control) induced with castor oil (1 mL/kg) and given no treatment showing mild exfoliation of the epithelial lining: Enterocytes (E), Villi (V), Lamina Propria (LP), Crypt of Lieberkühn (CL), and muscular architectures: Muscularis Interna (MI) and Muscularis Externa (ME). (HandE $\times$ 250)



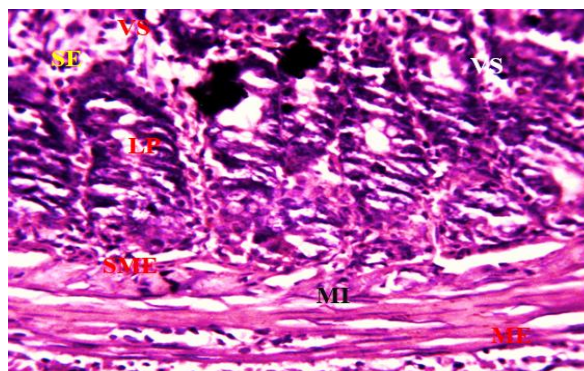
Group 3: Photomicrograph of intestine section of male Wistar rat in Group 3 (Standard control) induced with castor oil (1mg/kg) and treated with loperamide (2mg/kg) Showing marked destruction of the epithelial lining and shedding of the enterocyte (SE), Villi (VS), Lamina Propria (SLP), widening of the Crypt of Lieberkühn (WCL), and sub mucosal edema (SE). (HandE $\times$ 250)



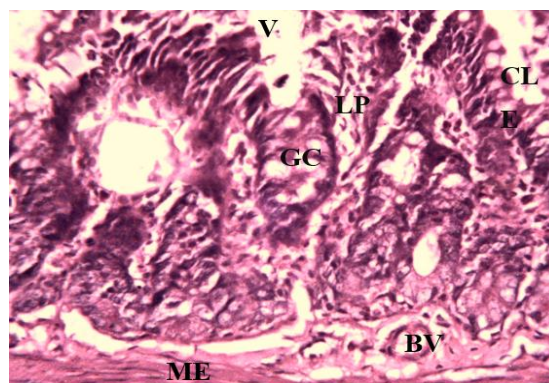
Group 4: Photomicrograph of intestine section of male Wistar rat in Group 4 (Aqueous Extract Low Dose) induced with castor oil (1 mL/kg) and treated with 100 mg/kg aqueous leaf extract of *Psidium guajava* showing marked exfoliation of the epithelial cells: Enterocytes (SE), Villi (VS), Lamina Propria (SLP), widening of the Crypt of Lieberkühn (WCL), submucosal edema (SE), and Muscularis Externa (ME). (HandE $\times$ 250)



Group 5: Photomicrograph of intestine section of male Wistar rat in Group 5 (Ethanol Extract Low Dose) induced with castor oil (1 mL/kg) and treated with 100 mg/kg ethanol leaf extract of *Psidium guajava* showing moderate restoration of the epithelial cells: Enterocytes (E), Villi (V), Lamina Propria (LP), reduced Crypt of Lieberkühn (CL), submucosal layers (SL), Goblet cells (GC), and Muscularis Interna (MI). (HandE $\times$ 250)



Group 6: Photomicrograph of intestine section of male Wistar rat in Group 6 (Aqueous Extract High Dose) induced with castor oil (1 mL/kg) and treated with 200 mg/kg aqueous leaf extract of *Psidium guajava* showing mild restoration of the epithelial lining and shedding of the Enterocytes (SE), Villi (VS), Lamina Propria (LP), widening of the Crypt of Lieberkühn (WCL), submucosal edema (SME), Muscularis Interna (MI), and Muscularis Externa (ME). (HandE $\times$ 250)



Group 7: Photomicrograph of intestine section of male Wistar rat in Group 7 (Ethanol Extract High Dose) induced with castor oil (1 mL/kg) and treated with 200 mg/kg ethanol leaf extract of *Psidium guajava* showing near-normal restoration of the epithelial tissues: Enterocytes (E), Villi (V), Lamina Propria (LP), Crypt of Lieberkühn (CL), Goblet cells (GC), and Blood vessel (BV). (HandE $\times$ 250)

DISCUSSION

Castor oil administration produced the expected pattern of experimental diarrhea, with significant haematological disturbances characterized by leukocytosis and thrombocytopenia. The WBC elevation indicates a systemic inflammatory response to the diarrheal insult, consistent with the established pathophysiology of castor oil-induced gastrointestinal inflammation, in which intestinal mucosal injury triggers release of pro-inflammatory cytokines and recruitment of leukocytes (Mascolo *et al.*, 1994; Nnadiukwu *et al.*, 2024; Okoye *et al.*, 2025). The thrombocytopenia observed may reflect platelet consumption from activation of the coagulation cascade or sequestration within the inflamed intestinal microcirculation, compounded by fluid and electrolyte loss and consequent haemodynamic changes (Lu *et al.*, 2005).

Treatment with both aqueous and ethanol extracts of *P. guajava* produced significant, dose-dependent reversal of these haematological abnormalities, with the 200 mg/kg ethanol extract producing near-complete restoration of RBC count and haemoglobin concentration. This is consistent with previous reports of the haematoprotective effects of guava leaf extracts (Emmanuel *et al.*, 2020; Nnadiukwu *et al.*, 2024). Flavonoids and phenolic compounds in guava leaves, particularly quercetin and ellagic acid, possess potent antioxidant properties that protect erythrocyte membranes from oxidative damage (Sharifi-Rad *et al.*, 2022; Sam Arul Raj *et al.*, 2023), and may stimulate erythropoiesis through effects on haematopoietic growth factors or iron metabolism (Saravani *et al.*, 2024). The higher quercetin and total phenolic content of the ethanol extract would be expected to confer superior antioxidant protection, consistent with its greater efficacy in restoring RBC and haemoglobin levels. The pronounced platelet recovery observed with the 200 mg/kg aqueous extract suggests thrombopoietic or platelet-protective activity, plausibly related to the higher tannin content of the aqueous extract and the known hemostatic and platelet-aggregating properties of tannins (Jayakumari *et al.*, 2023). The dose-dependent WBC reduction observed with both extracts further indicates anti-inflammatory activity, consistent with the ability of quercetin and related flavonoids to inhibit pro-inflammatory cytokine and chemokine production and reduce leukocyte recruitment (Kim *et al.*, 2012; Zamani-Garmsiri *et al.*, 2022).

The intestinal histopathological findings corroborate the biochemical and haematological evidence of mucosal injury and its reversal with treatment. Castor oil-

induced disruption of the epithelial barrier, with associated inflammation and increased fluid secretion, is well documented (Mascolo *et al.*, 1994; Lutterodt, 1992), and the near-normal restoration of villi, crypts of Lieberkühn, and goblet cells observed with the high-dose ethanol extract supports its superior efficacy in restoring normal intestinal architecture and function. This is consistent with reports that *P. guajava* extracts increase colonic water absorption and reduce gastrointestinal propulsion rates (Liu *et al.*, 2024) and inhibit intestinal motility and fluid secretion (Garrido *et al.*, 2024), mechanistically linking the histological improvement to the observed antidiarrheal and haematological benefits.

CONCLUSION

Both aqueous and ethanol leaf extracts of *Psidium guajava* possess significant antidiarrheal and haematoprotective activity against castor oil-induced diarrhea in male Wistar rats, reversing castor oil-induced leukocytosis, thrombocytopenia, and intestinal mucosal injury in a dose-dependent manner. The high-dose (200 mg/kg) ethanol extract showed the most pronounced restoration of red cell indices and intestinal histoarchitecture, while the high-dose aqueous extract showed the greatest platelet recovery, supporting the traditional use of guava leaves in the management of diarrheal disease and its haematological sequelae.

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