



CARICA PAPAYA LEAF EXTRACT ATTENUATES CYCLOPHOSPHAMIDE INDUCED MYELOSUPPRESSION THROUGH ANTIOXIDANT MEDIATED HEMATOPOIETIC RESTORATION IN WISTAR RATS

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ABSTRACT

Background and Purpose: Cyclophosphamide (CTX)-induced myelosuppression is characterized by impaired hematopoiesis resulting in anaemia, leukocyte abnormalities, and thrombocytopenia. Although conventional therapies are available, their long-term use may be associated with adverse effects. This study investigated the hematopoietic and antioxidant potentials of *Carica papaya* leaf extract in Wistar rats with CTX-induced bone marrow suppression. **Experimental Approach:** Twenty adult Wistar rats were randomly assigned into four groups (n = 5). Myelosuppression was induced using CTX, while treatment groups received either folic acid or ethanolic *C. papaya* leaf extract. Quantitative phytochemical analysis, ferric reducing antioxidant power (FRAP), and ABTS radical scavenging assays were performed. Hematological parameters including packed cell volume (PCV), hemoglobin (Hb), red blood cell (RBC), white blood cell (WBC), and platelet counts were evaluated. **Key Results:** Phytochemical analysis revealed abundant phenolic compounds (213.18 ± 0.37 mg GAE/g), followed by phytate and flavonoids. The extract exhibited concentration-dependent antioxidant activity, with FRAP values increasing from approximately 11.5 to 28.0 mg AAE/g and an ABTS IC₅₀ of 79.22 µg/mL. CTX administration significantly reduced PCV, Hb, RBC, and platelet counts. Treatment with *C. papaya* markedly improved these hematological indices relative to the CTX-only group. CTX treatment also resulted in leukopenia with an observed recovery upon *C. papaya* administration indicating substantial improvement of hematopoietic function. **Conclusion:** The hematopoietic restoration observed following *C. papaya* treatment may be attributed to its rich phytochemical profile and strong antioxidant activity. These findings suggest that *C. papaya* leaf extract possesses promising hematoprotective potential against CTX-induced myelosuppression.

KEYWORDS: *Carica papaya*, Cyclophosphamide, Myelosuppression, Hematopoiesis, Antioxidant activity, Hematoprotection.

1. INTRODUCTION

Anaemia continues to be a major public health concern worldwide, affecting nearly two billion individuals, particularly in low and middle income countries (WHO,

2015; Kassebaum, 2016). The condition is characterized by reduced hemoglobin concentration, red blood cell count, or packed cell volume, resulting in diminished oxygen transport to body tissues (WHO, 2011). Beyond

its impact on physical performance, anaemia contributes significantly to morbidity, reduced quality of life, and increased healthcare burden globally. Effective maintenance of blood cell production is therefore essential for normal physiological function. Disruption of hematopoiesis can predispose individuals to several hematological disorders, including anaemia, leukopenia, and thrombocytopenia. The hematopoietic system is crucial for keeping the body's balance by producing important blood components from stem cells in the bone marrow. When this system is disrupted, such as during bone marrow suppression, serious blood disorders like anaemia, leukopenia, and thrombocytopenia (platelet counts below $150 \times 10^3/\mu\text{L}$) can develop (Munir *et al.*, 2022). Cyclophosphamide (CTX), a common drug used in chemotherapy, is a major cause of this suppression. It works by linking DNA strands and causing oxidative stress, which damages the stem cells that make blood, reduces blood cell production, and can harm organs like the thymus and spleen in rat models (Zohirul Islam *et al.*, 2021). In Wistar rats, CTX treatment leads to lower body weight, reduced WBC and RBC counts, and smaller thymus and spleen sizes, with some cases showing temporary platelet increases as a response. These blood changes, along with oxidative stress damaging bone marrow and organs like the liver and kidneys, worsen overall health and quality of life making it a good model for studying chemotherapy-related blood problems (Luiz *et al.*, 2020; Zohirul Islam *et al.*, 2021). Because chemotherapy can be so harmful, scientists are exploring natural aids to lessen these side effects. *Carica papaya* L., a tropical plant from the Caricaceae family native to Southern Mexico and Central America, has been used in traditional medicine across Asia, Africa, and Latin America for hundreds of years. Studies have demonstrated that *Carica papaya* leaf extract possesses significant antioxidant and hematoprotective activities. The extract contains bioactive compounds capable of scavenging reactive oxygen species and protecting tissues from oxidative damage. In experimental models, papaya leaf extract has been reported to enhance platelet production through the upregulation of CD110 receptor expression on megakaryocytes, thereby promoting megakaryopoiesis and thrombopoiesis (Singh *et al.*, 2021). Furthermore, its antioxidant constituents have been shown to mitigate cyclophosphamide induced oxidative stress and cellular damage (Luiz *et al.*, 2020). Despite these promising findings, limited information exists regarding the ability of *C. papaya* to restore overall hematopoiesis following cyclophosphamide induced myelosuppression. In particular, the relationship between its antioxidant activity and recovery of hematopoietic cell lineages remains poorly understood. Therefore, this study investigated the hematopoietic effect of ethanolic leaf extract of *Carica papaya* in Wistar rats with cyclophosphamide induced myelosuppression.

2. MATERIALS AND METHODS

2.1 Materials

Materials used included an automated hematology analyzer (Sysmex KX-21N), centrifuge, micropipettes, syringes, and standard cage, EDTA sample bottle, sterile water, standard rat chow, consumables like gloves and disinfectants. Pharmaceutical grade cyclophosphamide was procured from a certified pharmacy in Lokoja, Kogi State, Nigeria, and used to induce myelosuppression.

2.2 Experimental Animals

Twenty (20) healthy adult Wistar rats (weighing approximately 150–200 g) were sourced from Ogbomosho, Oyo State, Nigeria. The rats were acclimatized for seven (7days) under standard laboratory conditions (temperature 24–28°C, relative humidity 60–70%, 12-hour light/dark cycle) with access to standard rat pellet and water *ad libitum*, strict adhere to ethical standards and protocol was ensured.

2.3 Plant Collection and Authentication

Fresh *Carica papaya* leaves were collected from Osara community, Kogi State, Nigeria, and authenticated at the Department of Biological Sciences, Confluence University of Science and Technology, Osara, Nigeria.

2.4 Specimen collection

Blood was collected via cardiac puncture and put into a properly labelled anticoagulant sample collection bottle.

2.5 Preparation of *Carica Papaya* extract

The leaves of the plant was air dried for 7 days. The dried leaves was grinded into powder using a dry blender. 50 grams of the powdered leaves was extracted using 70% ethanol via soxhlet extraction method. The filtrate will be evaporated in a water bath at 60°C to a constant weight as described by Nwanjo and Uze, (2007).

2.6 Induction of Bone Marrow Suppression

Cyclophosphamide was administered to Wistar rats in Groups II, III, and IV at a dose of 15 mg/kg body weight via intraperitoneal injection on days 1 and 3 to induce myelosuppression. The dose was selected based on previous studies demonstrating effective suppression of hematopoiesis (Adebayo *et al.*, 2023). On day 6, hematological parameters RBC count, WBC count, hemoglobin levels, and platelet count were measured using a hematology analyzer to confirm myelosuppression.

2.7 Experimental Design

The study employed a randomized controlled design with 20 Wistar rats divided into 4 groups, each containing 5 rats. The treatment schedules were as follows:

Group 1: Negative control and were giving food and water *ad libitum*.

Group 2: 15mg/kg Cyclophosphamide Day1 and 10mg/kg booster dose at Day3

Group 3: 15mg/kg Cyclophosphamide Day1 and 10mg/kg booster dose at Day3, 10mg/kg Folic acid was given from day 2-7

Group 4: 15mg/kg Cyclophosphamide Day1 and 10mg/kg booster dose at Day3, 10mg/kg of *Carica papaya* extract was administered from Day 2-7

At the end of the experiment (Day 8), the rats were anaesthetized by inhalation of chloroform. Blood sample were collected from the ophthalmic vein through the medical canthus of the rats, in the entire group.

2.8 Phytochemical Screening of *Carica papaya* Leaves

The quantitative determination of phytochemicals in the ethanol leaf extract of *Carica papaya* was carried out using standard analytical procedures.

Total Phenolic Content was determined using the Folin Ciocalteu method as described by Singleton and Rossi (1965).

Total Flavonoid Content was determined using the aluminium chloride colorimetric method described by Chang et al. (2002).

Tannin Content

Tannin content was determined using the Folin Denis spectrophotometric method described by Pearson (1976) and later adopted by AOAC (2005).

Alkaloid Content determination was carried out according to the gravimetric method described by Harborne (1998).

Saponin Content determined was carried out according to the method described by Obadoni and Ochuko (2001).

Phytate content was determined according to the titrimetric procedure described by Wheeler and Ferrel (1971).

Oxalate Content

Oxalate content was determined according to the method described by Day and Underwood (1986).

2.9 Ferric Reducing Antioxidant Power (FRAP) Assay

The ferric reducing antioxidant power (FRAP) of the ethanol leaf extract of *Carica papaya* was determined according to the method described by Benzie and Strain (1996). The FRAP reagent was freshly prepared by mixing acetate buffer (300 mM, pH 3.6), 10 mM TPTZ solution in 40 mM HCl, and 20 mM ferric chloride hexahydrate solution in the ratio of 10:1:1. An aliquot of the extract was mixed with the FRAP reagent and incubated at 37°C for 30 min. The reduction of ferric ion (Fe^{3+}) to ferrous ion (Fe^{2+}) produced a blue coloured ferrous TPTZ complex, and the absorbance was measured at 593 nm using a UV-visible spectrophotometer. Antioxidant capacity was expressed as Fe^{2+} equivalents.

2.10 ABTS Radical Scavenging Assay

The ABTS radical scavenging activity of the ethanol leaf extract of *Carica papaya* was determined according to the method described by Re et al. (1999). The ABTS radical cation ($\text{ABTS}^{\bullet+}$) was generated by reacting 7 mM ABTS stock solution with 2.45 mM potassium persulfate and allowing the mixture to stand in the dark at room temperature for 12 to 16 h before use. The resulting $\text{ABTS}^{\bullet+}$ solution was diluted with ethanol to obtain an absorbance of 0.70 ± 0.02 at 734 nm. Thereafter, the extract was mixed with the ABTS solution and incubated for 6 min. The decrease in absorbance was measured at 734 nm, and the percentage inhibition of the ABTS radical was calculated relative to the control. Trolox was used as the reference antioxidant standard.

2.11 Data Collection and Analysis

Hematological parameters were determined using an automated hematology analyzer (Sysmex KX-21N). Quantitative Phytochemical analysis and antioxidant assays were performed in duplicate, and the results were expressed as mean $\pm$ standard deviation. Statistical analysis of the phytochemical and antioxidant data was carried out using SPSS version 25.0, while haematological parameters were presented descriptively.

3. RESULTS

3.1 Phytochemical Screening of *Carica papaya* leaf extract

Table 1: Quantitative Phytochemical constituents of the Ethanol leaf extract of *C.papaya*.

Phytochemicals(mg GAE/g)	N	Minimum	Maximum	Mean $\pm$ SD	Variance
PHENOL	2	212.91	213.44	213.1750 ± 0.37477	0.140
FLAVONOID	2	105.30	107.39	106.3450 ± 1.47785	2.184
PHYTATE	2	161.11	162.50	161.8050 ± 0.98288	.0966
ALKALOID	2	92.16	94.43	93.2950 ± 1.60513	2.576
TANNINS	2	95.40	98.59	96.9950 ± 2.25567	5.088
OXALATE	2	1.51	1.84	1.6750 ± 0.23335	.054
SAPONINS	2	40.49	42.84	41.6650 ± 1.66170	2.761

Values are represented as Mean $\pm$ standard deviation ($n=2$), $P < 0.05$. The quantitative phytochemical analysis of the ethanol leaf extract of *Carica Papaya* is represented in Table 1. Phenolic compound were more abundant (213.1750 ± 0.37477), followed by phytate (161.8050 ± 0.98288) and flavonoid (106.3450 ± 1.47785), tannins (96.9950 ± 2.25567) and alkaloids (93.2950 ± 1.60513) were also in moderate amounts. Saponins were quantified at (41.6650 ± 1.66170),

while oxalate (1.6750 ± 0.23335) were present at the lowest level. The low standard deviation for most constituents indicate minimal variation between the replicates, suggesting good reproducibility of the measurements.

3.2 Ferric Reducing Antioxidant Power (FRAP) of Ethanolic Leaf Extract of *C.papaya*

The ferric reducing antioxidant power assay was used to determine the antioxidant capacity of the ethanolic leaf extract of *Carica Papaya*. The reducing power of the extract was expressed as milligrams of ascorbic acid

equivalents per gram of extract (mg AAE/g). The assay is based on the ability of antioxidant present in the extract to reduce ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}), thereby reflecting the electron donating potency of the extract.

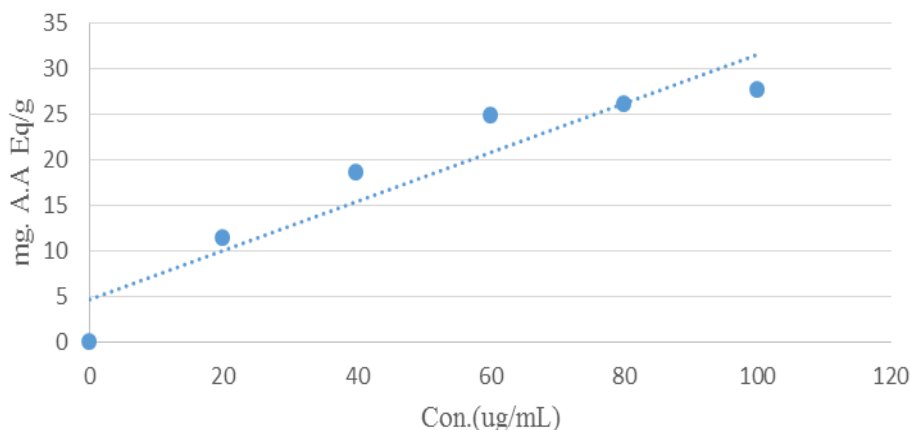


Figure 1: Ferric Reducing Antioxidant Power of ethanolic leaf extract of *C.papaya* expressed as mg ascorbic acid equivalents(AAE)/g extract. As shown above the, Ferric reducing antioxidant power of the extract increased with increasing concentration. The FRAP values increased from approximately 11.5mgAAE/g at 20µg/mL to about 28.0 mg AAE/g at 100µg/mL. This concentration dependent increase in reducing power shows that the extract possesses appreciable antioxidant activity.

3.3 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic Acid)(ABTS) Radical Scavenging Activity of Ethanolic Leaf Extract of *C.papaya*

The antioxidant activity of the ethanolic leaf extract of *C. papaya* was evaluated using 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic Acid)(ABTS) radical

scavenging assay. The assay measures the ability of antioxidant present in the extract to neutralize the ABTS radical cation (ABTS.+), resulting in a decrease in absorbance. The radical scavenging activity was expressed as a percentage inhibition at different concentrations of the extract.

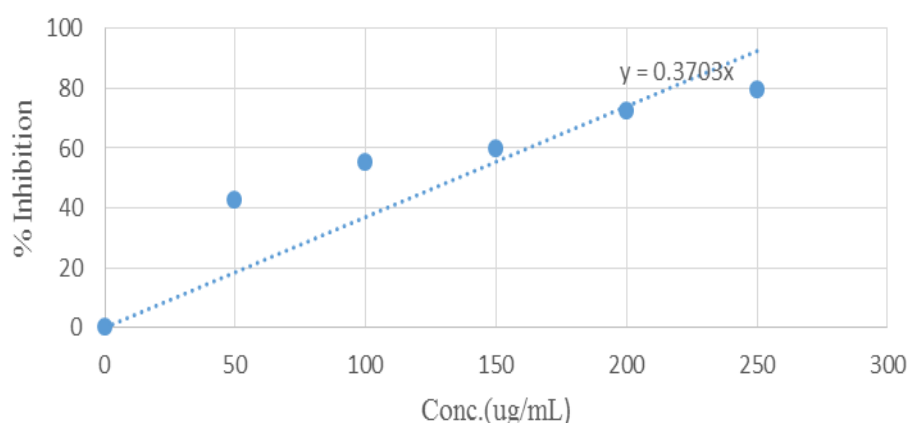


Figure 2: ABTS radical scavenging activity of ethanolic extract of *Carica papaya*. The extract exhibited concentration dependent ABTS radical scavenging activity. The percentage inhibition increased from 42.49% at 5µg/mL to 79.33% at 250µg/mL, which shows increased antioxidant activity with increasing extract concentration. The extract showed an I.C50 = 79.22µg/mL, suggesting a strong capacity to scavenge ABTS radicals.

3.4 Hematological Parameters of Experimental groups

The effect of treatment on haematological indices of experimental animals is presented in Table 2. Significant

variations were observed in the white blood cell(WBC) count and other haematological parameters across the experimental groups following Cyclophosphamide induction and treatment.

Table 2: Hematological Parameters of Wister rat treated with Ethanolic *C.papaya* leaf extract.

GROUP	PCV (%)	WBC(*10 ⁸ /L)	RBC(*10 ¹⁰ /L)	Hemoglobin g/l	Platelet(*10 ⁹ /L)
1	0.45	8.10	7.12	15.0	701
2	0.12	14.1	1.93	4.0	228
3	0.37	11.1	6.58	12.3	1164
4	0.43	9.0	6.61	14.3	764

Table 2 shows that CTX administration resulted in marked reductions in PCV, haemoglobin concentrations, RBC count, platelet count, and WBC count compared with normal control group, indicating haematological impairment and leukopenia. Treatment with folic acid and *C. papaya* leaf extract improved most haematological parameters relative to the CTX treated group.

4.0 DISCUSSION

The relationship between phenolic content and the activity of FRAP/ABTS has been well established, Cai *et al.*, 2021 reported that a higher phenolic and flavonoid content results in improved antioxidant capacity. Antioxidant investigation of the extract, shows a concentration-dependent increase in antioxidant activity. Result of the FRAP assays indicates an increased ferric reducing ability, implying that the extract contains strong electron donating compounds capable of neutralizing free radicals. Also, the ABTS assay showed enhanced radical scavenging activity with an IC₅₀ value of 79.22µg/mL, indicating its antioxidant potency. This suggests that the hematoprotection exhibited by *C.papaya* may be mediated through oxidative stress reduction.

Among the various chemotherapeutic agents, Cyclophosphamide is a well known to induces myelosuppression through the generation of reactive oxygen species, leading to lipid peroxidation, DNA cross linkage, and suppression of bone marrow activity. This adverse effect of CTX depletes production of major blood components, resulting in anaemia and immunosuppression (Emadi *et al.*, 2017). In our study, CTX administration causes a significant reduction in levels of packed cell volume (PCV), hemoglobin (Hb), and red blood cells (RBC) confirming the successful induction of hematotoxicity. Treatment with *C. papaya* leaf extract (Group 4), resulted in an elevation in the levels of these hematological parameters compared to both CTX-only (Group). This restorative effect may be attributed to the antioxidant potency of the extract, giving it the ability to counteract CTX induced oxidative stress, thereby protecting hematopoietic stem cells and enhancing blood cell regeneration.

The reduction in WBC count observed following cyclophosphamide administration is consistent with the

established myelosuppressive action of the drug, which impairs the proliferation of hematopoietic progenitor cells through oxidative stress mediated cellular damage. Consequently, leukocyte production is diminished, resulting in leukopenia. The recovery of WBC counts following treatment with folic acid and *Carica papaya* leaf extract suggests an improvement in hematopoietic function and immune competence. This effect may be connected to the high phenolic and flavonoid contents of the extract, which possess potent antioxidant properties capable of scavenging reactive oxygen species and protecting hematopoietic cells from oxidative injury. Furthermore, *Carica papaya* leaf has been reported to exhibit immunomodulatory activity through the regulation of cytokine production and immune cell function, thereby supporting hematological recovery (Jayasinghe *et al.*, 2017). Another study also reported the rich antioxidant bioactives of *Carica papaya* leaves and their role in mitigating oxidative stress and enhancing physiological resilience (Sharma *et al.*, 2022). Therefore, the improvement in leukocyte counts observed in this study may be associated with the antioxidant and immunomodulatory properties of *Carica papaya* leaf extract.

In conclusion, the observed restoration of blood parameters by *C. papaya* in our study is closely linked to its phytochemical composition and antioxidant potential. This positions *C. papaya* as a promising natural source of hematoprotective agents.

AUTHORS' CONTRIBUTIONS

ISM conceptualized the study and drafted the manuscript. All authors contributed to data extraction, analysis, and manuscript revision.

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Declaration of Conflict of Interest

No conflict of interest was reported by the author(s).

Data availability Statement

This is original data and not in any repository for now.

Ethical Approval

All animals used for the study were handled strictly in accordance with the Confluence University of Science and Technology Ethics Committee guidelines for the use of experimental animals in research.

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