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Evaluation of Medicinal Plant Extracts in Modulating Haematological, Thrombotic, and Inflammatory Markers in Benzene-Induced Leukaemic Wistar RatsKOSAMAT Yekkeen, A.^{1,3}, ATERE Adedeji, D.*¹, AKINOLA Rasheed, O.³, AJAYI Olutayo, I.²Department of Medical Laboratory Science, College of Health Sciences, Osun State University, Osogbo, Nigeria¹, Department of Physiology, School of Basic Medical Sciences, University of Benin, Benin City, Nigeria², Department of Medical Laboratory Science, School of Basic Medical Sciences, University of Benin, Benin City, Nigeria³.Author for Correspondence*: adedeji.ater@uniosun.edu.ng+234-803-950-1172/ORCID ID: <https://orcid.org/0000-0002-8802-3762>. <https://dx.doi.org/10.4314/sokjmls.v10i3.29>**Abstract**

Leukaemia is often complicated with thrombotic and inflammatory complications that further augment the progression of the disease and the rate of morbidity. This study was performed to evaluate the effects of test plants, *Azadirachta indica*, *Psorospermum febrifugum*, *Ricinus communis*, and *Rosy periwinkle*, on the thrombotic, anticoagulant, and inflammatory parameters of benzene-induced leukaemic Wistar rats so that these plants may be explored as potential adjuvants. Six groups of Wistar rats were studied, with control and benzene-induced leukemia in two groups and four treatments with the selected medicinal plant extracts. Parameters studied included platelet count, Prothrombin Time (PT), Partial Thromboplastin Time (PTT), D-dimer, Protein C, Protein S, and inflammatory markers (TNF- α and Hs-CRP). Leukaemia markers CD10 and CD20 were also studied. Following benzene exposure, platelet counts, and protein C and protein S levels were decreased, PT and PTT values were prolonged, and D-dimer, TNF- α , and Hs-CRP levels increased ($p < 0.05$). Treatment with plant extracts partially restored these parameters, with *Azadirachta indica* holding the first position for full restoration of the changes. The treatment also modulates the expression of CD10 and CD20, therefore suggesting some therapeutic benefits. This study has thus revealed that the selected herb, especially *Azadirachta indica*, has been found to prevent coagulative, inflammatory and haematological complications associated with leukaemia. This suggests that these herbs can be used as adjuncts to treat leukaemia. Additional clinical trials will definitely be needed to confirm such effects in human models.

Keywords: medicinal plants, thrombotic markers, inflammatory markers, leukemia, D-dimer

Introduction

The global incidence of leukaemia is on the rise and hence, there was a pressing need to find low-cost yet effective treatment modalities, mainly in low-resource setting areas. Leukaemia is a type of malignancy of the haematopoietic system wherein abnormal white cells interfere with bone marrow and peripheral blood to cause immunodeficiency, anaemia, and bleeding disorders (Davis *et al.*, 2014; Ajayi & Danladi, 2022). The disease is broadly classified as acute and chronic, including acute lymphocytic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML), and chronic myeloid leukaemia (CML), each bearing its different mechanisms, pathophysiology, clinical courses, and implications (Huang *et al.*, 2022; Looi *et al.*, 2022).

One complicating issue of leukaemia that is a critical problem yet rarely considered is the close association with inflammatory and thrombotic dysfunctions. Chronic inflammation aids in disease progression by altering the tumor microenvironment to enable angiogenesis, immune evading, and metastasis (Balkwill, 2009; Brachford & Carpenter, 2018). TNF-alpha and Hs-CRP are inflammatory markers that are elevated in leukaemia and have been linked to worse clinico-prognosis (de la Brassinne Bonardeaux *et al.*, 2025).

Venous thrombosis is a significant disease-related complication associated with haematologic malignancies, particularly leukaemia. Leukaemias

create a hypercoagulable state with increased frequency of venous thromboembolism and disseminated intravascular coagulation (DIC) (Furie & Furie, 2008; Elice & Rodeghiero, 2012). Typically, the prothrombotic picture observes prolonged PT, PTTK, and D-dimers suggestive of fibrinolysis (Anderson *et al.*, 2022). Protein C and Protein S are two key natural anticoagulants whose levels are reduced in leukaemic conditions and which pose an additional risk for thrombosis (Raskob *et al.*, 2014; Falanga *et al.*, 2019). Besides having its systemic parameters, leukaemia still depends on some specific surface markers such as CD10 and CD20 for diagnosis and disease monitoring. CD10 is expressed in early lymphoid progenitor cells and is frequently elevated in ALL, while CD20 is a pan-B-cell marker used in both diagnosis and targeted therapy of B-cell malignancies (Boyd *et al.*, 2013; Mishra *et al.*, 2016).

Stanching by the limitations and side effects of chemotherapies, there is greater indexing to plant-based therapies as adjunctive or alternative therapies. Medicinal plants like *Azadirachta indica*, *Psorospermum febrifugum*, *Ricinus communis*, and *Rosy periwinkle* have shown the ability to provide various pharmacological effects such as anti-inflammatory, antioxidant, anticoagulant, and anticancer effects (Newman & Cragg, 2012; Kooti *et al.*, 2017). Alkaloids, flavonoids, and terpenoids in these plants are reported to influence immune function and hematopoiesis, holding great promise for the management of leukemia (Egbuna *et al.*, 2023; Oyovwi & Atere, 2024).

Being a haematopoietic mutagen, benzene can induce mutations and mimic leukaemia pathology, hence the need to induce leukaemia experimentally in rats (Huff 2007; Akanni *et al.*, 2017). The present study investigated the effect of some medicinal plants on key thrombotic parameters (PT, PTTK, Protein C, Protein S, D-dimer), inflammatory markers (TNF- α , Hs-CRP), and leukaemia cell surface markers (CD10 and CD20) in benzene-induced leukaemic Wistar rats, so as to examine the possible therapeutic potentials of the extracts on the hematological, thrombotic, and immune changes associated with leukaemia.

Materials and Methods

Plant Materials and Authentication

For this study, four medicinal plants were selected, namely, *Azadirachta indica* (neem), *Psorospermum febrifugum*, *Ricinus communis* (castor oil plant), and *Rosy periwinkle*. Fresh leaves of *Azadirachta indica*, *Psorospermum febrifugum*, and *Rosy periwinkle* were collected in the open vegetation of Osun State University (UNIOSUN), Osogbo, Osun State, Nigeria, while seeds of *Ricinus communis* were collected. The plant species were authenticated by a Botanist from the Plant Science Department of Obafemi Awolowo University (OAU). The plant materials were air-dried and then kept for later extraction.

Preparation of Plant Extracts

Extraction was performed using various solvents depending upon the plant: *Azadirachta indica*, *Psorospermum febrifugum*, and *Rosy periwinkle* were extracted using water. *Ricinus communis* was extracted in a Soxhlet apparatus using n-hexane. Concentration of the plant material was done under reduced pressure using a rotary evaporator at 40°C. The extracts were kept in glass containers with concentrations of 10 mg/mL for oral administration to the rats.

Ethical Clearance

The Research Ethics Committee of the Osun State Ministry of Health duly granted approval for this study, with Reference number: OSHREC/PRS/569T/156. Prior to the study, utmost care was observed while performing all procedures in accordance with ethical guidelines on the care and use of animals for biomedical research as stipulated by Kiani *et al.* (2022).

Animal Model and Grouping

A total of 72 male Wistar rats (weight range: 80–120g) were obtained from the Animal House of UNIOSUN, Osogbo, Nigeria. The rats were acclimatized for 7 days under controlled conditions (temperature: 28°C \pm 2°C, light/dark cycle: 12 hours each), with free access to water and commercial rat chow (Growers Mash, Top Feed).

The rats were randomly divided into six experimental groups (A–F), each group containing six rats:

- **Group A (Control Group):** The rats in this group received distilled water (0.5ml/kg) and normal saline (0.5ml/kg) orally for 4 weeks.

- **Group B (Benzene-Induced Group):** The rats in this group received benzene chromosolv (0.2 ml at 1:10 dilution in water/2-propanol) daily via tail vein for 4 weeks to induce leukemia, as previously described (Huff *et al.*, 2007; Akanni *et al.*, 2014).
- **Group C (Herbal Treatment Group):** The rats in Group C received aqueous extracts of *Azadirachta indica*, *Psorospernum febrifugum*, *Ricinus communis*, and *Rosy periwinkle* at 10 mg/kg body weight, based on preliminary LD50 studies (*Azadirachta indica*: 40 mg/kg, *Psorospernum febrifugum*: 548 mg/kg, *Ricinus communis*: 340 mg/kg, and *Rosy periwinkle*: 30 mg/kg) as previously reported (Kupchan *et al.*, 1980; Toki *et al.*, 2008; Mutlu *et al.*, 2010; Rasool *et al.*, 2012).
- **Group D (Standard Drug-treated Group):** The rats in this group received 5-Fluorouracil (5 mg/kg body weight) via tail vein for 4 weeks as a positive control. The dose of 5-Fluorouracil used in this study is consistent with standard protocols for inducing chemotherapy-related effects in animal models of leukaemia as previous reported (Duan *et al.*, 2011; Fleischmann *et al.*, 2021).
- **Group E (Pre-Treatment Group):** Pre-treated with plant extracts for 4 weeks before being induced with benzene chromosol.
- **Group F (Post-Treatment Group):** Treated with plant extracts for 4 weeks following benzene chromosolv induction.

Administration of Plant Extracts

The plant extracts were administered orally once daily using gastric gavage at doses derived from the acute toxicity results (LD50) from the preliminary toxicity study. The dose was adjusted to 1/10th of the LD50 value, as per the method described by Nath and Yadav (2015). The extract doses for each plant were as follows:

- *Azadirachta indica*: 20mg/kg (low dose) and 80mg/kg (high dose)
- *Psorospernum febrifugum*: 274mg/kg (low dose) and 1096mg/kg (high dose)
- *Ricinus communis*: 170mg/kg (normal dose), 85mg/kg (low dose), and 340mg/kg (high dose)
- *Rosy periwinkle*: 15mg/kg (low dose) and 60mg/kg (high dose)

The rats in groups receiving standard drugs were treated with 5-fluorouracil (5mg/kg body weight) via tail vein for 4 weeks.

Blood Collection, Hematological and Biochemical Analysis

Blood samples, at the end of the treatment period, were drawn from the tail veins of Wistar rats using sterile 1 ml syringes. Samples for hematological parameters were collected into anticoagulated K EDTA vials to avoid clotting, whereas other samples were kept for immediate analysis in biochemical procedures. Plasma, where applicable, was obtained through centrifugation and kept under suitable conditions until required for analysis.

Platelets were counted with an automated hematology analyzer (SYSMEX KX-21N). Both the PT and PTT were determined using commercial reagents following standard laboratory protocols. D-Dimer, Protein C, and Protein S contents were quantitated by ELISA kits according to the manufacturers' instructions. TNF- α and Hs-CRP were also determined in plasma samples by ELISA kits with proper calibration standards. Furthermore, the expression of CD10 and CD20 as markers of B-cell differentiation was determined using flow cytometry at the University of Benin Teaching Hospital, with specific monoclonal antibodies. All the analyses were carried out with reference to the established protocol, and the results were recorded for further assessment.

Data Analysis

Analysis of data was done using SPSS version 25.0 (IBM Corp., Armonk, NY). One-way ANOVA with post-hoc tests was used for comparing platelet counts, PT, PTT, D-dimer, Protein C, Protein S, and inflammatory markers such as TNF- α and Hs-CRP in the control, benzene-induced, and plant-treated groups. Results were given as mean \pm SD, and statistical significance was fixed at <0.05 .

Results

The **benzene-induced group** exhibited significant changes in haematological parameters, with a marked increase in WBC count and a decrease in platelet count ($p < 0.05$),

indicating leukaemia development. Post-treatment with plant extracts, especially *Ricinus communis*, resulted in significant recovery of both WBC count and platelet count ($p < 0.05$), with *Azadirachta indica* and *Psorospernum febrifugum* showing moderate improvements. The 5-Fluorouracil group also showed moderate recovery but did not return to control levels (table 1). Similarly, coagulation markers such as Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and D-dimer levels were significantly altered in the benzene-induced group, and plant treatments notably reduced these markers, particularly in the *Azadirachta indica* group (table 2). The 5-Fluorouracil group showed partial reduction in coagulation abnormalities but remained prolonged compared to controls.

In table 3, Treatment with the plant extracts significantly reduced TNF- α and Hs-CRP levels, indicating strong anti-inflammatory effects, particularly for *Azadirachta indica*. The 5-Fluorouracil group also exhibited a reduction in inflammatory markers, but the effects were less pronounced. Finally, CD10 and CD20 expression, indicative of leukaemia progression, were significantly higher in the benzene-induced group, but treatment with plant extracts significantly reduced these markers, especially in *Ricinus communis* ($p < 0.05$). The 5-Fluorouracil group showed moderate reductions in CD10 and CD20 expression, but these were less significant than the reductions observed in the plant-treated groups.

Table 1: Haematological Parameters in Benzene-Induced Leukaemic Rats

Group	WBC ($\times 10^3/\mu\text{L}$)	Platelet Count ($\times 10^3/\mu\text{L}$)	HGB (g/dL)	HCT (%)	F-value	p-value
Control Group	7.5 \pm 1.0	250 \pm 15	13.2 \pm 1.2	44.6 \pm 2.5	NS	N.S
Benzene-induced Group	18.4 \pm 2.1	150 \pm 20	9.4 \pm 0.8	32.7 \pm 3.0	4.88	0.05*
Pre-treatment						
<i>Azadirachta indica</i>	9.3 \pm 1.5	220 \pm 15	11.2 \pm 1.0	41.5 \pm 2.6	5.67	0.05*
<i>Psorospernum febrifugum</i>	8.1 \pm 1.3	210 \pm 18	12.1 \pm 1.1	42.0 \pm 2.4	4.50	0.05*
<i>Ricinus communis</i>	7.8 \pm 1.2	230 \pm 22	12.5 \pm 1.0	42.5 \pm 2.7	5.20	0.05*
<i>Rosy periwinkle</i>	8.6 \pm 1.1	215 \pm 20	12.0 \pm 1.2	43.1 \pm 2.8	4.75	0.05*
Post-treatment						
<i>Azadirachta indica</i>	9.8 \pm 1.5	240 \pm 25	13.0 \pm 1.0	43.8 \pm 3.1	6.40	0.05*
<i>Psorospernum febrifugum</i>	8.5 \pm 1.3	235 \pm 22	12.8 \pm 1.1	42.0 \pm 3.0	5.80	0.05*
<i>Ricinus communis</i>	9.2 \pm 1.3	245 \pm 25	13.2 \pm 1.0	43.5 \pm 3.5	6.10	0.05*
<i>Rosy periwinkle</i>	9.0 \pm 1.1	225 \pm 20	12.9 \pm 1.2	43.2 \pm 2.9	5.75	0.05*
5-Fluorouracil Group	17.1 \pm 2.2	155 \pm 18	9.8 \pm 1.0	34.2 \pm 2.9	5.40	0.05*

*significant at $p < 0.05$

Data represent the mean \pm SD for each group (n = 6 per group)

Table 2: Coagulation and Thrombotic Markers in Benzene-Induced Leukemic Rats

Group	PT (s)	PTT (s)	D-dimer (ng/mL)	Protein C (ng/mL)	Protein S (ng/mL)	F-value	p-value
Control Group	12.5 ± 1.2	35.6 ± 4.5	180 ± 10	120 ± 15	115 ± 10	NS	N.S
Benzene-induced Group	21.4 ± 2.5	50.1 ± 5.2	420 ± 30	60 ± 10	55 ± 7	6.20	0.05*
Pre-treatment							
<i>Azadirachta indica</i>	17.0 ± 2.1	45.3 ± 4.0	380 ± 25	90 ± 12	85 ± 10	5.50	0.05*
<i>Psorospernum febrifugum</i>	18.2 ± 2.4	48.0 ± 4.2	400 ± 35	85 ± 11	80 ± 8	5.60	0.05*
<i>Ricinus communis</i>	16.8 ± 2.0	44.1 ± 3.8	350 ± 20	95 ± 14	90 ± 11	5.80	0.05*
<i>Rosy periwinkle</i>	18.5 ± 2.3	47.2 ± 4.0	410 ± 30	80 ± 13	75 ± 9	5.40	0.05*
Post-treatment							
<i>Azadirachta indica</i>	15.5 ± 1.8	42.0 ± 3.5	320 ± 15	110 ± 12	100 ± 10	6.40	0.05*
<i>Psorospernum febrifugum</i>	16.0 ± 1.9	43.5 ± 3.6	330 ± 18	105 ± 11	95 ± 9	6.00	0.05*
<i>Ricinus communis</i>	15.2 ± 1.7	41.0 ± 3.3	310 ± 20	115 ± 13	110 ± 12	6.10	0.05*
<i>Rosy periwinkle</i>	16.5 ± 2.0	44.0 ± 4.0	340 ± 25	95 ± 10	90 ± 8	5.80	0.05*
5-Fluorouracil Group	17.8 ± 2.0	155 ± 20	330 ± 25	75 ± 12	70 ± 9	5.30	0.05*

*significant at $p < 0.05$

Data represent the mean ± SD for each group (n = 6 per group)

Table 3: Inflammatory Markers and CD10/CD20 Expression in Benzene-Induced Leukaemic Rats

Group	TNF-a (pg/mL)	Hs-CRP (mg/L)	CD10 (%)	CD20 (%)	F-value	p-value
Control Group	45.2 ± 5.5	8.5 ± 1.2	15.0 ± 1.5	12.5 ± 1.2	NS	N.S
Benzene-induced Group	120.4 ± 10.2	25.8 ± 2.5	65.0 ± 5.5	60.0 ± 5.0	7.00	0.05*
Pre-treatment						
<i>Azadirachta indica</i>	95.3 ± 8.7	19.4 ± 1.8	55.0 ± 4.5	50.0 ± 4.0	6.50	0.05*
<i>Psorospernum febrifugum</i>	105.2 ± 9.5	22.0 ± 2.0	60.0 ± 5.0	55.0 ± 4.5	6.80	0.05*
<i>Ricinus communis</i>	85.4 ± 7.8	16.5 ± 1.7	55.0 ± 5.0	50.0 ± 4.0	6.60	0.05*
<i>Rosy periwinkle</i>	110.5 ± 10.0	23.5 ± 2.1	60.0 ± 5.0	55.0 ± 5.0	6.90	0.05*
Post-treatment						
<i>Azadirachta indica</i>	60.2 ± 6.5	13.2 ± 1.4	40.0 ± 3.0	35.0 ± 3.0	7.20	0.05*
<i>Psorospernum febrifugum</i>	70.3 ± 7.2	15.0 ± 1.5	45.0 ± 4.5	40.0 ± 3.5	7.10	0.05*
<i>Ricinus communis</i>	55.1 ± 5.8	12.0 ± 1.2	40.0 ± 3.0	35.0 ± 3.0	7.00	0.05*
<i>Rosy periwinkle</i>	75.0 ± 8.0	17.0 ± 1.9	50.0 ± 4.0	45.0 ± 4.0	6.80	0.05*
5-Fluorouracil Group	70.2 ± 7.1	18.3 ± 1.8	55.0 ± 5.0	50.0 ± 4.2	6.40	0.05*

*significant at $p < 0.05$

Data represent the mean ± SD for each group (n = 6 per group)

Discussion

This study was set to explore the effect of some medicinal plant extracts on thrombotic and inflammatory markers in benzene-induced leukaemic Wistar rats to study their potential as adjunct therapies for leukemia. Pre-treatment with medicinal plants such as *Azadirachta indica*, *Psorospernum febrifugum*, *Ricinus communis*, and *Rosy periwinkle* showed the highest therapeutic effect in restoring haematological, thrombotic, and inflammatory parameters. These results may advocate for the use of these plants in alleviating complications associated with leukaemia.

The fascinating finding was the impressive restoration of platelet counts with plants against benzene-treated leukaemia rats, where drastically suppressed platelet levels following benzene induction were severely associated due to haematopoietic disruption of leukaemic cases (De Kouchkovsky & Abdul-Hay, 2016; Yadav *et al.*, 2023). Among the plants, *Azadirachta indica* showed much better treatment potential in restoring platelet counts, thus confirming the haematoprotective potential of the plant (Alvi *et al.*, 2020; Chibuike Ikwuka *et al.*, 2020). In contrast, coagulation parameters such as PT and PTT showed significant prolongation in benzene-induced rats, thereby confirming the occurrence of coagulopathy in leukemia (Wang *et al.*, 2020). Plant treatments, especially *Azadirachta indica*, restored these factors significantly, thereby implying that the extracts may interfere with the clotting pathways to restore hemostatic balance (Alzohairy, 2016; Abdallah *et al.*, 2022).

Increased D-dimer levels in benzene-induced rats become further evidence of hypercoagulability and active fibrinolysis (Hansen *et al.*, 2021). Treatment with *Azadirachta indica* and *Psorospernum febrifugum* significantly decreased the concentration of D-dimer, indicating an inhibition of conversion from fibrinogen to fibrin, thus reduced thrombotic activity, with the possible regulation of fibrinolysis (Sibai *et al.*, 2020; Anderson *et al.*, 2022). On the other hand, Protein C and Protein S levels were much lower in the benzene-induced group, such being a

hallmark of compromised natural anticoagulant system found in leukaemia (Dixit *et al.*, 2006; Klostermeier *et al.*, 2015). After treatment, all plant extracts increased the concentrations of Protein C and Protein S, with the largest rise recorded for *Azadirachta indica*. Medicinal plants, especially *Azadirachta indica*, may thus be involved in normalizing both natural anticoagulant systems and conversely decrease leukemic thrombosis (Furie & Furie, 2008; Al Saiqali *et al.*, 2018).

The anti-inflammatory activities of plants were demonstrated by significant reduction of serum TNF- α and Hs-CRP levels. However, cytokines of inflammation are key factors in tumor progression, with higher cytokine levels reflecting an adverse prognosis in leukemia (Balkwill, 2009; Brachford & Carpenter, 2018). Thus, the decreases in TNF- α and Hs-CRP by *Azadirachta indica* support the findings relating to its immunomodulatory activity (Chen *et al.*, 2022). The treatment, in contrast to control, also helped to restore leukaemia markers CD10 and CD20 exposed to leukaemic pathogenesis and prognosis (Mishra *et al.*, 2016). Thereby, modulation of these markers denotes that the plant extracts interrupted leukaemic transformation and reinstated immune homeostasis, as indicated along with other further pieces of evidence (Huang *et al.*, 2021; Mouliou, 2023).

Conclusion

This study has provided substantial evidence indicating that the treatment of *Azadirachta indica*, *Psorospernum febrifugum*, *Ricinus communis*, and *Rosy periwinkle* is relevant as therapeutics against thrombotic and inflammatory complications of leukaemia. The extracts of these plants have shown pronounced antithrombotic activity by raising platelet count levels significantly and normalizing PT, PTT, and D-dimer levels. However, it inhibited pro-inflammatory cytokine levels (TNF- α , Hs-CRP) and regulated leukaemia markers (CD10 and CD20), with the strongest response recorded from the *Azadirachta indica* treated group. These findings on the medicinal plants for the therapeutic management of leukaemia require mechanistic and clinical studies for proving their safety and efficacy on an actual human model.

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