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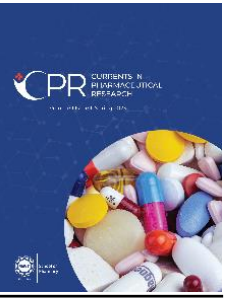

Title:	**Differential Hematopoietic Activities of Carica papaya Plant Parts: A Comparative Analysis of Erythropoietic, Leucopoietic, and Thrombopoietic Effects in Rabbits**
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Differential Hematopoietic Activities of Carica papaya Plant Parts: A Comparative Analysis of Erythropoietic, Leucopoietic, and Thrombopoietic Effects in Rabbits

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ABSTRACT

Carica papaya Linn. (Caricaceae) or commonly known as pawpaw and papaya, is extensively cultivated in tropical regions due to its nutritional and therapeutic properties. Recently, however, research into papaya leaves for its hematological effects as a thrombopoietic agent for infection-induced thrombocytopenia have gained traction. The use of papaya has been documented extensively in blood-related disorders. However, there is no comprehensive study available which evaluates the differential hematopoietic effects of its ripe fruit, seeds, unripe fruit, and leaves during prolong treatment periods. The current study addresses this critical literature gap by evaluating the hematological impact of these four distinct aerial parts. Healthy albino rabbits of both sexes were administered with aqueous preparations of four C. papaya parts over a two- month period in a controlled experimental study. Hematological assessments were performed during blood sample collection, analysis on day 11 during the acute phase and on day 61 of the subchronic phase to evaluate the erythropoietic, leucopoietic, and thrombopoietic effects was carried out. Complete Blood Count (CBC) parameters were analyzed to determine changes in Red Blood Cells (RBCs), White Blood Cells (WBCs), and platelet populations. Significant hematopoietic activity was observed across different C. papaya preparations. Unripe fruit and leaf extracts demonstrated notable broad-spectrum hematopoietic effects, enhancing multiple blood cell lineages. In contrast, ripe fruit and seed preparations exhibited selective activity, showing potent erythropoietic and thrombopoietic properties while demonstrating minimal leucopoietic potential. The differential effects were evident in both acute and subchronic treatment phases, suggesting time-dependent and part-specific bioactive mechanisms. Overall, these findings

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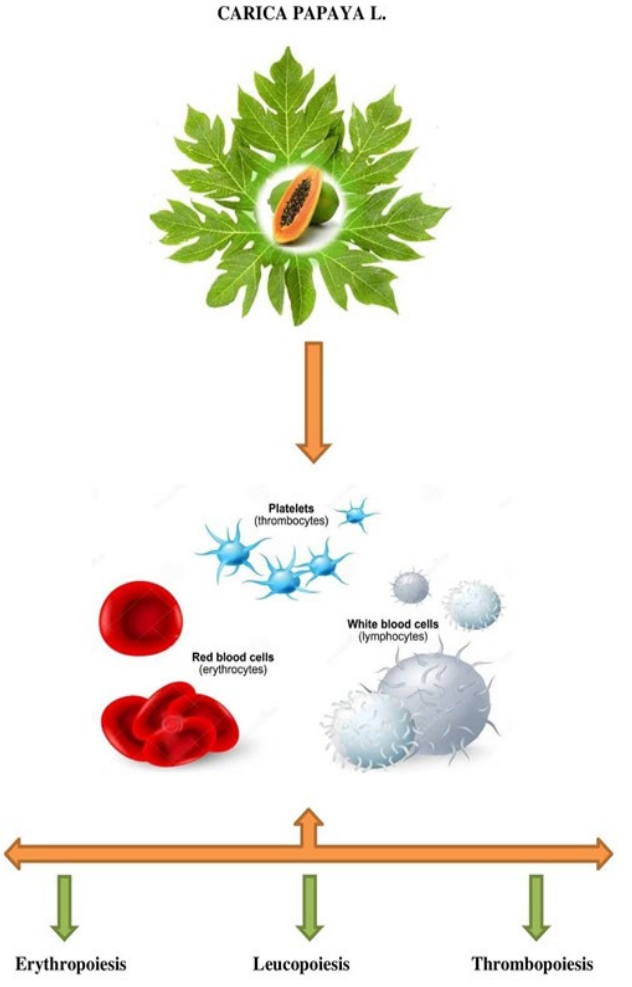
show the promising potential of C. papaya as a natural therapeutic application for anemic and thrombocytopenic conditions. Although the differential hematological effects observed across various plant parts may suggest distinct bioactive profiles which warrant future investigation. Furthermore, phytochemical characterization studies are needed to identify the active compounds responsible for the observed hematopoietic effects.

Keywords: anemia, erythropoiesis, leucopoiesis, leucopenia, natural remedy, thrombocytopenia, thrombopoiesis

GRAPHICAL ABSTRACT



1.INTRODUCTION

Hematologic disorders include a wide range of conditions that affect the synthesis, production, and function of blood cellular elements, such as Red Blood Cells (RBCs), White Blood Cells (WBCs), and platelets. Some of the most common and prevalent hematopoietic disorders include anemia, leukemia, lymphoma, myelodysplastic syndrome (MDS), thrombocytopenia, hemophilia, sickle cell disease, and aplastic anemia. The global burden of these conditions is significant with the World Health Organization (WHO) reporting that approximately 1.62 billion people, representing 24.8% of the world's population, were affected by anemia in 2013 [1]. Similarly, myelodysplastic syndromes present an emerging concern, with an estimated 10,000-20,000 new cases diagnosed worldwide in 2022 [2]. Thrombopoietic disorders, particularly thrombocytopenia and immune thrombocytopenic purpura (ITP), continue to affect thousands globally, highlighting the urgent need for effective therapeutic interventions.

1.1. Traditional Medicine and Natural Product Discovery

The search for novel therapeutic agents for hematologic disorders has increasingly turned toward natural products due to the fact that conventional drug discovery continues to rely on plant and herbal resources [3]. Traditional remedies have been utilized as standalone treatments over the centuries [4] for the management of blood-related conditions across various cultures, globally. These time-tested approaches often possess significant cultural and historical importance, utilizing natural compounds such as plant extracts that contain bioactive molecules with demonstrated therapeutic potential.

The accessibility and affordability of traditional remedies [5, 6] have established them as common therapeutic practices across various countries [7], with particularly widespread use documented in China, Japan, India, Pakistan, Thailand, and Sri Lanka [8, 9]. This global utilization pattern reflects both the efficacy and practical advantages of plant-based interventions in resource-diverse settings.

Natural products demonstrate remarkable pharmacological and therapeutic activities [10], with many edible vegetables, fruits, nuts, grains, and mushrooms exhibiting significant therapeutic effects against various health disorders [11]. Among these natural resources, Carica papaya Linn.

(family Caricaceae), commonly known as papita, pawpaw, or papaya has emerged as a plant of particular interest due to its documented anti-thrombotic effects, blood flow enhancement properties, and the capacity to stimulate platelet production [12].

1.2. Carica papaya: Botanical Characteristics and Global Cultivation

Carica papaya L. is a flowering plant species native to the tropical regions of Central America, now extensively cultivated in tropical and subtropical regions worldwide, including North America, various African countries (Angola, Chad, Democratic Republic of the Congo), and Asian nations (India, northern China) [13]. The widespread cultivation of papaya trees in tropical areas reflects their exceptional health benefits [12], distinctive nutritional composition, and biological advantages.

The papaya tree is characterized by its substantial size, reaching heights of approximately 17-34 feet. It has a single stem architecture and features large, spiral-shaped leaves with diameters of 66-72 cm, exhibiting palmate lobing with seven dominant lobes arranged around the trunk. The flower of this plant emerges from leaf axils and subsequently develops into the characteristic large, oval to pear-shaped fruit with a smooth, thin skin that transitions from greenish to yellow green, ultimately ripening to yellow, orange, or red coloration depending on the cultivar [14].

1.3. Traditional Uses and Phytochemical Properties

Traditional medicine systems utilize different parts of the papaya plant for distinct therapeutic purposes. The fruit is employed to enhance immunity and provide antibacterial and antioxidant benefits, while the pulp serves to manage acidic urine and rheumatic disorders. Papaya leaves are valued for their calming effects and utility in alleviating asthma symptoms, whereas the flower demonstrates efficacy in treating jaundice and managing hypertension [14].

The therapeutic potential of papaya is largely attributed to its rich phytochemical profile, particularly the presence of proteolytic enzymes papain and chymopapain (Fig. 1). These enzymes are widely utilized in the food industry as meat tenderizers and in cosmetic and pharmaceutical manufacturing [15]. They also facilitate protein degradation in the digestive system, thereby reducing flatulence, bloating, and constipation symptoms. Additionally, both papain and chymopapain possess anti-inflammatory properties that help alleviate the symptoms of chronic inflammatory

conditions, such as rheumatoid arthritis and sinusitis.

Papaya serves as an excellent source of essential nutrients including vitamins A, C, and E, folic acid, potassium, and dietary fiber. The high content of vitamin A and antioxidants, particularly beta-carotene, provides protection against harmful UV radiation and environmental pollutants, while promoting healthy skin cell growth and delaying the signs of aging. Beta-carotene and vitamin C work synergistically to protect against free radical damage, with vitamin C additionally supporting immune function through WBC production stimulation.

The substantial potassium and fiber content in papaya contributes to blood pressure regulation, cholesterol reduction, and cardiovascular risk mitigation. Furthermore, papaya fiber also promotes gastrointestinal health through enhanced bowel regularity and constipation prevention. Recent investigations suggest potential anti-cancer properties attributed to high concentrations of antioxidants including beta-carotene, lycopene, and flavonoids, which may prevent free radical formation and inhibit cancer cell growth and metastasis [16].

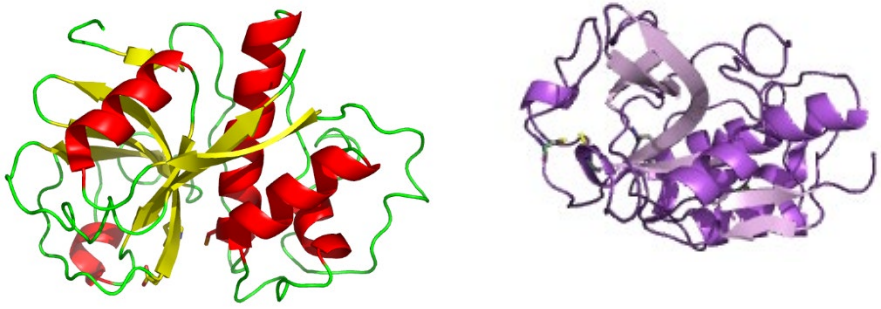


Figure 1. Papain and Chymopapain of Carica papaya Structures

1.4. Research Focus and Objectives

The growing scientific interest in papaya as a thrombopoietic agent, particularly for infection-induced thrombocytopenia, has prompted comprehensive investigation into its hematological effects. This study aims to evaluate the hematological impact of four distinct papaya parts, namely ripe fruit, ripe seeds, unripe fruit, and leaves, on blood cell counts as the evidence base for potential therapeutic applications in hematologic disorders.

2. MATERIALS AND METHODOLOGY

2.1. Plant Material and Authentication

All papaya plant materials utilized in this study were authenticated by Prof. Dr. Iqbal Azhar (Professor, Department of Pharmacognosy, Faculty of Pharmacy & Pharmaceutical Sciences, University of Karachi). Fresh mature papaya leaves (20-22 cm in length) were collected from the botanical garden of the University of Karachi. Ripe and unripe papaya fruits weighing 1.5-2.0 kg and measuring approximately 10-12 inches in length were procured from the Karachi fruit market during summer months to ensure optimal quality and consistency.

2.2. Preparation of Test Materials

2.2.1 Sample Processing and Standardization. All fruit samples underwent standardized washing procedures, including two washes with tap water followed by a final wash with deionized water. Fruit peels were carefully removed using sterile techniques to prevent contamination. All preparations were standardized to ensure a reproducible concentration and maintained under controlled storage conditions.

2.2.1.1. Aqueous Solution of Ripe Fruit (ASRF). Ripe fruit samples were homogenized with deionized water using a mixer and grinder (Braun, Model: MQ60). The mixture was further processed in a blender (Braun, Model: JB-1023) at 1000 rpm for 3 minutes to achieve complete homogenization. The final ASRF preparation was standardized to 100 mg/ml concentration, transferred to pre-sterilized glass bottles, and stored at 4°C until analysis [17]. Fresh ASRF was prepared every alternate day to maintain potency and prevent degradation.

2.2.1.2. Aqueous Solution of Unripe Fruit (ASURF). Unripe fruit preparations followed identical procedures to those described for ripe fruits, maintaining the same standardization protocols and storage conditions.

2.2.1.3. Aqueous Suspension of Ripe Seeds (ASRS). Seeds were carefully extracted from ripe fruits and thoroughly washed with deionized water. Following washing, seeds were air-dried at room temperature for 24 hours. The dried seeds underwent initial grinding using ceramic mortars and pestles, followed by mechanical grinding (Braun, Model: MQ60) and blending (Braun, Model: JB-1023) at 1000 rpm for 3 minutes to achieve complete homogenization. The resulting homogenate was transferred to

pre-sterilized glass bottles and stored appropriately [18]. Fresh ASRS was prepared on alternate days for dosing.

2.2.1.4. Aqueous Suspension of Mature Leaves (ASML). Fresh mature papaya leaves were subjected to standardized washing procedures (twice with tap water, followed by deionized water) and subsequently air-dried at room temperature for 24 hours. The dried leaves underwent initial grinding using ceramic mortars and pestles, followed by mechanical processing using a grinder (Braun, Model: MQ60) and blender (Braun, Model: JB-1023) at 1000 rpm for 3 minutes to achieve complete homogenization. Samples were transferred to pre-sterilized glass bottles and stored at 4°C until analysis[19]. Fresh ASML was prepared every alternate day for dosing [19].

2.3. Experimental Animals

2.3.1. Animal Selection and Housing. Adult albino rabbits of both sexes served as experimental subjects, with body weights ranging from 2.5 to 2.8 kg. The animals were obtained from the breeding facility of the Pharmacology Department, University of Karachi. All animals were housed under standardized environmental conditions with a controlled 12-hour light/dark cycle (08:15 AM to 08:15 PM light phase; 08:15 PM to 08:15 AM dark phase). Environmental parameters were maintained at 24 ± 2°C with relative humidity between 53-63%. The animals enjoyed *ad libitum* access to pure water and standard laboratory diet throughout the study period. All animal handling and care protocols adhered to National Research Council (NRC) guidelines [20].

2.3.2. Ethical Considerations. This study received ethical approval from the Advanced Studies and Research Board (ASRB), University of Karachi (ETHICAL APPROVAL: BASR/No./02145/Pharm). The research protocol strictly complied with internationally recognized standards for animal research and adhered to the 3Rs principle (replacement, reduction, and refinement). The ARRIVE (Animal Research: Reporting of *in vivo* Experiments) guidelines were implemented for reporting all experiments involving live animals, ensuring ethical research practices and scientific rigor.

2.3.3. Animal Welfare and Monitoring. Animal Welfare and Monitoring: All animals were monitored daily for their general health status, behavioral changes, and adverse effects throughout the 61-day study

period. Their body weight was recorded on a weekly basis to ensure normal growth patterns and detect any treatment-related effects. Animals showing signs of distress or abnormal behavior were individually assessed by veterinary staff. No significant body weight changes or adverse effects were observed during the study period, confirming the safety profile of all papaya preparations at the administered doses.

2.3.4. Experimental Design and Treatment Administration. A total of fifty (50) animals were randomly allocated into five groups of ten animals each. Group I served as the control group, while Groups II-V constituted the treatment groups. The study employed a randomized controlled design with a treatment duration of 60 days [21, 22]. All test materials were administered via oral gavage to ensure accurate dosing and minimize stress to the animals.

Table 1. Doses Administered per Group

	Dosing Material	Dose
Group I	Distilled water	2ml
Group II	ASRF	250mg/kg/day
Group III	ASRS	200mg/kg/day
Group IV	ASURF	250mg/kg/day
Group V	ASML	800mg/kg/day

2.3.5. Dose Selection Rationale. The doses were selected based on preliminary dose-finding studies and literature review. ASRF and ASURF were administered at 250 mg/kg/day based on previous efficacy studies showing optimal erythropoietic effects at this concentration. ASRS was administered at 200 mg/kg/day due to its higher potency and to prevent potential gastrointestinal irritation from seed extracts. ASML was administered at 800 mg/kg/day based on traditional usage patterns and previous safety studies, demonstrating tolerance at higher doses which is necessary to achieve therapeutic levels of the active compounds present in lower concentrations in leaf preparations.

2.4. Sample Collection and Processing

2.4.1. Blood Sample Collection. Blood samples were collected via marginal ear veins on days 11 and 61 of the treatment period to assess acute (short-term) and sub-chronic (long-term) hematological effects, respectively [22-24]. All blood samples were collected into EDTA-K3

anticoagulant tubes to prevent clotting and preserve cellular morphology. Samples were immediately stored at 4°C and processed within an appropriate timeframe to maintain sample integrity.

2.4.2. Hematological Analysis. Complete Blood Count (CBC) parameters, including hemoglobin concentration, RBC count, WBC count, and platelet count, were determined using an automated hematology analyzer (Humacount Plus, 3-part differential with histogram, Human Germany). This instrument provides standardized, reproducible results with built-in quality control measures.

2.5. Statistical Analysis

Data are expressed as mean ± standard deviation (SD) and analyzed using SPSS (version 20.0). One-way analysis of variance (ANOVA), followed by post-hoc Tukey's test, were employed to evaluate statistical significance between groups. All *p*-values of less than 0.05 were considered significant. Moreover, *p*-values $p<0.05$ *, $p<0.01$ **, and $p<0.001$ *** represented three levels of significance, namely significant, very significant, and highly significant differences in comparison to control, ASRF, ASRS, ASURF, and day 11^{th} of dosing, respectively.

3. RESULTS

3.1. Overview of Hematological Effects

The hematological impact of different papaya parts (ASRF, ASRS, ASURF, and ASML) was evaluated through a comprehensive analysis of hemoglobin concentration, RBC count, WBC count, and platelet count at two time points (day 11 and day 61). The results demonstrated distinct patterns of hematopoietic activity across different papaya components, with notable variations in temporal response patterns and cell-type specificity.

Statistical analysis using one-way ANOVA followed by post-hoc Tukey's test revealed significant improvements in most hematological parameters as compared to control groups. The effects of different papaya parts on hemoglobin, RBCs, WBCs, and platelet counts are presented in tables 2, 3, 4, and 5, respectively.

3.2. Hemoglobin Concentration Analysis

The analysis of hemoglobin concentrations revealed significant erythropoietic effects across all papaya preparations. ASRF demonstrated

the most pronounced effect, increasing hemoglobin levels from 8.33±0.46 g/dL (control) to 13.6±0.44 g/dL on day 11, representing a 63.2% increase. This superior performance was maintained relative to other treatments, with ASRF showing significantly higher hemoglobin levels as compared to ASRS, ASURF, and ASML on day 11.

Comparative analysis among treatment groups revealed that ASRF, ASURF, and ASML all produced significantly higher hemoglobin levels than ASRS after 11 days of treatment. However, this differential effect diminished by day 61, with all treatments showing similar hemoglobin-enhancing capabilities.

Temporal analysis indicated a significant decline in hemoglobin levels from day 11 to day 61 in both ASRF and ASML groups, while ASRS and ASURF maintained stable levels throughout the study period (Table 2).

Table 2. Effect of Different Parts of Carica papaya L. on Hemoglobin

	Hemoglobin (g/dL)	
	Day 11th	Day 61st
Control	8.33±0.46	8.49±0.46
ASRF	13.6±0.44***	10.55±0.36***
ASRS	10.28±0.73***	10.57±0.46***
ASURF	11.57±0.30***	11.3±1.27***
ASML	12.97±0.38***	11±0.36***

Note. *N*=10, Values are represented as Mean±S.D. All P-values of less than 0.05 were considered significant. However, *p*-values $p<0.05$ *, $p<0.01$ **, $p<0.001$ *** represent level of significance i.e., significant, very significant and highly significant differences in comparison to control, ASRF, ASRS, ASURF and day 11th of dosing respectively.

3.3. Red Blood Cell (RBC) Count Analysis

RBC count analysis corroborated the hemoglobin findings, with ASRF exhibiting the most substantial erythropoietic effect. The RBC count increased from 3.53±0.3 million/µL (control) to 6.52±0.22 million/µL on day 11, representing an 84.7% increase. This effect significantly exceeded that of all other papaya preparations.

Inter-group comparisons revealed that ASRF, ASURF, and ASML produced significantly higher RBC counts than ASRS after 11 days of treatment. By day 61, the differential effects among treatments had largely

equilibrated, with ASURF and ASML showing only marginally better results than ASRS.

Temporal analysis demonstrated a significant decline in RBC count for ASRF from day 11 to day 61, while ASRS, ASURF, and ASML maintained stable RBC counts throughout the study period (Table 3).

Table 3. Effect of Different Parts of Carica papaya L. on RBCs

	RBCs (million/µL)	
	Day 11th	Day 61st
Control	3.53±0.3	3.36±0.3
ASRF	6.52±0.22***	5.18±0.20***
ASRS	5.11±0.36***	5.05±0.13***
ASURF	5.51±0.30***	5.40±0.32***
ASML	5.71±0.34***	5.40±0.23***

Note. N=10, Values are represented as Mean±S.D. All p-values of less than 0.05 were considered significant. However, p values $p<0.05$, $p<0.01$ **, $p<0.001$ *** represent level of significance i.e., significant, very significant and highly significant differences in comparison to control, ASRF, ASRS, ASURF and day 11th of dosing respectively.

3.4. White Blood Cell (WBC) Count Analysis

WBC analysis revealed distinct leucopoietic patterns among papaya preparations. Notably, ASRF demonstrated a consistent leucopenic effect, significantly reducing WBC counts below control levels at both time points (day 11: 3.28±1.75 × 10^9/L; day 61: 3.31±1.66 × 10^9/L vs. control 4.39±1.99 and 4.48±0.3 × 10^9/L, respectively). In contrast, ASRS maintained WBC counts similar to control levels throughout the study period, showing no significant leucopoietic or leucopenic effects. ASURF and ASML demonstrated progressive leucopoietic activity, with both treatments producing significantly higher WBC counts than ASRF and ASRS at both time points. Temporal comparison revealed significant increases in WBC counts from day 11 to day 61 for both ASURF (5.10±2.13 to 6.05±1.45 × 10^9/L) and ASML (5.14±2.01 to 7.80±2.16 × 10^9/L), with ASML showing the most pronounced time-dependent enhancement. By day 61, ASML produced significantly higher WBC counts than all other treatments (Table 4).

Table 4. Effect of Different Parts of Carica papaya L. on WBCs

	WBCs ($10^{\wedge 9}$/L)	
	Day 11th	Day 61st
Control	4.39±1.99	4.48±0.3
ASRF	3.28±1.75***	3.31±1.66***
ASRS	4.33±2.51	4.42±2.11
ASURF	5.10±2.13*	6.05±1.45***
ASML	5.14±2.01*	7.80±2.16***

Note. *N*=10, Values are represented as Mean±S.D. All *p*-values of less than 0.05 were considered significant. However, *p*-values $p<0.05$ *, $p<0.01$ **, $p<0.001$ *** represent level of significance i.e., significant, very significant and highly significant differences in comparison to control, ASRF, ASRS, ASURF and day 11th of dosing respectively.

3.5. Platelet Count Analysis

Platelet count analysis revealed robust thrombopoietic effects across most papaya preparations, with ASML demonstrating exceptional activity. On day 11, ASML produced a significantly higher platelet count (4.28±1.49 × 10^11/L) as compared to all other treatments and controls, representing a 49.7% increase over control levels.

Table 5. Effect of Different Parts of Carica papaya L. on Platelet Count

	Platelet count ($10^{\wedge 11}$/L)	
	Day 11th	Day 61st
Control	2.86±0.67	2.94±0.27
ASRF	3.34±1.76***	4.53±1.69***
ASRS	3.65±1.65***	4.35±2.52***
ASURF	3.15±1.70	4.40±2.84***
ASML	4.28±1.49***	7.47±1.69***

Note. *N*=10, Values are represented as Mean±S.D. All *p*-values of less than 0.05 were considered significant. However, *p*-values $p<0.05$ *, $p<0.01$ **, $p<0.001$ *** represent level of significance i.e., significant, very significant and highly significant differences in comparison to control, ASRF, ASRS, ASURF and day 11th of dosing respectively.

The thrombopoietic effects were generally time-dependent, with all papaya preparations showing significantly enhanced platelet counts on day 61 as compared to day 11. ASML maintained its superior thrombopoietic

activity throughout the study, achieving a remarkable platelet count of 7.47±1.69 × 10^11/L on day 61, representing a 154.1% increase over control levels.

Notably, while ASRF, ASRS, and ASURF showed comparable thrombopoietic effects at both time points, ASML consistently outperformed all other treatments. The temporal enhancement pattern was observed across all groups, with significant increases from day 11 to day 61 for ASRF, ASRS, ASURF, and ASML (Table 5).

4.DISCUSSION

4.1. Rationale for Natural Hematopoietic Agents

The global interest in plant-derived therapeutics has increased dramatically, particularly for compounds capable of enhancing hematopoietic function and stimulating blood and immune system cellular components. Conventional therapies for improving blood cell counts present significant limitations, including high costs, parenteral administration requirements, and well-documented adverse effects. Consequently, there exists an urgent clinical need for safe, cost-effective, orally administered agents with demonstrated hematopoietic potential [25]. The current study addresses this need by investigating the hematological effects of different Carica papaya parts, contributing valuable evidence for potential therapeutic applications in hematologic disorders.

4.2. Erythropoietic Effects and Underlying Mechanisms

4.2.1. Hemoglobin and Red Blood Cell (RBC) Enhancement. Hemoglobin, a complex protein comprising heme and globin molecules synthesized in immature erythrocytes, serves the critical physiological function of oxygen transport throughout the body and also of carbon dioxide removal. Decreased RBC counts accompanied by reduced hemoglobin concentrations characterize anemic states, resulting in compromised oxygen delivery and consequent symptoms including weakness, confusion, fatigue, and diminished work performance [25]. Our investigation of papaya's erythropoietic properties across different plant parts, including ripe fruit, seeds, unripe fruit, and leaves, revealed significant therapeutic potential.

The results demonstrated that all examined papaya parts possessed the capacity to enhance hemoglobin and RBC counts at both acute (11 days) and subchronic (61 days) time points. Notably, ripe papaya fruit exhibited

the most pronounced erythropoietic activity during acute treatment phases, though this differential effect equilibrated across all parts following prolonged administration, suggesting similar long-term therapeutic potential among different papaya components.

4.2.2. Antioxidant-mediated Erythropoiesis. The observed erythropoietic effects align with the established literature regarding the antioxidant properties inherent in papaya parts. While antioxidant assays were not performed in this specific study, previous research indicated elevated free radical concentrations. Such concentrations and increased oxidative stress are known to promote hemolysis, while natural antioxidants demonstrate the capacity to reduce oxidative burden and prevent hemolytic processes [26]. Antioxidant-rich nutrition has been shown to promote hematopoiesis [27], providing a mechanistic foundation for the observed effects.

Comprehensive antioxidant activity has been documented across all four papaya parts including ripe fruit, seeds, unripe fruit, and leaves [28]. This antioxidant potential appears to be mediated by the flavonoid-rich composition of these plant components. Flavonoids, a polyphenol subclass, are responsible for numerous medicinal activities of natural products and function as antimicrobial, antioxidant, and anti-inflammatory agents. The substantial flavonoid content in papaya parts confers excellent free radical scavenging capacity and oxidative stress reduction capabilities [29].

4.2.3. Nutritional Components Supporting Erythropoiesis. The antioxidant properties of papaya parts are further enhanced by their distinctive nutritional profiles. The presence of vitamin A and vitamin C in fruits, vitamin C and vitamin E in leaves, and zinc in seeds significantly contributes to the antioxidant activity of these components [30-32]. These compounds (vitamin A, vitamin C, vitamin E, and zinc) are recognized as natural antioxidants with potent activity [33-35].

Beyond antioxidant protection, the nutritional composition of papaya fruit and seeds actively promotes erythropoiesis through iron supplementation. Both fruit and seeds represent rich iron sources, with iron playing a fundamental role in hemoglobin synthesis and RBC production stimulation. Multiple studies have confirmed iron presence in papaya fruit and seeds [31, 32], providing additional validation for the current findings regarding their strong erythropoietic potential and RBC stimulatory action.

4.3. Leucopoietic Effects and Immune System Modulation

4.3.1. Differential White Blood Cell (WBC) Responses. WBCs (leucocytes) serve as primary immune system components, functioning as frontline defenders against foreign invasions and infections [36]. This investigation of the leucopoietic activity of papaya parts revealed distinct response patterns among different plant components. Unripe fruit and leaves demonstrated the highest capacity for WBC count improvement at both acute and sub-chronic time points, while ripe fruit consistently decreased WBC counts throughout the study period. The seeds showed no significant effect on WBC parameters.

The leucocyte response patterns suggested distinct immunomodulatory mechanisms among papaya parts. The seeds demonstrated neither leucopenic nor leucopoietic effects, while ripe fruit decreased WBC counts as compared to controls. Importantly, these reductions remained within the normal acceptable ranges (normal rabbit WBC values: 2.6-12.7 × 10^9/L) [37], indicating that ripe fruit does not induce pathological leukocytopenia, rather lacks leucopoietic potential.

4.3.2. Immunomodulatory Mechanisms. The absence of leucopoietic effects in ripe fruit and seeds suggested that these components lacked the constituents responsible for WBC synthesis and production stimulation. However, this finding also indicates potential immune system stabilization through the prevention of foreign infections and inflammatory conditions. Inflammatory stimuli and foreign invasions typically result in leukocytosis (elevated WBC levels above normal ranges) [38]. The documented anti-inflammatory properties of ripe fruit and seeds [39] support their potential to inhibit inflammation-induced leukocytosis through inflammatory condition prevention.

Conversely, unripe fruit and papaya leaves demonstrated marked leucopoietic activity throughout the study period, indicating the presence of phytoconstituents capable of stimulating WBC synthesis. The differential leucopoietic activity between unripe and ripe fruit likely reflects their distinct nutritional compositions. Unripe fruit contains higher concentrations of calcium, phosphorus, magnesium, and ascorbic acid as compared to ripe fruit [40], potentially explaining the enhanced leucopoietic activity.

The leucopoietic activity of papaya leaves may be attributed to bone

marrow stimulation capabilities. Previous studies documented immune-stimulating effects of papaya leaves, with significant leucopoietic activity reported in 2013 and 2020 investigations [41, 42]. Importantly, no papaya part induced leukocytopenia in this study, suggesting the absence of immunosuppressive potential across all examined components.

4.4 Thrombopoietic Effects and Hemostatic Implications

4.4.1 Platelet Function and Clinical Significance. Platelets (thrombocytes) maintain hemostatic balance and play a crucial role in blood coagulation processes. Thrombocytosis refers to elevated platelet counts above normal ranges, while thrombocytopenia describes decreased counts leading to bleeding complications. Platelet counts below 50,000/mm³ in thrombocytopenic states represent frequent complications of various infections in both geriatric and pediatric populations. Current allopathic treatments for thrombocytopenia are expensive and associated with undesirable side effects [25].

The results demonstrated that all papaya parts including ripe fruit, seeds, unripe fruit, and leaves, possess the capacity to improve platelet counts at both acute and sub-chronic time points. The exception was unripe fruit, which showed no acute effects but significantly increased platelet counts following 61 days of treatment. Among all components, papaya leaves exhibited the highest thrombopoietic activity throughout the study period.

4.4.2. Mechanisms of Thrombopoietic Activity. The thrombopoietic potential of papaya leaves has been well-documented [43-46], with fresh leaves significantly improving blood platelet counts and demonstrating utility in thrombocytopenic patients. Clinical evidence supports the efficacy of papaya leaves in dengue-induced thrombocytopenia, where they significantly recover thrombocyte counts and prevent major dengue complications, particularly hemorrhage [47-49].

Thrombopoietic activity of papaya fruit has been attributed to papain, a major endopeptidase that includes caricain and chymopapain [50]. This enzyme induces thrombopoietic cytokine production by hematopoietic origin cells. Papain is present in high concentrations in ripe fruit, unripe fruit, leaves, and roots [51, 52], while the presence of caricain in papaya seeds has been confirmed [53]. The thrombopoietic activity observed in this study is consistent with previous findings attributing such effects to papain, chymopapain, and caricain content. Although cytokine profiling was

beyond the scope of this investigation, prior studies demonstrated that these enzymes can induce thrombopoietic cytokine production.

Additionally, the vitamin and mineral-rich composition of papaya parts may promote blood cell synthesis and healthy cell division, contributing to thrombopoietic effects. The comprehensive evidence presented supports strong thrombopoietic action across ripe fruit, seeds, unripe fruit, and leaves of papaya, establishing these components as potential therapeutic agents for thrombocytopenic conditions.

4.5. Clinical Implications and Future Directions

The differential hematopoietic profiles observed among papaya parts suggest targeted therapeutic applications. Ripe fruit and seeds demonstrate utility for erythropoietic disorders, while leaves show comprehensive hematopoietic activity with exceptional thrombopoietic potential. Unripe fruit and leaves may be particularly valuable for immune system enhancement through leucopoietic activity.

These findings support the development of standardized papaya-based preparations for specific hematologic indications, potentially offering cost-effective, accessible alternatives to conventional therapies. Future research should focus on clinical validation, optimal dosing regimens, and standardization protocols to facilitate therapeutic implementation.

4.6. Conclusion

To conclude, this study demonstrates that all examined parts of Carica papaya possess significant hematopoietic activity, with distinct therapeutic profiles that suggest targeted clinical applications. While ripe fruit and seeds exhibit exceptional erythropoietic and thrombopoietic activity but lack leucopoietic potential, unripe fruit and leaves demonstrate comprehensive hematopoietic effects across all blood cell lineages, with leaves showing particularly pronounced thrombopoietic activity. These differential hematological profiles indicate that specific papaya parts may serve as cost-effective, orally administered, natural therapeutic agents for distinct hematologic disorders: ripe fruit and seeds for anemic and thrombocytopenic conditions and unripe fruit and leaves for broader hematopoietic support including immune enhancement. Future investigations should focus on their phytochemical characterization to identify the specific bioactive constituents responsible for these hematopoietic effects, standardization of therapeutic preparations, and

comprehensive clinical evaluation of individual papaya parts in various disease-associated and drug-induced pancytopenic states to establish their clinical efficacy, optimal dosing regimens, and safety profiles for potential integration into modern therapeutic protocols. Additionally, clinical trials are warranted to establish optimal dosing regimens and safety profiles in human subjects, while mechanistic studies investigating the molecular pathways underlying the observed differential hematopoietic activities would provide valuable insights for targeted therapeutic development.

Author Contribution

Muhammad Osama: writing - original draft, investigation. **Rahila Ikram:** conceptualization, Supervision. **Calvin R. Wei:** writing-review & Editing. **Aisha Kamal:** writing -original draft

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

Data supporting the findings of this study will be made available by the corresponding author upon request.

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