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REVIEW ARTICLE

A Comparative Analysis of Effectiveness of Recombinant Interleukin-11 Versus Papaya Leaf Extract for Treatment of Thrombocytopenia: A Review

K. P. Mishra[1] · Jyotsana Bakshi[1] · Gitika Sharma[1] · Somnath Singh[1] · Usha Panjwani[1]

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Abstract Platelets or thrombocytes play an important role in thrombosis and maintaining hemostasis. Thrombocytes help in forming blood clots at the site of the wound. When the level of platelets decreases, uncontrolled bleeding occurs which can result in mortality. A decrease in the blood platelet level is known as thrombocytopenia which can be caused due to various reasons. A variety of treatment options are available for thrombocytopenia like platelet transfusion, splenectomy, platelet management with various types of corticosteroids, and recombinant interleukin-11 (rhIL-11). The use of rhIL-11 is approved by FDA for the treatment of thrombocytopenia. rhIL-11 is a recombinant cytokine that is administered to patients suffering from chemotherapy-induced thrombocytopenia as it enhances megakaryocytic proliferation which aids in platelet production. But this treatment has various side effects and is costly. Hence, there is a crucial need to identify cost-effective alternative strategies that present no side effects. The majority of the population in low-income countries requires a functional and cost-effective treatment for low thrombocyte count. *Carica papaya* is a tropical herbaceous plant that has been reported in recovering low platelet count during dengue virus infection. Even though multiple benefits of the *Carica papaya* leaf extract (CPLE) are popular, the active compound present in it, which mediates these benefits, remains to be identified. This review aims to highlight the different aspects of rhIL-11 and CPLE-induced platelet counts and their limitations and benefits in the treatment of thrombocytopenia. The literature related to the treatment of thrombocytopenia using rhIL-11 and CPLE from 1970 to 2022 was searched using PubMed and Google Scholar databases with the keywords Recombinant Interleukin-11, Papaya Leaf Extract, Thrombocytopenia, and Platelets.

Keywords Thrombocytes · Thrombocytopenia · Interleukin-11 · Papaya leaf extract · Hemostasis

Introduction

The thrombocytes (thrombo-clot; cyte-cell) or platelets are the smallest anucleated cells present in the blood, which play a crucial role in regulating various processes like clot formation, hemostasis, and repairing damaged blood vessels as well as wound healing. Platelets are derived from the differentiation of the megakaryocytes. A platelet count falling below the normal value i.e., 100,000 counts per cubic millimeters of blood is a hallmark of thrombocytopenia which can be caused due to various conditions like reduced production of platelet in the bone marrow, increased destruction of platelets in peripheral blood, sequestration of platelets in spleen and dilution [1, 2]. The reasons for decreased platelet production are numerous. A common reason is a dysfunctional state of the bone marrow which can arise due to multiple reasons like chemotherapy, anemia, or myelodysplasia. Whereas, increased destruction of thrombocytes is observed in patients suffering from medical conditions like Disseminated Intravascular Coagulation (DIC) [3]. The enlargement of the spleen or splenomegaly is the most common reason for thrombocyte sequestration. Different viral infections like dengue, varicella virus, and hepatitis C virus can also decrease platelet count [4]. There exist various treatments for controlling and reversing thrombocytopenia like temporary blood transfusions which rapidly increase the blood platelet

✉ K. P. Mishra
kpmpgi@rediffmail.com

[1] Defence Institute of Physiology and Allied Sciences, Delhi 110054, India

counts; another method involves the removal of the spleen in patients suffering from ITP as the immune cells destroy the circulating platelets [5], and certain types of steroids like dexamethasone and some immunoglobulins also help in reducing the destruction of platelet by self immune cells [6, 7]. Another type of treatment method for thrombocytopenia includes the use of rhIL-11 injections which are known to speed up platelet recovery and enhance the proliferation of megakaryocytic cells [8]. Therapeutic strategies like this are known to elicit side effects like liver dysfunctioning, increased reticulin staining of the bone marrow, conjunctiva infections, and arterial arrhythmia [9]. The population of some developing nations finds it difficult to meet up the cost of these expensive treatments hence alternative strategies are the need of the hour which present fewer side effects and are cost-effective. The use of *Carica papaya* to increase platelet count is reported in countries like India, Sri Lanka, and Myanmar, where Dengue viral infections are common and treatment options are restricted, they use papaya leaf extract as an alternative therapy to treat thrombocytopenia [10]. Around the globe, more than a hundred countries report cases of dengue viral infection every year [11]. Thrombocytopenia is one of the complications associated with dengue, leading to an increased mortality rate. Even though extensive research is going on to develop effective therapeutic strategies with nil side effects and cost-effectiveness, there exist few treatment options against dengue-induced thrombocytopenia, which has forced the researchers to explore alternative natural therapies for the same. The papaya leaves have been used throughout the world in the treatment of breakbone fever or dengue [10].*Carica papaya* leaf extract (CPLE) is known to possess hematological effects which are used to treat dengue infection. This article aims to make a comparative review of the use of papaya leaf extract and rhIL-11 for the treatment of thrombocytopenia. The use of papaya leaf extract has emerged as an alternative therapy that is cost-effective as well as presents fewer side effects for increasing the blood platelet count in patients suffering from thrombocytopenia.

Papaya

Carica papaya an angiosperm commonly belongs to the family Caricaceae. It is cultivated throughout the tropical world and in the warmest parts of the subtropic. The leaves of papaya are known to possess antioxidant, anti-cancer, anti-inflammatory, and immunomodulatory properties. Its leaves contain active components such as alkaloids, vitamins, glycosides, tannins, saponins, and flavonoids which possess various medicinal properties. Various parts of the papaya plant are used traditionally to treat digestive system disorders [12, 13], sickle cell anemia [14], management of the cardiovascular disease [15], and dengue fever [9, 16, 17]. There has been a long-standing interest in the use of papaya leaves for improving platelet counts, especially in dengue fever [9] or during chemotherapeutic cancer treatment. The most important finding on the efficacy of papaya leaves is their use in thrombocytopenia (low platelet count) management during dengue. At present, there is insufficient data available for the safety and toxicity parameters related to the consumption of papaya leaves. A study aimed at determining the acute and chronic toxicity of the CPLE on SD rats revealed that it is deemed safe for oral consumption [18]. A study was conducted to test whether the fresh leaf extract of the *Carica papaya* plant was able to increase the platelet count in a murine model. They reported that oral feeding of extract of papaya leaves caused a considerable increase in platelets, as well as red and white blood cell count in the murine model without causing any acute toxicity [19].

Chemotherapy-induced thrombocytopenia (CIT) is one of the major pathophysiological conditions observed in patients undergoing chemotherapy as a treatment for cancer. The treatment of cancer with various chemotherapeutic drugs like cyclophosphamide or temozolomide leads to decreased platelet count [20]. A condition like CIT can elevate the chances of hemorrhagic complications as well as the requirement for platelet transfusion which can compromise the outcomes of the treatment. The limitations associated with platelet transfusion like the risk of infection, high cost, and limited supply increase the demand to develop and evaluate alternative strategies to treat thrombocytopenia. A study reported the effect of CPLE in reversing the chemotherapy-induced thrombocytopenia in glioblastoma multiforme patients. A cancer patient undergoing temozolomide therapy manifested chemotherapy-induced thrombocytopenia which was successfully treated with regular treatment of CPLE [21]. A study also reported that CPLE was able to mitigate thrombocytopenia induced by the chemotherapeutic drug cyclophosphamide in rats by enhancing the expression of a receptor CD110 on platelet precursor cells [22]. It was reported in a study that CPLE was able to reverse the decrease in platelet count as well as WBCs count in a carboplatin-induced myelosuppressive mouse model [23].

A severe form of dengue is known to cause thrombocytopenia which is caused due to loss of platelet progenitor cells production and maturation along with the suppression of bone marrow [24].The role of CPLE in treating dengue-induced thrombocytopenia has been mentioned in Indian traditional folk medicine [22]. A large number of clinical and pre-clinical studies have also reported the ability of papaya leaf decoction to increase platelet count [25–28]. A study conducted by Sathyapalan et al. [29], demonstrated that the administration of 1100 mg of CPLE in patients suffering from dengue-induced severe thrombocytopenia improved the platelet count significantly. Subenthiran et al.

[9] also reported the use of CPLE on 28 dengue viral infection patients. He reported that the use of *Carica Papaya* Leaf Juice (CPLJ) prepared from 50 gm of papaya leaves in patients for 3 consecutive days greatly increased the count of platelets in comparison to the control group [30]. A preliminary study was performed by Kala et al., to test the potential of papaya leaf extract in increasing the platelet count in patients suffering from dengue fever. He extracted the fresh juice from papaya leaves and administered two tablespoons to each patient thrice a day. He observed that only after 24 h the platelet count increased by approximately 11,000 per microliter [31]. Moreover, another study reported the direct effect of freshly prepared CPLE on platelet-rich and platelet poor plasma isolated from dengue virus infected and healthy individuals respectively. They observed that the incubation of CPLE with dengue infected plasma when added to platelet rich plasma causes a significant decrease in platelet aggregation, whereas no change in platelet aggregation was observed when control plasma was added to the same. These results strongly suggested that CPLE conforms direct platelet protection specific to dengue virus infection by preventing platelet aggregation [32]. Saraf et al. tested the effect of papaya leaf extracts prepared in acetone, methanol, n-hexane and ethanol on male Sprague Dawley rats. The rats were given carboplatin to induce thrombocytopenia after which the papaya leaf extracts prepared in different solvents were given orally to the rats. They observed that the number of platelets increased in treatment with papaya leaf extract prepared in all solvents with no visible toxic effects. The study concluded that papaya leaf extract exerts its effect irrespective of the solvent in which the extract is prepared [33]. Another animal study aimed to evaluate the effect of oral administration of CPLE on female Wistar rats given cyclophosphamide to induce thrombocytopenia has reported similar observations. They reported that the level of platelet count increased from 408.5×10^3 cells/mm^3 on day 3rd to 1014.83×10^3 cells/mm^3 on the 15th day, suggesting a positive role of CPLE in normalising the low platelet count [30]. A study conducted to test the effect of CPLE in children upto the age of 16 years suffering from dengue fever having a platelet count < 1,50,000/uL, reported that a significant increase was observed in individuals given CPLE (1100 mg) in the form of tablet in comparison to control group [34]. A study was conducted by Sharma et al. on the evaluation of the anti-dengue activity of *Carica papaya* aqueous leaf extract and its role in platelet augmentation. This study concluded that papaya leaf extract decreases the expression of NS1 and Envelope protein in Dengue virus-infected THP-1 cells and thus reported it as an antiviral agent. It also increased platelet counts in the drug-induced thrombocytopenic rat models by increasing IL-6 and thrombopoietin [17]. A number of clinical trials have also analysed the effect of Caripill, a tablet prepared from CPLE in increasing the platelet count rapidly with minimum side effects [25, 35, 36]. Kasture et al. reported the effect of Caripill in a group of patients reported to be suffering from dengue fever induced thrombocytopenia. The 5 day treatment with Caripill significantly enhanced the platelet count in the patients [25, 35]. A similar study reported that patients suffering from dengue hemorrhagic fever receiving Caripill syrup thrice a day for 5 days reported a consistent increase in total platelet counts with a significant increase in WBC counts also [36].

Mechanism of Action of *Carica papaya* Leaf Extract

We have reviewed several papers and found that CPLE increases cytokines such as IL-6, stem cell factor (SCF), and thrombopoietin which could be responsible for enhanced thrombocyte counts [17, 30]. The potential benefits of CPLE as a method of increasing platelet count deserve further investigation, especially as a treatment option for those who are not suited for other thrombocytopenia therapies. The CPLE was reported to possess alkaloids and polyphenolic compounds which may be responsible for increasing platelet counts [17, 30]. Another study used the qTOF technique to conclude that the leaves of the papaya plants contain beneficial phytochemicals like kaempferol, palmitic amide, luteolin, and carpaine which are known to possess antioxidant and free radical scavenging properties which aid in increasing thrombocytes [37, 38]. Zunjar et al. aimed at identifying the active compounds present in CPLE responsible for increasing the platelet counts in the murine model of thrombocytopenia induced by busulfan [38]. They attributed the anti-thrombocytopenic activity of papaya leaf extract to the alkaloid carpaine which is majorly present in the papaya plant. The genes responsible for regulating the production of platelets as well as the aggregation of platelets are Arachidonate 12-lipoxygenase (ALOX12) and Platelet Activating Factor Receptor (PTAFR) (Fig. 1). The platelet progenitor cells megakaryocytes express ALOX12 and PTAFR genes whose expression increases during platelet production [39–41]. Subenthiran et al. observed that treatment of patients with papaya juice extracted from 50 g of leaves for 7 days resulted in a 15-fold increase in ALOX12 gene expression in the control group. Similarly, there was 13 fold increase in PTAFR after consumption of papaya leaf juice [9]. Another study reported that the CPLE is rich in flavonoids which are known to repress NS2B-NS3 proteins involved in the assembly of the dengue virus inside the cell, thereby decreasing the viral load and the Dengue virus-induced thrombocytopenia was thus prevented [42]. Furthermore, some reports suggest that CPLE possesses certain compounds which have the property to maintain the stability of cell membrane and prevent the lysis of thrombocytes [43].

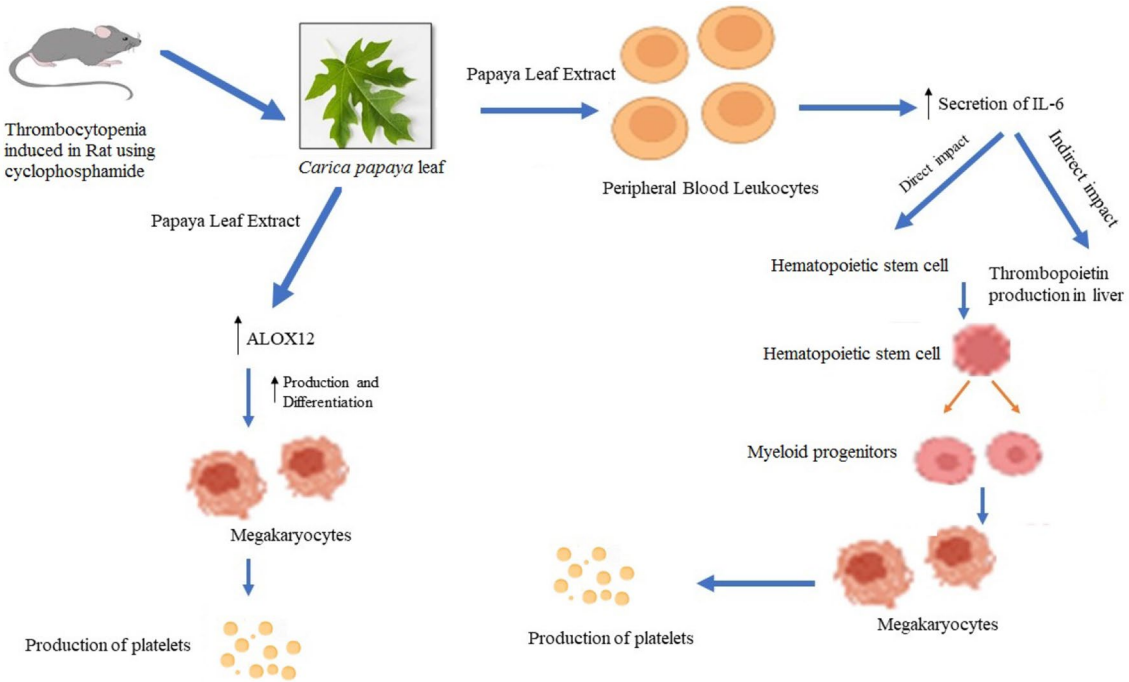

Fig. 1 Mechanism of CPLE-induced thrombocyte (platelet) counts

Recombinant Human Interleukin-11

Interleukin-11 also known as adipogenesis inhibitory factor is a secreted thrombopoietin cytokine that was first reported in the year 1990 in stromal cells derived from bone marrow. The secreted IL-11 binds to its membrane-bound receptor IL-11Rα, this interaction regulates the activation of various signaling pathways involved in the process of maturation of platelets, neuronal cells, adipocytes, and osteoclasts. The rhIL-11 is a multifunctional growth factor that is clinically proven to enhance megakaryocytic proliferation and maturation which leads to an increase in the number of platelets specifically in patients undergoing chemotherapy [8, 38]. The use of rhIL-11 was approved by the Food and Drug Administration in 1997 to cure decreased platelet count in CIT patients [44]. The effectiveness of rhIL-11 in increasing the platelet count of patients undergoing treatment for dengue fever has been reported by multiple studies and clinical trials. Suliman et al. [45] reported that the use of 1.5 mg of rhIL-11 subcutaneously in patients suffering from dengue fever induced thrombocytopenia revealed a 50% increase in platelet count in comparison to control group. It has been reported that the use of rhIL-11 in patients undergoing chemotherapy results in an increase in total platelet count alongside a reduction in the requirement of platelet transfusion in these patients [46]. A similar study in sepsis patients reported that the group treated with rhIL-11 was able to recover platelet loss much more quickly than the control group thereby decreasing the rate of mortality in patients going through thrombocytopenia and sepsis together [47, 48]. A study from phase 1 clinical trials for the rhIL-11 drug neumega in breast cancer patients receiving chemotherapeutic drug cyclophosphamide and doxorubicin, revealed that a subcutaneous injection of neumega for 28 days increased the platelet count by 76%, thus decreasing the chances of CIT [49]. Tepler et al. conducted a randomized human trial of rhIL-11 on 93 patients suffering from CIT receiving platelet transfusion. He observed that rhIL-11 at a dose of 50 µg/kg was able to combat CIT [50].

The risk associated with the use of rhIL-11 is not negligible as it presents some side effects besides having a very narrow therapeutic index, which limits the use of rhIl-11 as a sole treatment of thrombocytopenia [8, 51]. A summary of a comparative analysis of the efficacy of rhIL-11 and CPLE for enhancing platelet counts is given in Table 1.

Mechanism of Action of rhIL-11

rhIL-11directly stimulates the proliferation of hematopoietic stem cells and megakaryocytic progenitor cells, by interacting with the transmembrane interleukin receptor (Fig. 2). It decreases the G0 period which leads to the activation of the proliferation phase in the cell cycle and this leads to an increase in the number of platelets [52]. These effects include megakaryocytic maturation,

Table 1 A comparative analysis of the efficacy of recombinant interleukin-11 (rhIL-11) and papaya leaf extract (CPLE) for thrombocytopenia

	Disease	Dosage	Form	Frequency of dose administered	Increase in Platelets	References
Recombinant interleukin-11 (rhIL-11)						
Adults dose	Dengue fever	1.5 mg	Subcutaneously	Once	˃ or = 20,000/μL	[45]
Adults dose	Chemotherapy induced thrombocytopenia	50 μg/kg	Subcutaneously	Once Daily	˃ or = 50,000/μL	[54]
Pediatric dose	Chemotherapy induced thrombocytopenia	75 μg/kg	Subcutaneously	Once Daily	˃ or = 50,000/μL	[54]
Carica papaya leaf extract (CPLE)						
Adults dose	Dengue fever	25 mL aqueous CPLE	Oral route	Twice daily for 5 consecutive days	From 55 to 168×10^3/ml	[55]
Children's dose						
Aged between 1 and 5 years	Dengue fever	275 mgCPLE	Oral route	Three times daily for 5 days	From 89,739.31/μL to 168,922.75/μL	[36]
Above 5 years	Dengue fever	550 mg CPLE	Oral route	Three times daily for 5 days	From 89,739.31/μL to 168,922.75/μL	[36]
Adult	Chemotherapy induced thrombocytopenia	1100 mg CPLE	Oral route	Three times daily for 2 weeks	> 149,320 cu/mm	[56]

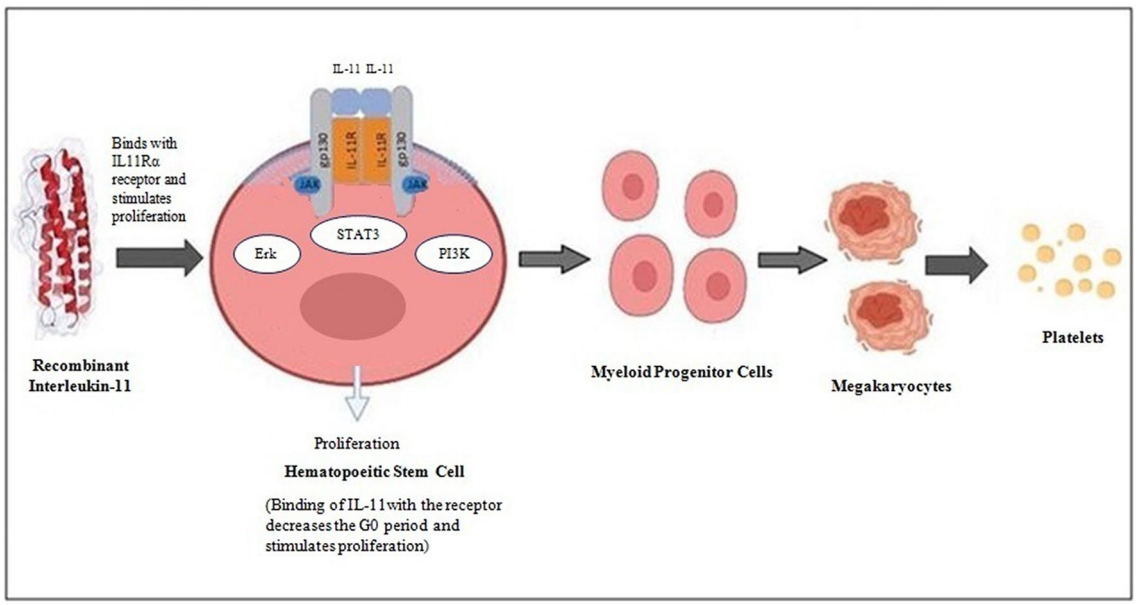

Fig. 2 Mechanism of thrombocyte enhancement by rhIL-11

resulting in increased platelet production. Platelets thus produced in response to rhIL-11 are morphologically and functionally normal and possess a normal life span. It is currently approved by FDA. rhIL-11 is not widely used because of its adverse effects, such as dilution anemia, fluid retention, congestive heart failure, arrhythmias, and anaphylaxis. A comparative analysis of the mechanism for enhancement of platelets by rhIL-11 and CPLE has been given in Table 2.

Conclusion

Based on the available literature, it can be concluded that both CPLE and rhIL-11 have their benefits and limitations in the treatment of thrombocytopenia. In developing countries, where most of the population remains in middle or low-income groups, they require efficient and cost-effective treatment of low thrombocyte count. Hence, CPLE emerges as an alternative therapy for the same which has fewer side effects

Table 2 A comparative analysis of the mechanism for enhancement of platelets by recombinant interleukin-11 (rhIL-11) and CPLE

Mechanism of rhIL-11	Mechanism of CPLE	References
IL-11 binds to the IL-11Rα receptor expressed in hematopoietic stem cells and this leads to a cascade of signal transduction events. This stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells which leads to the production of platelets	CPLE increases the secretion of IL-6 and IL-6 increases platelet count directly by stimulating the proliferation of hematopoietic progenitors and indirectly by its action on thrombopoietin production in liver cells	[17, 57, 58]
IL-11 acts synergistically with IL-3 and TPO and stimulates the proliferation of megakaryocyte progenitors by shortening the G0 period and thus resulting in increased platelet production	CPLE activates ALOX 12 and PTAFR genes and this leads to platelet production	[20, 52, 57]
IL-11 stimulates $CD34^+$ cell differentiation into megakaryocytes and this causes the production of platelets	CPLE increases platelet count in Chemotherapy-induced thrombocytopenia by increasing the expression of the CD110 receptor on megakaryocytes	[22, 59]

and is cost-effective as well [35]. On the other hand, the side effects of rhIL-11 cannot be ignored [53]. The use of CPLE is safe and non-toxic for short-term purposes, though people with liver disorders and pregnancy are advised to avoid its use. Thus, CPLE could be an effective therapeutic strategy for the management of thrombocytopenia cases. There is a need to identify the active compounds in papaya leaf which are responsible for increasing platelet count and thus can be developed in the form of an affordable pharmaceutical drug.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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