INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD)
© 2026 IJNRD | Volume 11, Issue 5, May 2026 | ISSN: 2456-4184 | IJNRD.ORG

A Review on Platelet Enhancement in Thrombocytopenia

Varsharani B. Patil[1] , Ayush N. Badade[2] , Deepak P. Misal[3] , Datta V. Avchar[4] , Anurag S. Sanap[5]

[1]Department Of Chemistry, Abhinav Education Society's College Of Pharmacy, Narhe,Pune.

[2,3,4,5]Student of Bachelor of Pharmacy, Abhinav Education Society's College of Pharmacy, Narhe, Pune.

Address for Correspondence:

Varsharani Patil

AES College Of Pharmacy, Narhe , Pune 411041

Abstract

Platelet enhancers, also known as thrombopoietic agents or thrombopoiesis stimulating compounds represent a diverse group of pharmaceutical drugs, biologics, nutritional supplements, and natural substances that increase platelet production, reduce platelet destruction, or improve platelet function. They are used in conditions such as immune thrombocytopenia (ITP), chemotherapy-induced thrombocytopenia, chronic liver disease–associated thrombocytopenia, aplastic anemia, and viral-associated thrombocytopenia. Understanding platelet enhancers requires knowledge of the underlying mechanisms of thrombopoiesis, including the role of thrombopoietin (TPO), megakaryocyte maturation, immune-mediated platelet clearance, and bone marrow microenvironment dynamics. Modern therapeutic advances particularly TPO receptor agonists (TPO-RAs) like romiplostim and eltrombopag have transformed the management of chronic thrombocytopenia, while research continues into small molecules, gene therapy, and nutraceuticals. This review aims to provide a comprehensive evaluation of platelet enhancers, including their mechanisms of action, clinical applications, evidence from trials, limitations, adverse effects, and future perspectives.

Keywords: Thrombocytopenia, Platelet Enhancers, Thrombopoiesis, Thrombopoietin (TPO), TPO Receptor Agonists (TPO-RAs), Romiplostim, Eltrombopag, Megakaryocyte Maturation, Immune Thrombocytopenia (ITP), Chemotherapy-Induced Thrombocytopenia (CIT), Chronic Liver Disease Associated Thrombocytopenia, Bone Marrow Suppression, Platelet Destruction Mechanisms, Papaya Leaf Extract, Curcumin, Nutraceuticals & Micronutrients, IVIG (Intravenous Immunoglobulin), Splenectomy, Adverse Effects (Thrombosis, Hepatotoxicity, Fibrosis), Future Therapies.

Introduction

Thrombocytopenia, a condition marked by a low platelet count can lead to increased risk of bleeding, bruising, and even major hemorrhagic events in severe cases [(4)]. Platelets play a pivotal role in hemostasis, vascular integrity, and repair; thus, ensuring adequate platelet numbers and function is a key aspect of managing many hematologic and non- hematologic disorders. The development and use of agents that enhance platelet production or function broadly termed platelet enhancers is an evolving field with significant clinical relevance. Historically, treatment of thrombocytopenia has focused on reducing platelet destruction (for example, via immunosuppression) or replacing platelets via transfusion. However, it is now well recognised that in many disorders (such as immune thrombocytopenia) impaired platelet production by megakaryocytes is a substantial contributor. This shift in understanding has spurred interest in therapies that stimulate thrombopoiesis, i.e., the production of platelets [(2)(4).]

Central to platelet production is the hormone thrombopoiesis, regulated chiefly by the cytokine Thrombopoietin (TPO) and its receptor (MPL) on megakaryocytes and hematopoietic stem cells. Early research identified TPO as the primary physiological regulator of platelet production [(1)(3)]. More recently, receptor-agonist therapies, growth factors, and even natural/nutraceutical-based approaches to enhancing platelet production have moved from concept to clinic or are under investigation [(5)(2)].

In the context of platelet enhancers, the objective of this review is to comprehensively examine the mechanisms of platelet production and thrombocytopenia, categorise the available and investigational platelet-enhancing agents, assess clinical evidence and safety, and explore future directions. By doing so, clinicians and researchers

can better understand how to integrate platelet enhancers into therapeutic algorithms and identify gaps for further investigation.

Physiology of Platelet Production

Platelet production, or thrombopoiesis, is a tightly regulated multistep process involving hematopoietic stem cells (HSCs), megakaryocyte (MK) lineage differentiation, maturation, and platelet release into the bloodstream. This process occurs primarily in the bone marrow but is also influenced by systemic hormones, cytokines, and bone-marrow niche interactions [13].

3.1 Hematopoiesis and Megakaryocyte Differentiation

Platelets arise from multipotent hematopoietic stem cells, which differentiate into common myeloid progenitors and subsequently into megakaryocyte–erythroid progenitors (MEPs). These cells differentiate into megakaryoblasts, and with progressive DNA replication without cell division (a process called endomitosis), they become large, polyploid megakaryocytes capable of producing thousands of platelets each [12].

Megakaryocyte differentiation is regulated by transcription factors including GATA-1, FOG-1, NF-E2, and RUNX1, which govern lineage commitment and cytoplasmic maturation. Dysregulation of these transcription factors is implicated in inherited and acquired thrombocytopenias [7].

Table 1. Stages of Megakaryocyte Development[12][13]

Stage	Key characteristics	Functional Notes
Hematopoietic stem cell	Multipotent, Self-renewing	Gives rise to all blood lineages
Megakaryocyte-erythroid progenitor (MEP)	Committed precursor	Shared lineage with erythrocyte
Megakaryoblast	Start of MK lineage	No granules, beginning of Endomitosis
Promegakaryocyte	Early cytoplasmic maturation	Granule Formation begins
Mature megakaryocyte	Highly polyploid, large cytoplasm	Produces platelets via proplatelets

3.2 Role of Thrombopoietin (TPO) and the TPO Receptor (c-Mpl)

Thrombopoietin (TPO) is the master regulator of megakaryocyte proliferation, maturation, and platelet production. It is produced mainly in the liver, with smaller contributions from the kidney and bone marrow stroma [9].

TPO binds to its specific receptor c-Mpl, expressed on HSCs and megakaryocytes, activating the JAK–STAT, PI3K–AKT, and MAPK signaling pathways to stimulate thrombopoiesis [10].

TPO levels are inversely related to circulating platelet mass because platelets and megakaryocytes bind and clear TPO. Thus, in thrombocytopenia, free TPO rises, promoting increased platelet production [8]. Conversely, in states of thrombocytosis, TPO availability decreases.

Table 2. Key Signaling Pathways Activated by TPO[9][10]

Pathway	Function in Thrombopoiesis
JAK-STAT	MK survival, proliferation, Gene Transcription
PI3K-AKT	Anti-apoptotic signals, cytoplasmic maturation
MAPK	Endomitosis, MK differentiation

3.3 Regulation of Platelet Life Cycle

Platelets have a lifespan of 7–10 days in circulation. Their life cycle is regulated by:

a. Production Rate

Platelet count is controlled by feedback loops involving TPO levels, bone marrow activity, and systemic inflammatory signals. Interleukins such as IL-6 can upregulate TPO production during infection or inflammation [(14)].

b. Destruction and Clearance

Platelet senescence is associated with desialylation, exposure of galactose residues, and hepatic clearance via the Ashwell–Morell receptor system [(11)]. Apoptotic markers such as phosphatidylserine also lead to macrophage-mediated clearance.

c. Splenic Sequestration

Approximately 30% of platelets are stored in the spleen. Splenomegaly can shift a larger proportion of platelets to the spleen, contributing to thrombocytopenia [(6)].

d. Bone Marrow Microenvironment

Bone marrow stromal cells, extracellular matrix proteins, and biomechanical forces guide megakaryocyte migration toward blood vessels, proplatelet elongation, and platelet shedding [(13)].

Pathophysiology of Thrombocytopenia

Thrombocytopenia is defined as a platelet count below 150 × 10^9/L and results from abnormalities in platelet production, platelet destruction, splenic sequestration, or a combination of these mechanisms. Understanding the underlying pathophysiological processes is essential for selecting appropriate platelet-enhancing therapies. Different clinical forms of thrombocytopenia vary widely in their mechanisms, severity, and therapeutic responses [(19)].

4.1 Decreased Platelet Production

Decreased platelet production occurs when the bone marrow fails to produce adequate megakaryocytes or functional platelets. This is commonly due to bone marrow suppression, infiltration, congenital defects, or impaired megakaryopoiesis.

a. Bone Marrow Suppression and Aplasia

Chemotherapy, radiation, toxins (e.g., benzene), HIV infection, and aplastic anemia reduce hematopoietic stem cell reserves, impairing megakaryocyte development. In these states, thrombocytopenia coexists with anemia and leukopenia, reflecting generalized marrow failure [(21)].

b. Bone Marrow Infiltration

Malignancies such as leukemia, lymphoma, and metastatic cancers replace normal marrow elements, reducing megakaryocyte numbers. Fibrosis (e.g., myelofibrosis) also impairs megakaryocyte maturation [(20)].

c. Defective Megakaryocyte Maturation

Certain viral infections (e.g., dengue virus), nutritional deficiencies (vitamin B12, folate), and congenital genetic defects (MYH9 mutations) disrupt megakaryocyte maturation and lead to reduced platelet production [(10)]

Table 3. Causes of Decreased Platelet Production[(21)(20)(10)]

Cause	Mechanism	Examples
Stem cell suppresion	Reduced hematopoiesis	Chemotherapy, aplastic anemia
Marrow infiltration	Replacement of normal tissue	Leukemia, lymphoma, metasis
Fibrosis	Megakaryocyte trapping	Myelofibrosis
Maturation defects	Ineffective thrombopoiesis	B12 defiency, congenital disorders

4.2 Increased Platelet Destruction

Pathologic platelet destruction may be immune-mediated or non-immune, leading to shortened platelet lifespan despite normal or increased marrow production.

a. Immune-Mediated Destruction

Autoantibodies (typically IgG) target platelet antigens, leading to macrophage-mediated clearance in the spleen. Classic examples include immune thrombocytopenia (ITP) and drug-induced immune thrombocytopenia [15]. In ITP, impaired megakaryopoiesis contributes as well, meaning platelet destruction and production defects coexist.

b. Alloimmune Destruction

Occurs in neonatal alloimmune thrombocytopenia or post-transfusion purpura. Maternal or transfusion-derived antibodies cross-react with host platelet antigens [18].

c. Non-Immune Destruction

Disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), and mechanical shear stress (prosthetic valves) lead to accelerated consumption and fragmentation of platelets [17]

Table 4. Mechanisms of Increased Platelet Destruction[15][17]

Category	Mechanism	Example
Immune-mediated	Autoantibody opsonization → splenic clearance	ITP, DITP
Alloimmune	Maternal/alloantibodies	Neonatal alloimmune thrombocytopenia
Consumption	Platelets consumed in clots	DIC, TTP
Mechanical	Shear stress → fragmentation	Prosthetic valves

4.3 Splenic Sequestration

Approximately one-third of platelets normally reside in the spleen. Splenomegaly caused by portal hypertension, infections (e.g., malaria), or hematologic disorders increases sequestration to as much as 80–90% of total platelets, dramatically reducing circulating platelet counts. [6]

In these cases, platelet production may be normal or increased, but effective circulating platelets remain low.

4.4 Multifactorial Thrombocytopenia

Many clinical conditions involve combinations of production defects, destruction, and sequestration.

Examples include:

- Chronic liver disease: reduced TPO, splenic sequestration, decreased marrow function
- Sepsis: cytokine-driven consumption + marrow suppression
- Viral infections (e.g., dengue, COVID-19): marrow suppression + immune destruction + plasma leakage [16]
- Chemotherapy: direct marrow toxicity + immune dysregulation

These conditions often require multi-pronged therapeutic strategies, making platelet enhancers especially useful.

Categories of Platelet Enhancers

Platelet enhancers encompass a wide range of pharmacological, biological, nutraceutical, and supportive therapies designed to increase platelet count by stimulating production, enhancing maturation, reducing destruction, or improving platelet survival. Their use depends on the underlying mechanism of thrombocytopenia and patient-specific factors [10]. This section categorizes platelet enhancers into major classes and discusses their mechanisms, indications, and limitations.

5.1 Pharmacological Agents

Pharmacologic platelet enhancers include Thrombopoietin receptor agonists (TPO-RAs), growth factor therapies, and investigational small-molecule stimulators. These agents are among the most effective therapies for chronic thrombocytopenia, especially immune thrombocytopenia (ITP) and liver-disease–associated thrombocytopenia.

5.1.1 Thrombopoietin Receptor Agonists (TPO-RAs)

TPO-RAs mimic the action of endogenous TPO by stimulating the c-Mpl receptor on megakaryocytes and hematopoietic stem cells. They are now considered first-line second- tier therapy for ITP and are widely used in chronic liver disease and chemotherapy- induced thrombocytopenia. (15)

Major TPO-RAs:

- Romiplostim (subcutaneous; peptibody)
- Eltrombopag (oral; small molecule)
- Avatrombopag (oral; used in chronic liver disease)
- Lusutrombopag (oral; used peri-procedurally in CLD) Mechanism
- Stimulates megakaryocyte proliferation
- Enhances polyploidization
- Increases platelet production without increasing immune destruction (24)

Limitations

- Risk of thrombosis
- Marrow fibrosis (rare, reversible)
- Hepatotoxicity (notably with eltrombopag)
- Requires continuous therapy

Table 5.1 – Comparison of FDA-Approved TPO Receptor Agonists(24)(28)

Agent	Route	Indications	Advantages	Limitations
Romiplostim	SC weekly	ITP	Durable response	Injection; risk of rebound
Eltrombopag	Oral	ITP, aplastic anemia	Oral; strong efficacy	Hepatotoxic; food restrictions
Avatrombopag	Oral	CLD thrombocytopenia	No food restrictions	Costly
Lusutrombopag	Oral	CLD peri-procedural	Predictable platelet rise	Limited indications

5.1.2 Growth Factors and Cytokine-Based Therapies

These agents stimulate thrombopoiesis through pathways complementary to or independent of TPO.

Types include:

Interleukin-11 (Oprelvekin)

- Stimulates megakaryocyte maturation
- Limited by edema, arrhythmias, electrolyte imbalance (25)

Stem Cell Factor (SCF)

- Enhances early hematopoiesis; used experimentally EPO + G-CSF combinations
- Improve multilineage recovery after chemotherapy

Limitations
- Significant side effects
- Largely replaced by TPO-RAs in modern practice

5.1.3 Investigational Small-Molecule Platelet Stimulators

New molecules aim to induce thrombopoiesis with fewer adverse effects. Examples:
- Hetrombopag
- Efamatopagan
- TG-0054 (CXCR4 inhibitor) – enhances progenitor cell trafficking
- AKR1C3 activators

Early studies show enhanced megakaryocyte differentiation and platelet output. (23)
These remain in clinical trials and are not FDA-approved.

5.2 Natural and Nutraceutical Platelet Enhancers

Many natural compounds have shown platelet-increasing effects through immunomodulatory, antioxidant, or marrow-stimulatory pathways. Evidence varies, and most support comes from small trials or traditional medical systems.

5.2.1 Papaya Leaf Extract (Carica papaya)

Widely studied in dengue-associated thrombocytopenia. Mechanisms
- Increases ALA (Arachidonic acid) expression → enhanced platelet formation
- Stabilizes platelet membranes
- Reduces oxidative stress (27)

Evidence
- Clinical trials show significant platelet rise within 24–48 hours in dengue patients.

5.2.2 Tinospora cordifolia (Giloy) A traditional Ayurvedic herb.

Effects
- Immunomodulation
- Improved megakaryocyte differentiation in animal models

5.2.3 Curcumin

Potent antioxidant and anti-inflammatory compound. Actions
- Decreases immune-mediated destruction
- Improves marrow microenvironment
- Inhibits autoantibodies in ITP (22)

5.2.4 Vitamins and Micronutrients

These correct nutritional thrombocytopenia.

Deficiency	**Mechanism**
Vitamin B12	Defective DNA synthesis → ineffective megakaryopoiesis
Folate	Impaired cell division
Iron deficiency	Paradoxically causes thrombocytosis or thrombocytopenia
Vitamin D	Modulates immune destruction

Nutrient repletion restores normal platelet count.

5.3 Supportive and Adjunctive Therapies

These therapies do not directly stimulate platelet production but reduce destruction, provide temporary increases, or correct associated pathology.

5.3.1 Immunomodulators

a. Corticosteroids
- First-line therapy in ITP
- Suppress autoantibody formation
- Rapid response (25)

b. IVIG (Intravenous Immunoglobulin)
- Blocks Fc receptors
- Decreases splenic platelet destruction
- Used in severe bleeding or surgery settings

5.3.2 Platelet Transfusion

Provides immediate but temporary platelet elevation. Limitations
- Short lifespan (hours)
- Alloimmunization
- Not effective in ITP unless life-threatening bleed

5.3.3 Splenectomy

Historically a major therapy for ITP. Benefits
- 70–80% long-term remission [26]

Risks
- Infection (encapsulated organisms)
- Thrombosis
- Now less commonly used due to TPO-RAs

Table 5.4 – Summary of Platelet Enhancers

Category	Example	Primary mechanism	Evidence level
Pharmacological	TPO-RAs, IL-11	Increase Production	Strong (RCTs)
Natural	Papaya leaf, curcumin	increase Production, decrease Destruction	Moderate
Nutritional	B12, folate	Correct ineffective thrombopoiesis	Strong
Immunomodulators	Steroids, IVIG	Decrease Destruction	Strong
Supportive	Transfusion	Temporary increase	Strong
Surgical	Splenectomy	Decrease Immune destruction	Strong but invasive
Investigational	Hetrombopag	Increase Megakaryopoiesis	Emerging

Mechanisms of Action of Platelet Enhancers

Platelet enhancers modulate thrombopoiesis and platelet homeostasis through a variety of biological pathways. Their mechanisms can be broadly categorized into five major domains: (1) stimulation of megakaryopoiesis, (2) enhancement of megakaryocyte maturation, (3) reduction of immune-mediated platelet destruction, (4) improvement of platelet survival, and (5) modulation of the bone marrow microenvironment. Understanding these mechanisms is essential for selecting appropriate therapies based on the underlying etiology of thrombocytopenia. [10]

6.1 Stimulation of Megakaryopoiesis

Megakaryopoiesis refers to the early stages of megakaryocyte development from hematopoietic stem cells (HSCs). Platelet enhancers that target this stage work by promoting proliferation and lineage commitment toward the megakaryocytic pathway.

Mechanisms

- Activation of thrombopoietin (TPO) receptors (c-Mpl) on hematopoietic stem cells
- JAK–STAT pathway activation , increased transcription of pro-thrombopoietic genes
- PI3K–AKT signaling , enhanced cell survival and proliferation
- MAPK activation , increased megakaryocyte lineage expansion

TPO receptor agonists (TPO-RAs) such as romiplostim, eltrombopag, avatrombopag, and lusutrombopag are the strongest stimulators of megakaryopoiesis. (24)

Impact:

Increase megakaryocyte progenitor cells , Increase platelet production capacity.

6.2 Promotion of Megakaryocyte Maturation and Polyploidization

Megakaryocyte maturation involves cytoplasmic enlargement, nuclear polyploidization, and formation of platelet-producing proplatelets.

Mechanisms

- TPO-RAs enhance polyploidization, leading to large, functional megakaryocytes
- IL-11 and growth factors accelerate cytoplasmic maturation
- Certain natural compounds (e.g., papaya leaf extract) modulate arachidonic acid pathways, increasing proplatelet formation (27)

Impact:Increase mature megakaryocytes , Increase platelet release into bloodstream.

6.3 Reduction of Immune-Mediated Platelet Destruction

In conditions such as ITP, autoantibodies bind platelets and mark them for destruction via splenic macrophages. Several therapies reduce this immunologic attack.

Mechanisms

- Corticosteroids reduce Fc receptor expression on macrophages and inhibit antibody production
- IVIG competes for splenic Fc receptors, preventing platelet clearance
- Curcumin and Tinospora suppress antibody formation and reduce inflammatory cytokines. (22)

Impact:

Decrease autoantibody generation + Decrease splenic clearance = Increase circulating platelet count.

6.4 Enhancement of Platelet Survival

Some therapies improve platelet lifespan by stabilizing platelet membranes, reducing senescence, or lowering oxidative stress.

Mechanisms

- Natural compounds (papaya leaf, curcumin) reduce reactive oxygen species
- Vitamin antioxidants minimize membrane degradation
- Repletion of deficiencies (B12, folate, iron) restores normal platelet life cycle dynamics

Impact:

Longer platelet lifespan , higher steady-state platelet levels.

6.5 Bone Marrow Microenvironment Modulation

Megakaryocyte maturation and platelet release depend on the stromal scaffold, extracellular matrix, and cytokine milieu.

Mechanisms

- TPO-RAs improve marrow stromal signaling
- Nutraceuticals reduce inflammation-induced bone marrow suppression
- Iron/vitamin supplementation restores hematopoietic integrity
- CXCR4 inhibitors (investigational) mobilize progenitor cells out of marrow niches (23)

Impact:

A healthy microenvironment enhances platelet production efficiency.

6.6 Combined or Overlapping Mechanisms

Many platelet enhancers act through more than one mechanism: Examples

- Papaya leaf extract:

Increase megakaryocyte production + Decrease platelet destruction

- Eltrombopag:

Increase megakaryocyte proliferation + iron chelation effects that indirectly enhance hematopoiesis

- Steroids in ITP:

Decrease immune destruction + mild Increase in platelet survival

These overlapping effects explain the synergistic benefits of combining therapies (e.g., IVIG + steroids in acute ITP).

Table 6.1 – Mechanisms of Various Platelet Enhancers

Category	Mechanism Activated
TPO-RAs	Increase Megakaryopoiesis , maturation , platelet release
Natural Enhancers	Antioxidant, anti-inflammatory, Increase platelet formation
Nutritional Agents	Correct ineffective thrombopoiesis
Steroids / IVIG	Decrease immune destruction, Increase survival
Transfusion	Immediate platelet replacement
Investigational Agents	CXCR4 inhibition, AKR1C3 activation

Clinical Evidence and Applications

Platelet enhancers are used across a broad spectrum of clinical conditions characterized by impaired platelet production, increased destruction, or multifactorial thrombocytopenia. Their effectiveness depends on the underlying pathology, disease severity, and patient-specific characteristics. Over the past decade, robust clinical trials and real-world data have expanded the therapeutic landscape, especially for immune thrombocytopenia (ITP), chemotherapy-induced thrombocytopenia (CIT), chronic liver disease (CLD), aplastic anemia, and viral infections. This section summarizes clinical applications supported by evidence-based data.

7.1 Immune Thrombocytopenia (ITP)

Immune thrombocytopenia is the condition with strongest evidence for platelet enhancers, particularly TPO receptor agonists (TPO-RAs). ITP involves both immune-mediated platelet destruction and impaired platelet production. [15]

7.1.1 Thrombopoietin Receptor Agonists (TPO-RAs) Romiplostim

Multiple randomized trials show romiplostim increases platelet counts in 70–90% of chronic ITP patients. The pivotal NEJM trial showed a median platelet count of 100–200 $\times 10^9$/L with significant reduction in rescue therapy [35].

Eltrombopag

The RAISE trial demonstrated response in 79% of adults with chronic ITP, with durable platelet rises even after multiple prior therapies [32]. Eltrombopag also improves quality of life and reduces bleeding events.

Avatrombopag

Given orally without food restrictions, avatrombopag shows response in 65–75% of ITP patients, with good tolerability [34].

7.1.2 Steroids and Immunomodulators

Steroids remain first-line, achieving initial responses in 70–80%, although relapses are common [25].

IVIG provides rapid but transient platelet increases, especially useful in:

- life-threatening bleeding
- pre-operative optimization
- pregnancy-associated ITP

7.1.3 Natural and Adjunctive Therapies

Small clinical series indicate papaya leaf extract and curcumin improve platelet counts in mild to moderate ITP, though evidence remains limited [22].

7.2 Chemotherapy-Induced Thrombocytopenia (CIT)

CIT results from marrow suppression due to cytotoxic chemotherapy. TPO-RAs

- Romiplostim improves platelet counts and reduces chemotherapy dose delays.
- Phase II trials showed romiplostim increased platelet counts in 85% of solid-tumor patients with CIT [31].
- Eltrombopag demonstrated benefit in lymphoma patients receiving gemcitabine-based regimens.

Growth factors

IL-11 was previously used but is no longer recommended due to edema, arrhythmia, and toxicity.

Clinical limitation

TPO-RAs are not FDA-approved specifically for CIT but used off-label.

7.3 Chronic Liver Disease (CLD)–Associated Thrombocytopenia

CLD leads to thrombocytopenia via:

- Decrease thrombopoietin production
- splenic sequestration
- marrow suppression

Avatrombopag & Lusutrombopag

Both are FDA-approved for peri-procedural thrombocytopenia in liver disease. Evidence:

- Avatrombopag (ADAPT-1 and ADAPT-2 trials):

65–88% avoided platelet transfusion before procedures [28].

- Lusutrombopag (L-PLUS trials):

79% maintained ≥50 ×10⁹/L platelets without transfusion [29].

These agents reduce bleeding risk and eliminate the need for transfusion.

7.4 Aplastic Anemia and Bone Marrow Failure Disorders

Eltrombopag

A breakthrough therapy for refractory aplastic anemia. Evidence:

- The NIH trial showed 40% trilineage hematologic response with eltrombopag monotherapy [36].
- Combined with immunosuppression, response increases to 65–70%, including some complete remissions.

Eltrombopag stimulates early hematopoiesis in addition to megakaryopoiesis.

7.5 Viral Infections

7.5.1 Dengue

Papaya leaf extract consistently demonstrates accelerated platelet recovery.

- Clinical trials show platelet counts increase within 24–48 hours, with reduced hospital stay [27].

7.5.2 COVID-19

COVID-19 thrombocytopenia results from marrow suppression and immune destruction.

- Small studies show eltrombopag improves platelet counts in COVID-associated ITP without worsening coagulopathy [30].

7.5.3 HIV

Thrombocytopenia in HIV (ITP-like mechanism) responds to:

- TPO-RAs
- Steroids
- IVIG

TPO-RAs are useful in refractory cases.

7.6 Other Conditions

Pregnancy-induced thrombocytopenia

- IVIG and steroids remain first choice.
- TPO-RAs are used in refractory life-threatening cases

[25]. Post-transplant thrombocytopenia

- Eltrombopag improves engraftment and early platelet recovery. Myelodysplastic syndromes (MDS)
- Mixed results; concerns about blast increase limit routine use.

Table 7.1 – Summary of Clinical Applications of Platelet Enhancers

Condition	**Most effective agents**	**Response agents**	**Evidence level**
ITP	TPO-RAs, steroids, IVIG	70–90%	Strong
CIT	TPO-RAs (off-label)	60-85%	Moderate
CLD	Avatrombopag, Lusutrombopag	65-88%	Strong
Aplastic anemia	Eltrombopag	40-70%	Strong
Dengue	Papaya leaf extract	Good	Moderate
COVID-19 ITP	Eltrombopag	Good	Emerging

Safety, Adverse Effects, and Limitations

The use of platelet enhancers whether pharmacological, natural, or supportive comes with important safety considerations. Understanding adverse effect profiles and treatment limitations is crucial when selecting appropriate therapies and monitoring patients. Although many agents effectively raise platelet counts, their long-term consequences, risk of thrombosis, organ toxicity, or immunologic complications must be carefully assessed.
(25)

8.1 Safety and Adverse Effects of TPO Receptor Agonists (TPO-RAs)

TPO-RAs such as romiplostim, eltrombopag, avatrombopag, and lusutrombopag are the most widely used platelet enhancers. They are generally safe but have important risks.

8.1.1 Thromboembolic Events TPO-RAs may increase the risk of:

- Deep vein thrombosis (DVT)
- Pulmonary embolism
- Portal vein thrombosis, especially in chronic liver disease
- Arterial thrombosis (rare) Risk correlates with:
- Rapid platelet rise
- Pre-existing thrombophilia
- Immobility or cancer. (24)(28)

Although risks are modest, careful titration and monitoring are recommended.

8.1.2 Bone Marrow Reticulin Fibrosis Long-term TPO-RA use may lead to:

- Increased reticulin deposition
- Mild bone marrow fibrosis (reversible with discontinuation)

This occurs due to megakaryocyte overstimulation and cytokine release (37).
Routine monitoring with peripheral smear (teardrop cells) or biopsy is suggested for long-term therapy.

8.1.3 Hepatotoxicity

Eltrombopag-specific risk

- Elevated ALT/AST
- Hyperbilirubinemia
- Rare hepatotoxicity

(Less common with avatrombopag or lusutrombopag)
Frequent liver function monitoring is required, especially in liver disease patients.

8.1.4 Rebound Thrombocytopenia

Abrupt discontinuation of TPO-RAs may cause:

- Sudden platelet count drop
- Return to below baseline values

Seen particularly with romiplostim; tapering is recommended.

8.2 Safety and Limitations of Natural/Nutraceutical Enhancers

Natural platelet enhancers such as papaya leaf extract, curcumin, and Tinospora cordifolia are commonly used as adjuncts. Although generally safe, they have limitations.

8.2.1 Limited Standardization

- Variable potency
- Lack of standardized dosing
- Differences in extraction and formulation This leads to unpredictable clinical responses.

8.2.2 Possible Allergic or Gastrointestinal Effects Papaya leaf extract may cause:

- Nausea
- Mild GI upset
- Rare allergic reactions Curcumin may cause:
- Reflux symptoms
- Antiplatelet effects at high doses (caution in bleeding risk). [22]

8.2.3 Insufficient Large-Scale Clinical Trials

Most evidence comes from small studies or traditional practices.
Thus, natural enhancers should complement not replace approved therapies.

8.3 Safety Issues with Immunomodulators

Steroids and IVIG are frontline agents for ITP but come with notable adverse effects.
Steroid Toxicities
Long-term steroid use causes:

- Hyperglycemia
- Weight gain
- Hypertension
- Mood changes
- Increased infection risk
- Osteoporosis

For this reason, short courses (≤ 6 weeks) are recommended as per ASH guidelines [25].

8.3.2 IVIG-Related Complications IVIG is generally safe but may cause:

- Headache or aseptic meningitis
- Flu-like symptoms
- Renal dysfunction (rare)
- Thrombotic events in high-risk individuals
- Hemolysis due to blood group antibodies These risks are dose-dependent.

8.4 Risks and Limitations of Platelet Transfusion

Platelet transfusion temporarily increases platelet count but has significant drawbacks.

8.4.1 Short Platelet Lifespan

Transfused platelets last only 3–5 days, limiting their usefulness except in acute bleeding.

8.4.2 Alloimmunization Repeated transfusions can lead to:

- Anti-HLA antibody formation
- Platelet refractoriness
- Poor response to future transfusions Leukocyte reduction reduces this risk.

8.4.3 Transfusion Reactions May include:

- Febrile reactions
- Allergic reactions
- Sepsis (bacterial contamination is higher in platelets than in RBCs)

Because platelets are stored at room temperature, bacterial growth is more common [38].

8.5 Limitations of Platelet Enhancers in Special Populations

Pregnancy:
TPO-RAs cross the placenta; limited data suggest caution [38]. Pediatric patients:
Romiplostim and eltrombopag are approved for pediatric ITP, but long-term safety is still being evaluated.
Cancer patients:
TPO-RAs may theoretically stimulate malignant clones, particularly in MDS, though evidence is mixed.

8.6 Cost, Accessibility, and Compliance Limitations

Cost barriers:
TPO-RAs are expensive (often >$7,000/month). Monitoring requirements:
Frequent CBC and liver function tests increase healthcare utilization. Adherence issues:
Daily oral dosing (eltrombopag) or weekly injections (romiplostim) may reduce adherence.

Table 8.1 – Safety Summary of Major Platelet Enhancers

Agent type	Major Risks	Notes
TPO-RAs	Thrombosis, fibrosis, hepatotoxicity, rebound thrombocytopenia	Most effective but require monitoring
Natural agents	GI upset, allergy, limited evidence	Useful adjuncts
Steroids	Metabolic effects, infection risk	Use short courses
IVIG	Headache, thrombosis, renal effects	Rapid response therapy
Transfusion	Alloimmunization, sepsis	Temporary effect

Future Directions & Emerging Therapies in Platelet Enhancement

The landscape of platelet enhancers is evolving rapidly, with research focused on improving efficacy, safety, durability of response, and personalization of therapy. While current agents like TPO receptor agonists have transformed the management of chronic thrombocytopenia, important unmet needs remain particularly long-term safety, clonal evolution risk in marrow failure syndromes, and accessibility in resource-limited settings [24][43].

9.1 Next-Generation TPO Receptor Agonists and Novel Small Molecules

Future TPO-RAs and small molecules are being designed to:

- Provide more physiologic stimulation of thrombopoiesis
- Minimize off-target effects (e.g., hepatotoxicity, fibrosis)
- Improve oral bioavailability and adherence

Examples under investigation include hetrombopag, efamotrombopag, and other non-peptidyl agonists that bind distinct epitopes on the c-Mpl receptor or modulate downstream signaling with greater selectivity [23]. These agents aim to maintain robust platelet responses while lowering thrombotic risk and marrow fibrosis.
There is also interest in dual-acting agents that not only stimulate megakaryocytes but also support erythroid or neutrophil lineages, which could be particularly valuable in bone marrow failure states [43].

9.2 Gene and RNA-Based Therapies

Gene-based strategies are being explored to correct inherited thrombocytopenias and severe marrow failure:

- Gene addition or gene editing (e.g., CRISPR-Cas9) to correct mutations in MYH9, RUNX1, or other megakaryopoiesis-related genes.
- RNA-targeting approaches (siRNA, antisense oligonucleotides) to modulate negative regulators of

thrombopoiesis.
Although still in preclinical and very early clinical stages, these techniques hold promise for curative therapy in congenital thrombocytopenia and selected bone marrow failure syndromes, potentially reducing the need for chronic pharmacologic platelet enhancers
(40)(44).

9.3 Targeting the Bone Marrow Niche and CXCR4 Pathways

Emerging therapies increasingly focus on the bone marrow microenvironment and the CXCR4–SDF-1 axis, which regulate megakaryocyte trafficking and progenitor retention:

- CXCR4 antagonists (e.g., plerixafor, and other experimental agents) mobilize hematopoietic stem/progenitor cells and may enhance megakaryopoiesis and platelet release when combined with TPO-RAs (23).
- Agents that modify stromal-cell signaling, reduce inflammatory cytokines, or restore normal niche architecture may improve platelet production in conditions such as myelodysplastic syndromes or post-chemotherapy marrow injury (45).

These strategies represent a shift from purely cell-intrinsic approaches to therapies that also correct the extracellular milieu supporting thrombopoiesis.

9.4 Personalized and Biomarker-Driven Therapy

One major goal is to move toward personalized platelet-enhancer regimens, where:

- Genetic markers (e.g., polymorphisms in TPO or MPL, or immune signatures in ITP)
- Clinical predictors (age, comorbidities, thrombosis risk)
- Dynamic biomarkers (serum TPO levels, reticulated platelet fraction, marrow megakaryocyte burden)

are used to choose the optimal agent, dose, and combination for each patient (41). This could help:

- Identify which patients will respond best to TPO-RAs vs immunomodulators
- Minimize overtreatment and adverse events
- Guide duration and tapering strategies

Machine-learning models based on large ITP and CLD registries are also being explored to predict response and relapse patterns (41).

9.5 Safer Long-Term Strategies in Marrow Failure Syndromes

In aplastic anemia and related marrow failure conditions, future work focuses on:

- Clarifying the long-term risk of clonal evolution (e.g., MDS/AML) with eltrombopag and other enhancers.
- Developing agents that stimulate hematopoiesis without driving malignant clones.
- Combining TPO-RAs with novel immunosuppressive regimens (e.g., alemtuzumab, regulatory T-cell therapies) to promote durable, safe, multilineage recovery (43).

Long-term prospective registries are essential to define risk benefit profiles over decades of therapy.

9.6 Integration of Nutraceuticals and Adjunctive Therapies into Evidence-Based Protocols

While natural products such as papaya leaf extract, curcumin, and Tinospora cordifolia show encouraging platelet-enhancing effects, future research must:

- Conduct large, randomized controlled trials
- Standardize preparations and dosing
- Evaluate long-term safety and interactions with conventional drugs

If validated, these agents could provide low-cost adjunctive options in dengue, ITP, and resource-limited settings
(42)(22)

9.7 Novel Indications and Combination Strategies

Ongoing and future studies are exploring platelet enhancers in:

- Post-transplant thrombocytopenia
- Myelodysplastic syndromes (with careful monitoring for blast increase)
- Autoimmune diseases with secondary thrombocytopenia
- Perioperative optimization in high-risk surgical patients

Combination regimens, or example TPO-RA + low-dose steroids, or TPO-RA + rituximab in ITP may achieve faster responses and more sustained remissions with lower cumulative toxicity (33)\Conclusion

Platelet enhancers play a crucial role in managing thrombocytopenia across conditions involving reduced platelet production or increased destruction. Among available options, TPO receptor agonists remain the most effective, offering reliable platelet increases and reducing the need for steroids and transfusions. However, risks such as thrombosis, reversible marrow fibrosis, and hepatotoxicity highlight the need for careful monitoring.

Natural agents and supportive therapies provide useful adjunctive benefits but require stronger clinical validation. Emerging advances , including next-generation TPO-RAs, gene-based therapies, and personalized treatment approaches promise safer and more targeted strategies. Overall, platelet enhancers continue to evolve, improving outcomes while expanding therapeutic possibilities in thrombocytopenia management.

Reference

1. Kaushansky, K. (1995). The primary regulator of platelet production. Blood, 86(12), 419–431.
2. Kuter, D. J. (2009). Thrombopoietin and platelet production in chronic thrombocytopenia. Seminars in Hematology, 46(1 Suppl 1), S79–S82.
3. Kuter, D. J. (2013). The biology of thrombopoietin and thrombopoietin receptor agonists. International Journal of Hematology, 97(6), 683–696.
4. Zufferey, A., Kapur, R., Semple, J. W. (2017). Pathogenesis and therapeutic mechanisms in immune thrombocytopenia. Journal of Clinical Medicine, 6(2), 16.
5. Huang, L., et al. (2023). Application and investigation of thrombopoiesis-stimulating agents in thrombocytopenia treatment. Therapeutic Advances in Hematology, 14, 20406207231152746.
6. Aster, R. H., & Bougie, D. W. (2007). Drug-induced immune thrombocytopenia. New England Journal of Medicine, 357(6), 580–587.
7. Goldfarb, A. N., Megosh, L. C., Prkachin, I., & Nicholas, N. S. (2017). Transcriptional regulation of megakaryopoiesis. Experimental Hematology, 47, 1–9.
8. Hitchcock, I. S., & Kaushansky, K. (2014). Thrombopoietin from beginning to end. British Journal of Haematology, 165(2), 259–268.
9. Kaushansky, K. (2005). The molecular mechanisms that control thrombopoiesis. Journal of Clinical Investigation, 115(12), 3339–3347.
10. Kuter, D. J. (2013). Thrombopoietin and thrombopoietin receptor agonists. International Journal of Hematology , 97(6), 698-707.
11. Li, J., van der Wal, D. E., Zhu, G., & Chen, P. (2017). Aging platelet clearance. Platelets, 28(4), 341–348.
12. Machlus, K. R., & Italiano, J. E. (2013). The incredible journey: From megakaryocyte development to platelet formation. Journal of Cell Biology, 201(6), 785–796.
13. Patel, S. R., Hartwig, J. H., & Italiano, J. E. (2020). Mechanisms of megakaryocyte maturation and platelet formation. Annual Review of Pathology, 15, 193–214.
14. Wang, J., Sun, C., & Zheng, J. (2019). Cytokine regulation in thrombopoiesis. Frontiers in Medicine, 13(1), 111–119.
15. Cooper, N., & Ghanima, W. (2019). Immune thrombocytopenia. New England Journal of Medicine, 381(10), 945–955.
16. Hottz, E. D., Bozza, F. A., & Bozza, P. T. (2020). Platelets in immune response to viral infections. Clinical & Translational Immunology, 9(3), e1138.
17. Sadler, J. E. (2019). Hemostasis: A balance between bleeding and thrombosis. New England Journal of Medicine, 368, 249–260.
18. Slichter, S. J. (2018). Platelets: Production, morphology, and transfusion therapy. Hematology/Oncology Clinics, 32(3), 363–382
19. Stasi, R. (2020). How to approach thrombocytopenia. Hematology, 25(1), 43–50.
20. Tefferi, A., & Barbui, T. (2019). Polycythemia vera and essential thrombocythemia: 2020 update on diagnosis, risk-stratification, and management. American Journal of Hematology, 94(1), 133–143.
21. Young, N. S. (2018). Aplastic anemia. New England Journal of Medicine, 379(17), 1643–1656
22. Chong, B. H., et al. (2021). Curcumin and hematological disorders. Journal of Hematology & Oncology, 14(1), 30.
23. Huang, L., et al. (2023). Advances in thrombopoiesis-stimulating agents. Therapeutic Advances in Hematology, 14, 1–18.
24. Kuter, D. J. (2015). The role of TPO receptor agonists. Blood, 125(13), 2161–2167.
25. Neunert, C., et al. (2019). American Society of Hematology guideline: Immune thrombocytopenia. Blood Advances, 3(23), 3829–3866.

26. Rodeghiero, F. (2009). Splenectomy in ITP. Haematologica, 94(5), 664–666.
27. Subenthiran, S., et al. (2013). Papaya leaf juice study. Journal of Ethnopharmacology, 150(3), 815–823.
28. Terrault, N., et al. (2018). Avatrombopag and lusutrombopag for CLD. New England Journal of Medicine, 378(12), 1111–1120.
29. Afdhal, N., et al. (2018). Lusutrombopag for thrombocytopenia in patients with chronic liver disease. Journal of Hepatology, 68(4),
686–693.
30. Bhattacharjee, S., & Banerjee, M. (2020). Immune thrombocytopenia in COVID-19. British Journal of Haematology, 190(3), e129–e132.
31. Bussel, J. B., et al. (2019). Romiplostim in chemotherapy-induced thrombocytopenia. Haematologica, 104(5), 947–954.
32. Cheng, G., et al. (2011). Eltrombopag for chronic ITP. Lancet, 377(9763), 393–402.
33. Cooper, N., & Ghanima, W. (2019). Immune thrombocytopenia. NEJM, 381, 945–955
34. Jurczak, W., et al. (2018). Avatrombopag in ITP. British Journal of Haematology, 183(3), 479–490.
35. Kuter, D. J., et al. (2008). Romiplostim in chronic ITP. NEJM, 359(18), 1939–1947.
36. Olnes, M. J., et al. (2012). Eltrombopag in refractory aplastic anemia. NEJM, 367(1), 11–19
37. Ghanima, W., et al. (2019). Thrombopoietin receptor agonists and bone marrow fibrosis. Blood, 133(2), 248–257.
38. Slichter, S. J. (2018). Platelet transfusion risks and prevention. Hematology/Oncology Clinics, 32(3), 363–382.
39. Sankaran, J., et al. (2020). TPO-RA safety in pregnancy. British Journal of Haematology, 190(6), 854–865.
40. Pecci, A., & Balduini, C. L. (2014). Inherited thrombocytopenias: Molecular mechanisms. Thrombosis Research, 133(2), 171–176.
41. Provan, D., et al. (2019). Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Advances, 3(22), 3780–3817.
42. Subenthiran, S., et al. (2013). Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with
dengue fever and dengue hemorrhagic fever. Journal of Ethnopharmacology, 150(3), 815–823.
43. Townsley, D. M., Desmond, R., Dunbar, C. E., Young, N. S. (2017). Eltrombopag added to standard immunosuppression for aplastic anemia. New England Journal of Medicine, 376(16), 1540–1550.
44. Wilcox, R. A., et al. (2020). Gene therapy and gene editing for hematologic disorders. Hematology/Oncology Clinics of North America, 34(1), 1–16.
45. Zhang, J., et al. (2019). The bone marrow niche in hematological malignancies and therapy. Frontiers in Oncology, 9, 102.