



Exploring Alternative Therapies for Thrombocytopenia: Efficacy of Papaya Leaf Extract and Kiwi Fruit

¹ Kale Ruchira Dattatraya, ²Thorat Tejas Vilas, ³ Kulat Pratap Sandeep, ⁴Wadage Vaibhav Dattu, ⁵Attar Jahir Nuruddin, ⁶ Wayse Siddheshwar Sunil

^{1,2,3,4,5,6} Samarth College of Pharmacy, Belhe

ABSTRACT :

Thrombocytopenia is a haematological condition characterised by a reduced platelet count, which can result from various causes including bone marrow disorder, autoimmune diseases, viral infections, and medication effects. Its clinical presentation can range from mild bruising to severe bleeding, necessitating accurate diagnosis and appropriate management. This review explores the role of natural therapies, specifically papaya leaf extract (PLE) and kiwi fruit, in managing thrombocytopenia. Papaya leaf extract has shown promise in increasing platelet counts, particularly in dengue-induced thrombocytopenia, by stimulating platelet production, protecting platelets from oxidative damage, and moulding immune responses. While papaya leaf extract is well-tolerated, its efficiency may be less significant in severe or acute cases. On the other hand, kiwi fruit, rich in essential nutrients like Vitamin C, Vitamin, and folate, plays a supportive role in mild to moderate thrombocytopenia by enhancing platelet production, offering antioxidant protection, and reducing inflammation. Although its effects are gradual, kiwi fruit can complement conventional treatments and improve general health. Conventional therapies, such as platelet transfusions and immunosuppressants, are necessary for severe cases but come with higher costs and potential side effects. This review highlights the complementary roles of natural remedies like PLE and kiwi fruit in thrombocytopenia management, suggesting their use as adjuncts to more conventional treatments.

Keywords – Thrombocytopenia, Platelet count, Papaya leaf extract (PLE), Kiwi fruit, Dengue-induced thrombocytopenia, Natural remedies, Platelet production, Antioxidant protection, Immune modulation, Complementary treatments, Vitamin C, Vitamin K, Folate, Oxidative damage, Inflammation reduction, Adjunct therapy, Conventional treatment, Platelet transfusion.

Introduction to Thrombocytopenia :

Thrombocytopenia is haematological condition characterized by a reduced platelet count, typically below 150,000 platelet per microliter of blood. Platelet, also known as thrombocytes, are essential for normal blood clotting and wound healing. A deficiency in platelet count can lead to increased bleeding risks, ranging from mild bruising to severe internal haemorrhages, depending on the underlying cause and severity.

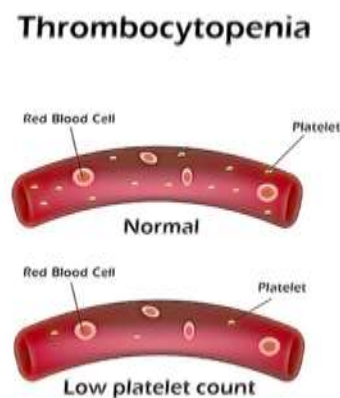


Fig 1. Introduction of thrombocytopenia

Classification :

Thrombocytopenia can be classified based on its causes :

1. **Decreased platelet production:** Often due to bone marrow disorders, such as aplastic anaemia, leukaemia, or chemotherapy-induced myelosuppression.
2. **Increased platelet destruction:** Common in autoimmune condition like immune thrombocytopenia purpura (ITP), or infections (HIV, dengue).
3. **Sequestration in the spleen :** Seen in cases of splenomegaly where platelet is trapped within an enlarged spleen.
4. **Dilutional thrombocytopenia :** Occurs following massive blood transfusions where platelet concentration becomes diluted.
 - **Common Causes**
 - Autoimmune diseases (e.g., lupus, ITP)
 - Viral infection (e.g., dengue, Epstein-Barr virus)
 - Medications (e.g., heparin-induced thrombocytopenia)
 - Bone marrow failure syndromes
 - Chronic liver disease and hypersplenism
 - **Clinical Presentation**

Patients with thrombocytopenia may be asymptomatic or present with:

- Petechiae (small, pinpoint haemorrhages)
- Ecchymoses (bruises)
- Prolonged bleeding from cuts
- Menorrhagia (heavy menstrual bleeding)
- Spontaneous bleeding, especially in severe cases (platelet count <10,000/ μ L)
- **Diagnostic Workup**

Diagnosis involves a combination of :

- Complete blood count (CBC) to assess platelet levels.
- Peripheral blood smear to evaluate platelet morphology.
- Bone marrow biopsy, if indicated ,to investigate production issues .
- Screening for underlying condition, including autoimmune disease, infection, or liver dysfunction.
- **Management**

The treatment of thrombocytopenia depends on its causes and severity :

- **Mild cases:** Observation and monitoring may suffice.
- **Severe or symptomatic cases :** Platelet transfusion, immunosuppressants (e.g., corticosteroids), or treatment of the underlying causes (e.g., antibiotics for infection or splenectomy for hypersplenism).

Causes of Thrombocytopenia :

Thrombocytopenia, or a reduced platelet count, can result from a variety of condition. These causes are broadly categorised into three main mechanisms: decreased platelet production, increase platelet destruction or consumption, and sequestration of platelet. Below is a detailed description of each category :

- **Decreased Platelet Production**

The bone marrow may fail to produce an adequate number of platelet due to various reasons:

- Bone Marrow Disorders :
 - Aplastic Anaemia : The bone marrow stops producing enough blood cells, including platelets.

- Leukemia and Other Cancers : Abnormal proliferation of cells in the bone marrow suppresses platelet production.
- Myelodysplastic Syndrome (MDS) : A group of disorders causing ineffective blood cell production in the bone marrow
- Nutritional Deficiencies :
 - Vitamin B12 or Folate Deficiency : Essentials Nutrients for cel Production ; their lack leads to sufficient platelet formation.
- Infections:
 - Viral infections like HIV, hepatitis C, Epstein-Barr virus (EBV), or parvovirus B19 can damage bone marrow.
- Chemotherapy or Radiation Therapy :
 - These treatments target rapidly dividing cells, including those in the bone marrow, reducing platelet production.
- Medication and Toxins :
 - Certain drugs (e.g., alcohol, thiazides, chemotherapy agents) can impair bone marrow function.
- **Increased Platelet Destruction or Consumption**

This occurs when platelets are destroyed faster than they can be produced :

- Immune-Mediated Thrombocytopenia :
 - Immune Thrombocytopenia Purpura (ITP): An autoimmune condition where the immune system attacks and destroys platelets.
 - Drug Induced Thrombocytopenia: Certain drugs (e.g., quinine, penicillin, heparin) can trigger an immune response that targets platelets (e.g., Heparin-Induced Thrombocytopenia [HIT]).
- Sepsis or Severe Infections:
 - Infections can cause wide spread inflammation, leading to platelet destruction.
- Disseminated Intravascular Coagulation (DIC):
 - A condition where wide spread clotting depletes and clotting factors, leading to bleeding complications.
- Thrombotic Microangiopathies :
 - Conditions such as Thrombotic Thrombocytopenic Purpura (TTP) or Haemolytic Uremic Syndrome (HUS) cause small clots that trap and consume platelets.

2.3 Sequestration of Platelets :

Platelets are normally stored in the spleen. If the spleen becomes enlarged, it may sequester (trap) more platelets than usual, leading to thrombocytopenia.

- Splenomegaly (Enlarged Spleen) :
 - Common in conditions like liver cirrhosis, portal hypertension, or certain cancers (e.g., lymphoma)
 - Infectious Diseases: Malaria or mononucleosis may cause spleen enlargement.

2.4 Other Causes :

- Pregnancy :
 - Gestational thrombocytopenia, a mild condition, can occur in late pregnancy without a clear cause.
 - Preeclampsia/ HELLP Syndrome : severe complications of pregnancy can lead to thrombocytopenia.
- Genetic Disorders :
 - Rare inherited conditions , such as Wiskott-Aldrich syndrome or Branded-Soulier syndrome, may cause low platelet counts.

3. Papaya Leaf Extract in Thrombocytopenia : Mechanism and Potency :

Papaya leaf extract (PLE), derived from the leaves of the *Carica papaya* plant, is widely recognised for its therapeutic potential in increasing platelet count. Especially in condition like thrombocytopenia, it's use is particularly popular in dengue fever, where thrombocytopenia is a hallmark syndrome. Below is a detailed analysis of it's role, mechanism of action, and potency :



Fig 2. Papaya Leaf Extract

3.1 Role of Papaya leaf Extract in Thrombocytopenia :

1. Restores Platelet Count :
 - Papaya leaf extract has been shown to significantly increase platelet counts in thrombocytopenic patients, particularly in dengue fever.
 - Studies indicate that PLE may reduce the severity and duration of thrombocytopenia.
2. Immune Modulation :
 - PLE is believed to boost the immune system, which may help in mitigating autoimmune mechanisms that lead to platelet destruction, such as in immune thrombocytopenic purpura (ITP).
3. Antioxidant Activity :
 - Rich in Flavonoids and phenolic compounds, papaya leaf extract helps reduce oxidative stress, which can otherwise contribute to platelet damage and destructio

3.2 Mechanism of Action :

The mechanisms by which papaya leaf extract alleviates thrombocytopenia are still under study, but some proposed actions include :

1. Stimulation of Platelet Production

- Thrombopoiesis:
 - PLE may stimulate the bone marrow to produce more megakaryocytes (precursor cells for platelets), thus increasing platelet count.

- This effect is thought to be mediated by compounds such as flavonoids and glycosides found in the extract.

2. Protection of Platelets

- Antioxidant Effects :

- Compounds like quercetin and ascorbic acid in papaya leaf extract neutralize free radicals, protecting platelets from oxidative damage.

3. Regulation of Immune Response

- Immune Modulation :

- Papaya Leaf extract contains immunomodulatory components such as alkaloids and flavonoids, which may reduce excessive immune-mediated platelet destruction (as seen in conditions like ITP or Viral infections).

4. Anti-inflammatory Effects

- Inflammation exacerbates platelet destruction in various thrombocytopenia conditions. Papaya leaf extract reduces inflammatory mediators, thereby minimizing platelet loss.

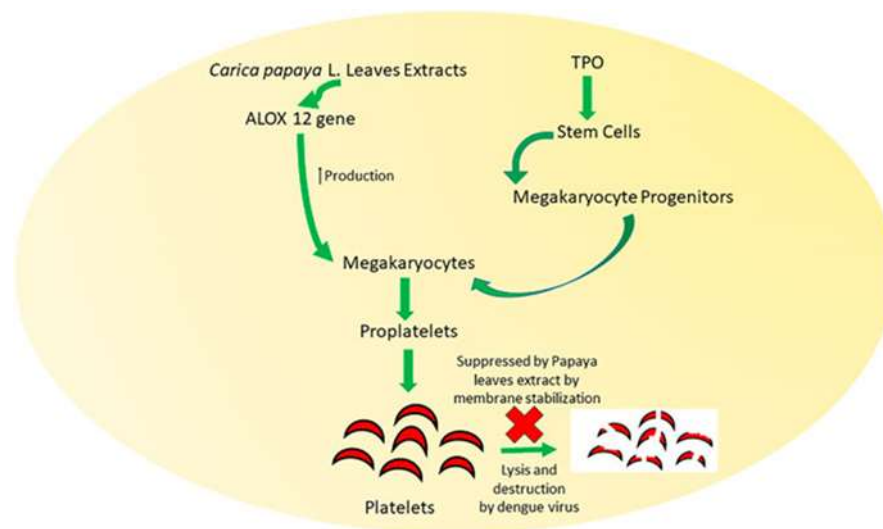


Fig 3. MOA of Papaya leaf on thrombocytopenia

3.3 Potency of Papaya Leaf Extract

1. Clinical Evidence :

- Several studies have demonstrated the efficacy of papaya leaf extract in increasing platelet counts in dengue-induced thrombocytopenia. Platelet levels often improve within 24-48 hours of administration in responsive cases.

2. Active Compounds :

- Key bioactive compounds include caprine, flavonoids, glycosides, and alkaloids, which collectively contribute to its effects on thrombopoiesis and platelet protection.

3. Safety and Tolerability :

- Papaya leaf extract is generally well-tolerated, with minimal side effects like nausea or mild gastrointestinal discomfort reported in some cases.

4. Limitations:

- The efficacy of PLE may vary based on the underlying cause of thrombocytopenia (e.g., bone marrow failure VS immune-mediated destruction).
- While effective in dengue-induced thrombocytopenia, its role in condition like chemotherapy-induced thrombocytopenia or aplastic anaemia is less clear.

Papaya leaf extract holds significant promise as a natural adjunct therapy for thrombocytopenia, especially in cases related to infections like dengue. Its ability to boost platelet production, protect platelets, and modulate the immune response makes it a potent therapeutic option. However, its efficacy can depend on the underlying cause of thrombocytopenia, and further research is needed to standardize dosages, identify active components, and validate its effects in other thrombocytopenic conditions.

3.4 Comparative table format to contrast papaya leaf extract (PLE) with conventional therapeutic approaches for thrombocytopenia :

Aspect	Papaya Leaf Extract (PLE)	Therapeutic Approaches
Source	Natural, derived from the <i>Carica papaya</i> plant.	Synthetic drugs (e.g., corticosteroids, immunosuppressants, or biologics).
Mechanism of action	- Stimulates bone marrow to increase platelet production. - Protects platelets via antioxidant activity. - Modulates immune responses to reduce platelet destruction.	- Immune suppression (e.g., corticosteroids). - Stimulates platelet production (e.g., thrombopoietin receptor agonists). - Immediate platelet replacement (e.g., transfusions).
Onset of action	- Gradual (24–48 hours).	- Depends on treatment: transfusions act immediately, drugs vary (hours to days).
Efficacy	- Effective in mild to moderate thrombocytopenia (e.g., dengue). - Evidence in autoimmune or chemotherapy-induced thrombocytopenia is limited.	- Proven efficacy in severe and chronic thrombocytopenia, including immune and chemotherapy-related cases.
Cost	- Affordable and accessible, especially in resource-limited areas.	- Expensive, particularly for advanced treatments like immunoglobulins or biologics.
Side effects	- Mild: nausea, gastrointestinal discomfort, or rare allergies.	- Moderate to severe: infections, hypertension, organ damage (from long-term drug use).
Availability	- Widely available as herbal supplements, juices, or teas.	- Requires prescriptions; advanced therapies may need hospital settings.
Safety Profile	- Generally safe for most individuals.	- Requires careful monitoring due to potential adverse effects (e.g., immunosuppression).
Use in severe Cases	- Limited evidence; less effective for acute severe thrombocytopenia.	- Essential in critical conditions (e.g., severe bleeding, bone marrow failure).
Standardization	- Lack of standardized dosing; variability in product quality.	- Dosages are well-regulated and based on clinical guidelines.

3.5 Conclusion :

- **When to choose Papaya Leaf Extract :**
 - Ideal for mild to moderate thrombocytopenia caused by infectious (e.g., dengue).
 - Preferred for patients seeking natural, cost-effective options with minimal side effects.
- **When to Choose Therapeutics Drugs:**
 - Necessary for severe or life-threatening thrombocytopenia
 - Essential for cases with complex underlying causes (e.g., bone marrow disorders, autoimmune conditions).

4. Role of Kiwi Fruit in Thrombocytopenia: Mechanism of Action and Potency :

Kiwi fruit (*Actinidia deliciosa*), rich in essential vitamins, minerals, and antioxidants, is recognized for its potential in supporting platelet recovery and overall blood health. While not as extensively studied as papaya leaf extract, kiwi fruit is gaining attention as a dietary aid for improving platelet count in thrombocytopenia. Here's an in-depth analysis of its role mechanism of action, and potency :



Fig. 4 Kiwi Fruit

4.1 Nutritional Profile of Kiwi Fruit

Kiwi fruit is a nutrient-dense food that contains:

- Vitamin C: A Powerful antioxidant essential for collagen synthesis and blood vessels integrity .
- Vitamin K: Plays a role in blood clotting and platelet function
- Folate: Supports DNA synthesis and blood cell production in the bone marrow.
- Potassium and Magnesium: Maintain electrolyte balance, which supports cellular health.
- Phytonutrients: Flavonoids, carotenoids, and polyphenols that have antioxidant and anti-inflammatory properties.

4.2 Mechanism of Action :

The potential of kiwi fruit in thrombocytopenia is attributed to its combined nutritional and biochemical effects:

1. Enhances Platelet Production (Thrombopoiesis)

- Bone Marrow Support :
 - Folate in kiwi helps stimulate the production of megakaryocytes (platelet precursor cells) in the bone marrow.
 - Vitamin C enhances iron absorption, indirectly supporting red and white blood cell production, which can help overall haematopoiesis.

2. Antioxidant Protection

- Kiwi's high levels of antioxidants (e.g., vitamin C, Flavonoids) reduce oxidative stress, which is a significant factor in platelet destruction.
- This protective mechanism stabilizes existing platelets and improves their lifespan in the bloodstream.

3. Anti-inflammatory Effects

- Chronic inflammation can lead to platelet dysfunction or destruction.
- Kiwi contains bioactive compounds (e.g., quercin, lutein) that reduce pro-inflammatory cytokines, helping to preserve platelet count.

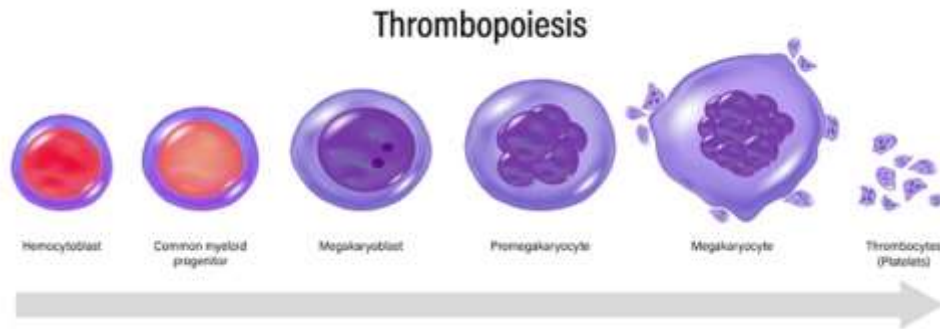


Fig 5 MOA of Kiwi Fruit in thrombocytopenia

4. Blood Vessel Health and Haemostasis

- The vitamin K content in kiwi supports blood clotting mechanisms.
- By strengthening blood vessel walls, kiwi reduces the risk of minor bleeds, a common complication in thrombocytopenia.

5. Immune System Support

- Thrombocytopenia often results from infectious or immune-mediated conditions.
- Kiwi boosts immune function through its vitamin C content, potentially reducing the severity of infectious contributing to low platelet counts.

4.3 Potency of Kiwi Fruit in Thrombocytopenia

1. Clinical Evidence :

- Limited direct studies link kiwi fruit to increased platelet counts. However, its nutritional components are well-established in promoting overall blood health.
- Anecdotal and observational reports suggest that regular consumption of kiwi can contribute to faster recovery in mild to moderate thrombocytopenia.

2. Onset of Action:

- The effects of kiwi fruit are gradual and supportive, making it more suitable as a dietary adjunct rather than a standalone treatment for acute thrombocytopenia.
- Visible improvements in platelet counts, if any, may take several days to weeks of consistent intake.

3. Comparative Effectiveness:

- Kiwi fruit is less potent than targeted treatments like papaya leaf extract or thrombocytopenia receptor agonists. However, it plays a valuable complementary role in dietary management.

4.4 Limitations

- Kiwi is not a substitute for medical treatment in severe thrombocytopenia or cases requiring immediate intervention (e.g., platelet transfusions).
- Its effectiveness may vary depending on the cause of thrombocytopenia.

Kiwi fruit serves as a supportive dietary intervention for improving platelet count in mild to moderate thrombocytopenia. Its rich antioxidant, vitamin, and mineral content helps enhance platelet production, protect against oxidative stress, and maintain blood vessels health. While not a standalone treatment, kiwi fruit complements medical therapies and can contribute to faster recovery when included in a balanced diet.

For best results, regular consumption of 1-2 kiwi fruits daily can be recommended as part of a thrombocytopenia management plan, alongside medical treatment as needed.

4.5 Comparative table to contrast kiwi fruit with conventional therapeutic approaches for thrombocytopenia :

Aspect	Kiwi Fruit	Therapeutic Approaches
Source	Natural food, rich in vitamins, antioxidants, and fibre.	Synthetic drugs, biologics, and medical treatments.
Mechanism of Action	- Provides essential nutrients (e.g., vitamin C, K, folate) that support platelet production and reduce oxidative stress. - Anti-inflammatory and antioxidant effects protect platelets and blood vessels.	- Immediate platelet replacement (e.g., platelet transfusions). - Immune modulation (e.g., corticosteroids, immunoglobulins). - Stimulating platelet production (e.g., thrombopoietin receptor agonists).
Onset of Action	- Gradual effects over days to weeks with consistent consumption.	- Varies: platelet transfusions act immediately, drugs (e.g., corticosteroids) may take hours to days.
Efficacy	- Limited direct evidence for platelet count increase. - Effective in mild/moderate thrombocytopenia, especially in diet-related recovery (e.g., viral infections).	- Proven efficacy in treating severe thrombocytopenia, especially in cases like ITP, bone marrow failure, and chemotherapy-induced thrombocytopenia.
Cost	- Very affordable, as it's a common fruit with high nutritional value.	- Expensive, especially for treatments like immunoglobulins, platelet transfusions, or thrombopoietin receptor agonists.
Side Effects	- Rare: mild gastrointestinal discomfort or allergic reactions in sensitive individuals.	- Moderate to severe side effects: immunosuppression, infections, hypertension, organ damage with long-term use of immunosuppressive drugs.
Availability	- Readily available in grocery stores and supermarkets.	- Prescription-only for most treatments; availability may be limited in some areas or require hospitalization.
Safety Profile	- Generally safe for most individuals, including long-term use.	- Requires monitoring for potential adverse effects, especially for long-term drug use.
Use in Severe Cases	- Not effective for critical or acute thrombocytopenia, especially in cases of active bleeding or bone marrow failure.	- Essential for severe or life-threatening thrombocytopenia, such as in cases of active bleeding, bone marrow disorders, or chemotherapy-induced thrombocytopenia.
Standardization	- No standardized dosage; intake is based on natural food consumption (1-2 fruits daily).	- Dosages are strictly regulated, based on clinical guidelines for each specific therapeutic agent.

4.6 Conclusion

- **Kiwi Fruit:**
 - Best suited for supportive management of mild to moderate thrombocytopenia's, especially where dietary improvement is as factor.
 - Rich in essential vitamins and antioxidants, kiwi fruit can support platelet production and overall blood health , but it is not a quick fix for severe cases.
 - Affordable, accessible, and safe it is a good complementary option for boosting general health and improving immune function, particularly in conditions like viral infections that lead to thrombocytopenia.
- **Therapeutic Approaches:**
 - Necessary for acute or severe thrombocytopenia, especially in cases where rapid intervention is needed, such as in autoimmune disorders, chemotherapy-induced thrombocytopenia, or bone marrow failure.
 - Targeted medical treatments (e.g., platelet transfusion, immunoglobulins, or thrombopoietin receptor agonist) are proven to effectively raise platelet counts and manage complications.

- More expensive and often associated with side effects, but essentials for critical cases.

Kiwi fruit offers a nutritional and complementary role in managing thrombocytopenia, while conventional therapies are crucial for addressing more severe or acute causes.

References :-

1. Kam T, Alexander M. Drug-induced immune thrombocytopenia. *J Pharm Pract.* 2014 Oct;27(5):430-9. [PubMed]
2. LAVY R. THROMBOCYTOPENIC PURPURA DUE TO LUPINUS TERMIS BEAN. *J Allergy.* 1964 Sep-Oct;35:386-9. [PubMed]
3. Arnold J, Ouwehand WH, Smith GA, Cohen H. A young woman with petechiae. *Lancet.* 1998 Aug 22;352(9128):618. [PubMed]
4. Achterbergh R, Vermeer HJ, Curtis BR, Porcelijn L, Aster RH, Deenik W, Daemen-Gubbels C. Thrombocytopenia in a nutshell. *Lancet.* 2012 Feb 25;379(9817):776. [PMC free article] [PubMed]
5. Azuno Y, Yaga K, Sasayama T, Kimoto K. Thrombocytopenia induced by Jui, a traditional Chinese herbal medicine. *Lancet.* 1999 Jul 24;354(9175):304-5. [PubMed]
6. Ohmori T, Nishii K, Hagihara A, Takeda M, Sekido K. Acute thrombocytopenia induced by jui, a traditional herbal medicine. *J Thromb Haemost.* 2004 Aug;2(8):1479-80. [PubMed]
7. Davies JK, Ahktar N, Ranasinge E. A juicy problem. *Lancet.* 2001 Dec 22-29;358(9299):2126. [PubMed]
8. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, Vondracek T. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med.* 1998 Dec 01;129(11):886-90. [PubMed]
9. Scaradavou A. HIV-related thrombocytopenia. *Blood Rev.* 2002 Mar;16(1):73-6. [PubMed]
10. Karimi O, Goorhuis A, Schinkel J, Codrington J, Vreden SGS, Vermaat JS, Stijnis C, Grobusch MP. Thrombocytopenia and subcutaneous bleedings in a patient with Zika virus infection. *Lancet.* 2016 Mar 05;387(10022):939-940. [PubMed]
11. Clare NM, Montiel MM, Lifschitz MD, Bannayan GA. Alport's syndrome associated with macrothrombopathic thrombocytopenia. *Am J Clin Pathol.* 1979 Jul;72(1):111-7. [PubMed]
12. Segal JB, Moliterno AR. Platelet counts differ by sex, ethnicity, and age in the United States. *Ann Epidemiol.* 2006 Feb;16(2):123-30. [PubMed]
13. Veneri D, Franchini M, Randon F, Nichele I, Pizzolo G, Ambrosetti A. Thrombocytopenias: a clinical point of view. *Blood Transfus.* 2009 Apr;7(2):75-85. [PMC free article] [PubMed]
14. Franchini M, Veneri D, Lippi G. Thrombocytopenia and infections. *Expert Rev Hematol.* 2017 Jan;10(1):99-106. [PubMed]
15. Mason KD, Carpinelli MR, Fletcher JI, Collinge JE, Hilton AA, Ellis S, Kelly PN, Ekert PG, Metcalf D, Roberts AW, Huang DC, Kile BT. Programmed anuclear cell death delimits platelet life span. *Cell.* 2007 Mar 23;128(6):1173-86. [PubMed]
16. Dowling MR, Josefsson EC, Henley KJ, Hodgkin PD, Kile BT. Platelet senescence is regulated by an internal timer, not damage inflicted by hits. *Blood.* 2010 Sep 09;116(10):1776-8. [PubMed]
17. Stasi R. Immune thrombocytopenia: pathophysiologic and clinical update. *Semin Thromb Hemost.* 2012 Jul;38(5):454-62. [PubMed]
18. Budman DR, Steinberg AD. Hematologic aspects of systemic lupus erythematosus. Current concepts. *Ann Intern Med.* 1977 Feb;86(2):220-9. [PubMed]
19. Kuwana M. Helicobacter pylori-associated immune thrombocytopenia: clinical features and pathogenic mechanisms. *World J Gastroenterol.* 2014 Jan 21;20(3):714-23. [PMC free article] [PubMed]
20. Leslie SD, Toy PT. Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. *Am J Clin Pathol.* 1991 Dec;96(6):770-3. [PubMed]
21. Counts RB, Haisch C, Simon TL, Maxwell NG, Heimbach DM, Carrico CJ. Hemostasis in massively transfused trauma patients. *Ann Surg.* 1979 Jul;190(1):91-9. [PMC free article] [PubMed]
22. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. *J Clin Invest.* 1966 May;45(5):645-57. [PMC free article] [PubMed]
23. Mant MJ, Doery JC, Gaudie J, Sims H. Pseudothrombocytopenia due to platelet aggregation and degranulation in blood collected in EDTA. *Scand J Haematol.* 1975 Oct;15(3):161-70. [PubMed]
24. Peters M, Heyderman RS, Klein NJ. Platelet satellitism. *N Engl J Med.* 1998 Jul 09;339(2):131-2. [PubMed]

25. Ladhani S, Khatri P, El-Bashir H, Shingadia D. Imported malaria is a major cause of thrombocytopenia in children presenting to the emergency department in east London. *Br J Haematol*. 2005 Jun;129(5):707-9. [PubMed]
26. Patel U, Gandhi G, Friedman S, Niranjana S. Thrombocytopenia in malaria. *J Natl Med Assoc*. 2004 Sep;96(9):1212-4. [PMC free article] [PubMed]
27. Blickstein D. [TREATMENT OF IMMUNE THROMBOCYTOPENIC PURPURA IN ADULTS: UPDATE]. *Harefuah*. 2019 Mar;158(3):196-199. [PubMed]
28. Bakchoul T, Marini I. Drug-associated thrombocytopenia. *Hematology Am Soc Hematol Educ Program*. 2018 Nov 30;2018(1):576-583. [PMC free article] [PubMed]
29. Lewis BE, Wallis DE, Berkowitz SD, Matthai WH, Fareed J, Walenga JM, Bartholomew J, Sham R, Lerner RG, Zeigler ZR, Rustagi PK, Jang IK, Rifkin SD, Moran J, Hursting MJ, Kelton JG., ARG-911 Study Investigators. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. *Circulation*. 2001 Apr 10;103(14):1838-43. [PubMed]
30. Alving BM. How I treat heparin-induced thrombocytopenia and thrombosis. *Blood*. 2003 Jan 01;101(1):31-7. [PubMed]
31. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, Spasoff RA. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med*. 1991 Aug 08;325(6):393-7. [PubMed]
32. Veneri D, Franchini M, Gottardi M, D'Adda M, Ambrosetti A, Krampera M, Zanetti F, Pizzolo G. Efficacy of *Helicobacter pylori* eradication in raising platelet count in adult patients with idiopathic thrombocytopenic purpura. *Haematologica*. 2002 Nov;87(11):1177-9. [PubMed]
33. Kado R, McCune WJ. Treatment of primary and secondary immune thrombocytopenia. *Curr Opin Rheumatol*. 2019 May;31(3):213-222. [PubMed]
34. Stasi R, Amadori S, Osborn J, Newland AC, Provan D. Long-term outcome of otherwise healthy individuals with incidentally discovered borderline thrombocytopenia. *PLoS Med*. 2006 Mar;3(3):e24. [PMC free article] [PubMed]
35. Franchini M. Heparin-induced thrombocytopenia: an update. *Thromb J*. 2005 Oct 04;3:14. [PMC free article] [PubMed]
36. Finazzi G, Brancaccio V, Moia M, Ciavarella N, Mazzucconi MG, Schinco PC, Ruggeri M, Pogliani EM, Gamba G, Rossi E, Baudo F, Manotti C, D'Angelo A, Palareti G, De Stefano V, Berrettini M, Barbui T. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: a four-year prospective study from the Italian Registry. *Am J Med*. 1996 May;100(5):530-6. [PubMed]
37. Lockshin MD, Druzin ML, Goei S, Qamar T, Magid MS, Jovanovic L, Ferenc M. Antibody to cardiolipin as a predictor of fetal distress or death in pregnant patients with systemic lupus erythematosus. *N Engl J Med*. 1985 Jul 18;313(3):152-6. [PubMed]
38. Lacey JV, Penner JA. Management of idiopathic thrombocytopenic purpura in the adult. *Semin Thromb Hemost*. 1977 Jan;3(3):160-74. [PubMed]