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The Potential Haematoprotective Effects of Hibiscus Sabdariffa against Cisplatin-Induced Thrombocytopenia: A Review

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Abstract

Roselle, or Hibiscus sabdariffa, is a medicinal plant containing a variety of bioactive phytochemicals such as anthocyanins, flavonoids, phenolic acids and organic acids, all of which have been linked to antioxidant and other pharmacological effects. The present review looks at the possible haematological effects of Hibiscus sabdariffa, focusing especially on platelet production and cisplatin-induced thrombocytopenia. Platelets are vital for haemostasis and their production is controlled by thrombopoietin, megakaryocytes and the relevant cellular signalling pathways. Thrombocytopenia, which is marked by a lower than normal number of platelets in the circulation, can arise due to reduced production in the bone marrow, increased destruction of platelets or an abnormal distribution. Cisplatin, a chemotherapeutic drug based on platinum, can cause haematological toxicity via oxidative stress, damage to the bone marrow, apoptosis of the haematopoietic and megakaryocytic progenitor cells and a disruption of platelet production. The evidence considered in this study indicates that Hibiscus sabdariffa has antioxidant properties and might affect various haematological parameters, such as red blood cell count, haemoglobin concentration, packed cell volume and platelet count. Yet the results differ depending on the part of the plant, the preparation used, the dosage and the length of time for which it is administered. Even though these properties point to a possible use of Roselle in protecting blood-forming tissues from toxicity caused by chemotherapy, there is still limited direct evidence showing that it is effective against cisplatin-induced thrombocytopenia. It is therefore necessary to carry out further controlled experimental studies in order to determine its efficacy, safety and the mechanisms involved.

Keywords: Hibiscus Sabdariffa, Platelet Count, Thrombocytopenia, Cisplatin, Haematoprotection

Introduction

Hibiscus sabdariffa (Roselle) is a shrub from the Malvaceae family and the genus Hibiscus [1]. Hisbiscus sabdariffa is thought to be native to Tropical Africa, East Africa, or Asia (from Malaysia to India). The plant is widely grown as a home patio nursery crop in tropical regions such as the Caribbean, Central America, India, Africa, Brazil, Australia, Hawaii, Florida, and the Philippines [2]. Roselle is a woody-based sub-shrub or annual or perennial herb that can reach a height of 2.0 to 3.5 meters [3]. The leaves are palmately formed, triangular in shape, and measure 8 to 15 cm in length [3]. They are placed alternately on the stalk and have three to five lobes. The stem has a delicate rose hue and is glabrous. The plant has a tap root system and somewhat thin, branching roots. The flowers are upright, axillary, solitary, and have a diameter of 8 to 10 cm. Flowers have soft, fleshy calyces and range in hue from white to pale yellow. The flower's lanceolate-shaped, crimson calyx has two marginal ribs in each calyx lobe in addition to a noticeable central rib (Fig 1) [4].The petals might be white, pink, red, orange, purple, or yellow in colour. The seeds are reniform and glabrous, and the fruit is ovoid and capsular. Mature fruits have a vivid red hue [3]. Common names for Hibiscus sadariffa include "Roses of anthea," "African mallow," "Roselle," "Rose mallow," "Indian sorrel," "Flore de Jamaica," and "Jamaica tea" [5]. Hibiscus sabdariffa is referred to as "Roselle" in Australia, "Tengamoran" in Asam, "Gongura" in Hindi, "Krajeab" in Thailand, and "Bissap" in Senegal, Guinea Bissau, Mali, Burkina Faso, Ghana, Benin, Niger, Congo, and France. "Wonjo" in the Gambia, "Torosh" in Iran, "Sorrel" in the Caribbean, "Karkade" in Egypt, "Asam Paya" in Malaysia, "Luoshen Hua" in Chinese, "Lamanda" in Zambia, and "Zobo" in Nigeria [5]. Although it originated in India, the plant is now grown all over the world. It was brought to Central America, the West Indies, and Africa. Because of the suitable climate, it is widely grown in northern Nigeria [5].

Source: Adopted from [4]

Fig 1: Roselle plant (A) (Hibiscus sabdariffa L.) with the leaves (B), flowers (C) and calyces (D)

Phytochemical Constituents of *Hibiscus sabdariffa*

Hibiscus sabdariffa is made up from a range of substances that may be classed based on the different sections of the plant harvested such as leaves, stems, roots and flowers. Different pharmacological effects and defensive mechanisms are caused by the chemicals found in the plant (Table 1) [6].

Table 1: Phytochemicals Present in Different Parts of *Hibiscus sabdariffa*

Part of the plant	Chemical constituents
Flower	Carbohydrates, arabinans, mannose, sucrose, thiamin, xylose, mucilages, niacin, pectin, proteins, fat, arabinogalactans, rhamnogalacturans, riboflavin, β-carotene, phytosterols, citric acid, ascorbic acid, fruit acids, maleic acid, malic acid, hibiscic acid, oxalic acid, tartaric acid, (+)-alloxycitronic acid-lactone, allohydroxycitric-acid, glycolic acid, utalonic acid, protocatechuic acid, cyanidin-3-glucoside, cyanidin-3-sambubioside, cyanidin-3-xylglucoside, delphinidin, delphinidin-3-glucoside, delphinidin-3-sambubioside, delphinidin-3-xylglucoside, delphinin, gossypetin, gossypetin-3-glucoside, hibiscetin, hibiscin, hibiscitrin, sabdaretin, sabdaritrin, fibre (crude), resin, fibre (dietary), minerals and ash.
Seed	Starch, cholesterol, cellulose, carbohydrates, campesterol, β-sitosterol, ergosterol, propionic acid, pentosen, pelargonic acid, palmitoleic acid, palmitic acid, oleic acid, myristic acid, methanol, malvalic acid, linoleic acid, sterculic acid, caprylic acid, formic acid, stearic acid, cis-12,13-epoxy-cis-9-octadecenoic acid, isopropyl alcohol, isoamyl alcohol, ethanol, 3-methyl-1-butanol, fibre and minerals.
Leaf	α-Terpinyl acetate, anisaldehyde, β-carotene, β-sitosterol, β-D-galactoside, β-sitosteryl benzoate, niacin, fat, isoamyl alcohol, iso-propyl alcohol, methanol, 3-methyl-1-butanol, benzyl alcohol, ethanol, maleic acid, fibre and ash.
Fruit	α-Terpinyl acetate, pectin, anisaldehyde, ascorbic acid, calcium oxalate, caprylic acid, citric acid, acetic acid, ethanol, formic acid, pelargonic acid, propionic acid, isopropyl alcohol, methanol, benzyl alcohol, 3-methyl-1-butanol, benzaldehyde and minerals.
Root	Tartaric acid and saponin.

Source: Adopted from [6]

Nutritional Composition of Roselle

Early research revealed that calyces of Hibiscus sabdariffa (cHs) include fiber, protein, fat, and carbs. They are high in iron, calcium, β-carotene, and vitamin C [7]. Protein, fat, carbohydrates, and minerals (phosphorus, iron, thiamin, β-carotene, riboflavin, and ascorbic acid) are all present in the leaves [8]. Crude fatty oil, crude protein, carbohydrates, crude fiber, and ash were all present in the seeds. Potassium is the most common mineral, followed by sodium, calcium, phosphorus, and magnesium. The primary unsaturated fatty acids found in the seed oil are linoleic and oleic acid, whereas the primary saturated fatty acids are palmitic and stearic acids [8]. Because of their high protein content, the seeds can be roasted, crushed into a powder, and added to soups and sauces.

Traditional and Ethnomedicinal Uses of Roselle

The hibiscus sabdariffa plant has been utilized for a variety of industrial and therapeutic purposes. It has long been used as a cure for a number of illnesses as well as in culinary techniques (in dishes, food coloring, and beverages). For example, various parts of the Roselle plant, such as the flower, leaves, calyx, and corolla, are frequently drank as a thirst-quenching beverage in places like China and Thailand [9]. Numerous conditions, including cancer, neurosis, hypertension, arterioclerosis, and others, have been treated with it [9]. Numerous industrial items are made from hibiscus sabdariffa. They can be used fresh to make wine, juice, jam, jello, syrup, gelatin, pudding, cakes, ice cream, and flavors. They can also be dried and brewed into tea, spices, butter, pies, and sauces. To make roselle juice, boil it for a while, then strain the flowers to extract the juice, sweeten it with sugar, and add ginger. This yields a delicious juice [10]. The herb has been utilized in numerous traditional remedies and for the treatment of numerous illnesses. A tonic tea made from the leaves and blossoms is used to support kidney and digestive health. Flavonoids (gossypetine), glycosides, and other antioxidants are found in the leaves and flowers [9]. They are also believed to have diuretic, antiscorbutic, and fever-lowering properties. The flower lowers blood viscosity, which lowers blood pressure and promotes intestinal peristalsis. Abscesses, bilious conditions, cancer, cough, debility, dyspepsia, dysuria, fever, hangover, heart disease, hypertension, neurosis, scurvy, and strangurg are all treated with it in traditional medicine. Additionally, it can be used to treat arteriosclerosis [10].

Pharmacological and Biological Activities of Roselle

The pharmacological potential of Roselle, including its antihypertensive, anti-hyperlipidaemic, anti-inflammatory, antimicrobial, diuretic, uricosuric, and anaemia-treating effects (Table 2) (Fig 2). Apart from its nutritional and culinary applications, H. sabdariffa has drawn a great deal of scientific attention due to its various biological and pharmacological properties. These effects are mainly linked to the large amount of anthocyanins, flavonoids, phenolic acids and organic acids it contains, such as protocatechuic acid, hibiscus acid and hydroxycitric acid.

Table 2: Reported Biological Activities of Selected *Hibiscus* Species

Species	Biological activities reported
Hibiscus sabdariffa	Antioxidant, antihypertensive, antimicrobial, anti-inflammatory, antidiabetic, hepatoprotective, nephroprotective, hypolipidaemic, cardioprotective, anti-obesity and neuroprotective activities
Hibiscus rosa-sinensis	Antioxidant, antimicrobial, anti-inflammatory, antidiabetic, anticancer, antihypertensive, antifungal and antifertility activities
Hibiscus syriacus	Antioxidant, anti-inflammatory, antimicrobial and anticancer-related activities
Hibiscus acetosella	Antioxidant, antimicrobial and anti-inflammatory activities

Source: Adapted from [11]

Antioxidant activity

Roselle is perhaps best known for its antioxidant properties. Extracts of H. sabdariffa, especially those obtained from the calyces, contain polyphenols and anthocyanins which are able to eliminate reactive oxygen species and other free radicals. Among the anthocyanins mentioned are delphinidin-3-sambubioside and cyanidin-3-sambubioside. These substances might help in reducing oxidative damage to cellular components such as lipids, proteins and DNA. Experimental study results have shown that roselle consumption increases antioxidant capacity and provides protection against oxidative stress [7].

Antihypertensive and cardiovascular activity

Roselle has been given a great deal of attention for its possible antihypertensive effects. Experimental evidence indicates that H. sabdariffa might affect blood pressure by means such as inhibition of the enzyme angiotensin-converting enzyme (ACE), producing a diuretic and natriuretic effect, causing vasorelaxation and possibly modifying calcium channels [7].

There is also evidence from studies involving humans. A systematic review and meta-analysis of 13 randomized controlled trials with 1,205 participants found that, compared to a placebo, both systolic and diastolic blood pressure were reduced in adults who had mild to moderate hypertension. The authors, however, stated that further trials are needed in order to determine the long-term efficacy and to identify the groups most likely to benefit [12]. A more recent overview of the reviews and a dose-response meta-analysis also looked at the effects of H. sabdariffa on blood pressure, lipid profiles, glycaemic control, inflammatory markers and oxidative stress, while stressing the variation in the certainty of the evidence among the different outcomes [13].

Antidiabetic and metabolic activity

Roselle also shows potential as a substance that can lower blood sugar. Experimental studies indicate that its polyphenolic components might interfere with the digestion of carbohydrates by inhibiting enzymes such as α-amylase and α-glucosidase, which would then possibly decrease the rate at which dietary carbohydrates are turned into absorbable glucose [7]. A meta-analysis of randomized clinical trials showed that taking H. sabdariffa led to a small decrease in fasting plasma glucose; nevertheless, its effects on the various lipid parameters were inconsistent, which means that more well-designed clinical trials are required before it is possible to draw definite conclusions regarding its use in the management of diabetes [14].

Hypolipidaemic activity

The impact of roselle on lipid metabolism has been examined in both experimental and clinical studies. The proposed mechanisms involve effects on lipid absorption and metabolism, as well as antioxidant activity which may affect lipid oxidation. Several clinical meta-analyses have found that total cholesterol and low-density lipoprotein (LDL) cholesterol are reduced as a result of supplementation with H. sabdariffa [15].

The findings have not been entirely consistent. A previous systematic review of randomized trials revealed no significant overall effects on total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides [16]. It therefore seems reasonable to describe the lipid-lowering action of roselle as promising but not yet conclusively proven, especially since variations in preparation, dose, duration and the study populations can affect the results.

Anti-inflammatory activity

Because of its polyphenol-rich calyx extracts, Hibiscus sabdariffa (Roselle) has shown potential anti-inflammatory action [9]. These compounds may participate in the regulation of inflammatory responses by reducing oxidative stress and modulating inflammatory signaling pathways. The plant contains a high amount of polyphenolic compounds and anthocyanins, which may be responsible for the anti-inflammatory effects reported in experimental studies [7].

Anti-microbial activity

Roselle also possesses antimicrobial properties. Laboratory experiments have shown that extracts from various parts of *H. sabdariffa* have inhibitory activity against certain microorganisms. Phenolic compounds, organic acids, flavonoids and other secondary metabolites may be responsible for these effects. It has been suggested that the antimicrobial action takes place by disrupting the membranes of microbial cells, interfering with cellular metabolism and inhibiting the growth of microorganisms. Numerous pathogenic microbes, such as *Staphylococcus aureus, Bacillus cereus, Listeria monocytogenes, Shigella flexneri, Salmonella Typhimurium, Escherichia coli*, and *Bacillus anthracis*, have been shown to be susceptible to the antibacterial action of Roselle calyces [17]. Roselle calyces have strong antibacterial action against multidrug-resistant A. baumannii [18]. The plant's calyces have also been shown to exhibit antibacterial qualities against a range of pathogens, such as Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus, Klebsiella pneumonia, and foodborne infections. Hibiscus blossoms (Hibiscus rosa-sinensis) contain antibacterial compounds called saponins, flavonoids, and tannins [17]. The fact that roselle has antimicrobial properties may be one of the reasons why it has long been used in food and in herbal remedies. Yet the presence of antimicrobial activity in laboratory tests does not mean that roselle preparations can take the place of currently established antimicrobial drugs.

Hepatoprotective activity

The hepatoprotective effects of H. sabdariffa have also been reported. Experimental studies show that roselle extracts may protect liver tissue from oxidative and chemical damage, possibly due to their antioxidant properties and

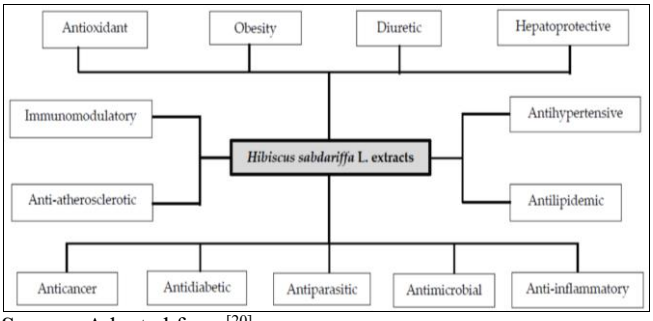
ability to reduce lipid peroxidation. Protocatechuic acid, anthocyanins and other phenolic compounds have been suggested as factors contributing to these effects [7].

Nephroprotective and diuretic activity

Roselle has shown potential effects on the kidneys, such as diuretic and nephroprotective actions. Both experimental and human studies have found changes in the excretion of electrolytes and other metabolites after consumption of H. sabdariffa. Its diuretic and natriuretic properties may also help to explain its reported ability to lower blood pressure [7].

Anti-obesity activity

More recent research has looked into the possible role of H. sabdariffa in weight control and in the case of obesity. The suggested mechanisms involve its effects on lipid metabolism, on adipocyte function and on carbohydrate metabolism. Yet the clinical results are still inconsistent. A systematic review and meta-analysis published in 2024 specifically pointed out that the evidence regarding the effectiveness of H. sabdariffa as a treatment for obesity is still inconclusive [19].



Source: Adopted from [20]

Fig 2: Pharmacological activities of Roselle

Haematological Effects of *Hibiscus sabdariffa*

The hematological effects of H. sabdariffa could be due to its nutritional and phytochemical composition. The vitamin C and organic acids in the plant might help with iron utilization, and the polyphenols and other antioxidants may assist in protecting blood cells from oxidative damage [21]. The haematological effects of Hibiscus sabdariffa L., especially regarding the production of red blood cells, hemoglobin concentration, packed cell volume (PCV), platelet count and the white blood cell (WBC) indices, have been studied. These effects are partly due to the vitamin C, iron, organic acids and other phytochemicals contained in the calyces and leaves. Yet the results differ depending on which part of the plant is used, the method of preparation, the dose and the duration of administration [21].

Effect on erythrocytes and haemoglobin

Several experimental studies indicate that H. sabdariffa might have a haematopoietic effect, especially regarding erythrocytic parameters. In a study carried out on Wistar rats, giving them an aqueous extract of H. sabdariffa leaf at doses of 200, 400 and 600 mg/kg body weight for 21 days resulted in significant increases in the number of red blood cells (RBC), PCV and haemoglobin concentration when compared with the untreated control group. The researchers believed that the extract could improve the erythrocytic profile, even though the study was carried out on animals and so it cannot directly prove an anti-anaemic effect in humans [22]. Anthocyanin compounds can stimulate erythropoietin production, affecting red blood cells or erythrocytes [23].

Effect on anaemia and iron status

Roselle's possible anti-anaemic properties have also been studied. Since the plant contains vitamin C and organic acids, these substances might in theory help with iron absorption and erythropoiesis. A clinical trial carried out on adults in a region where malaria is common looked at a standardised aqueous extract of H. sabdariffa for a period of 30 days. Even though the extract did not result in a significant improvement in the iron status of anaemic adults, the researchers stated that there was evidence of its safety and suggested that because of its iron and organic-acid content it should be the subject of further investigation regarding possible haematopoietic effects [24]. A review of the clinical studies also found that in healthy subjects who consumed a beverage made from the calyx of H. sabdariffa there were increases in the number of RBCs, haemoglobin, PCV and serum iron. Nevertheless, these results should be interpreted with caution since the existing human evidence is limited and the studies vary greatly in dose and preparation [21].

Effect on white blood cells

Roselle may also have an effect on the values of the white blood cells. In a study in which various aqueous preparations of H. sabdariffa ('zobo') were given to Wistar rats, the white blood cell count and the percentage of lymphocytes were found to be significantly lower in the treated animals, whereas the haemoglobin, PCV, red blood cell and platelet counts were all significantly higher than in the control animals [25]. Yet other experimental studies have found relatively small or non-significant changes in the leukocyte indices after administration of H. sabdariffa. For instance, the aqueous leaf extract caused no significant alterations in the total WBC, neutrophil and lymphocyte counts in Wistar rats. This indicates that the effect of Roselle on the leukocytes may vary according to the preparation, dose and physiological state of the individual [22].

Platelets and Haemostasis

Structure and Morphology of Platelets

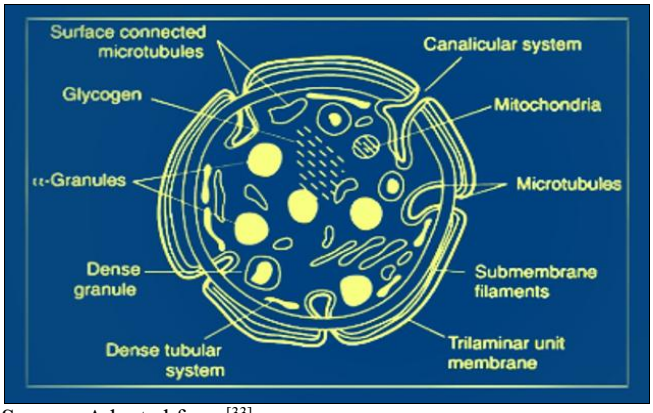
Platelets are significantly smaller than the other blood elements that have been previously identified, including erythrocytes and leukocytes. Typical mammalian platelets have a diameter of approximately 2–3 μm and are anucleated cells that are produced by the cytoplasmic fragmentation of megakaryocytes in the bone marrow [26]. On a stained peripheral blood film, normal platelets appear as small, discoid to oval entities with pale blue-grey cytoplasm with fine reddish-purple cytoplasmic granules (Fig 3) [27]. Platelet granules include α-granules, dense granules and lysosomal granules, which carry mediators involved in platelet activation, haemostasis, coagulation, inflammation and tissue repair (Fig 4) [28]. Following activation, platelets undergo typical morphological changes, including shape change, pseudopod formation, degranulation and spreading, which enable platelet adhesion and aggregation during primary haemostasis [29]. Abnormal platelet morphology, including large or giant platelets, platelet anisocytosis, hypogranular platelets and platelet

clumping, may provide valuable diagnostic information in individuals with thrombocytopenia and inherited or acquired platelet problem.

The average lifespan of platelets in humans is approximately 7-10 days [30], and they circulate in a discoid shape. Nevertheless, they endure significant alterations in shape and ultrastructure subsequent to activation; the membranes become ruffled with cytoplasmic projections, and the granules are centralised and discharged [30]. The typical human platelet count ranges from 150 to 450 × 10^9/L of blood [31]. However, spontaneous bleeding that is the result of reduced (but functionally normal) platelets is uncommon at levels exceeding 10,000/µl. Consequently, the stability of the circulating platelet count is essential for the preservation of health. This is accomplished by maintaining a dynamic equilibrium between platelet production and consumption/clearance, which must be rigorously regulated to regulate the total platelet count within a narrow physiological range.

Source: Adopted from [32]

Fig 3: Platelets on a stained blood film

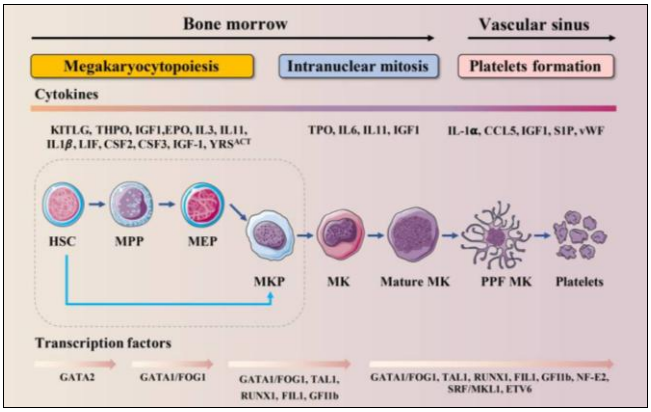


Source: Adopted from [33]

Fig 4: Platelets morphology

Platelet Production and Thrombopoiesis

Thrombopoiesis, the process by which MKs mature to form and release functional platelets into the circulating blood, can be split into three consecutive stages (Fig 5) [34]. The first stage is megakaryocytopoiesis, the process by which MKs are formed from bone marrow hematopoietic stem cells (HSCs), the biggest cells in the bone marrow, with a diameter of 40–70 µm and up to 100 µm, and comprising <0.05% of the total number of nucleated cells in the bone marrow [31]. As per the progressive hematopoietic differentiation concept, HSCs asymmetrically differentiate into multipotent progenitor cells (MPPs) that ultimately lose their self-renewal ability and pluripotency to form megakaryocytic/erythroid progenitors (MEPs). MEPs can develop into unipotent megakaryocyte progenitors and megakaryocyte precursor cells (MKPs), which eventually mature into MKs [35]. However, this concept has been questioned during the past decade. Recently, HSCs with a differentiation propensity toward the MK lineage have been discovered. These bypass MPPs generation and directly generate unipotent MK-restricted progenitors when mature cells must be rapidly supplied [36]. MK-restricted progenitor plays a vital function in response to acute platelet demand. In the second stage, MKs undergo endomitosis to generate polyploids [37]. During this stage, MKs are filled with cytoskeletal proteins, platelet-specific granules, and sufficient membrane and undergo a surge in nuclear proliferation and cytoplasmic expansion. The completion of this process yields several highly differentiated and mature polyploid MKs with huge cytoplasmic regions. On the third stage, mature MKs undergo plenty of biomolecular activities, such as caspase activation and significant cytoskeletal reorganisation, which drive the creation of cytoplasmic extensions called proplatelets [31]. These are loaded with granules and organelles, and are released as platelets into the blood under the action of blood-flow shear forces. This step is pretty rapid and completed within an hour. Demarcated membrane system (DMS), a considerable invagination of the plasma membrane, may be visible in the cytoplasm under an electron microscope, which separates the cytoplasm of the cells into different zones described as platelet territories. It takes around 5 days for human MKs to complete polyploidization, maturation and platelet release, and roughly 2–3 days for rodent MKs. Once discharged into the blood, human platelets live for 7–10 days, but rat platelets survive for 4 to 5 days [31].



Source: Adopted from [31]

Fig 5: Developmental stages of thrombopoiesis

Regulation of Thrombopoiesis

Thrombopoiesis is strictly regulated to maintain an adequate platelet count for normal haemostasis while allowing platelet production to grow when platelet demand rises. Regulation occurs through coordinated interactions between haematopoietic stem and progenitor cells, megakaryocytes,

bone marrow stromal cells, cytokines, transcription factors and signaling pathways. Among these regulatory systems, thrombopoietin (TPO) and its receptor, myeloproliferative leukaemia protein (MPL or c-Mpl), comprise the major physiological regulating axis of thrombopoiesis [38]. Thrombopoietin (TPO) is the key hormonal regulator of platelet formation [38]. It is produced largely by the liver and is continually discharged into the blood. TPO binds to the MPL receptor expressed on megakaryocytes, megakaryocyte progenitors and haematopoietic stem cells. Binding of TPO to MPL increases receptor activation and stimulates intracellular signalling pathways, including the Janus kinase 2 (JAK2)/signal transducer and activator of transcription (STAT), mitogen-activated protein kinase (MAPK), and phosphatidylinositol-3-kinase (PI3K)/AKT pathways. These mechanisms increase the survival, proliferation, differentiation and maturity of megakaryocytic progenitors and mature megakaryocytes, hence boosting platelet formation [39].

An important characteristic of thrombopoiesis is the feedback regulation of circulating TPO by platelets and megakaryocytes. TPO binds to MPL receptors on circulating platelets and megakaryocytes and is subsequently internalised and removed from the circulation. When platelet levels are normal or elevated, additional TPO is extracted from the plasma, leading to diminished free TPO concentrations and lowered stimulation of megakaryopoiesis. In contrast, when platelet levels decrease, a reduced amount of TPO is removed via MPL-mediated clearance. As a result, the levels of circulating free TPO rise, enhancing the development and maturation of megakaryocytes, which ultimately facilitates the restoration of platelet counts. This method offers a proficient feedback mechanism for sustaining platelet equilibrium [39].

The microenvironment of bone marrow significantly influences the regulation of thrombopoiesis. Megakaryocytes develop inside specific niches in close contact with bone marrow stromal cells, vascular endothelial cells and other cellular components. Interactions between megakaryocytes and the vascular niche influence their maturation, migration towards blood arteries and platelet release. Recent studies indicate that thrombopoiesis is influenced not solely by hormones but also by local cellular and extracellular cues inside the bone marrow microenvironment [40].

Throughout the development of megakaryocytes, cells undergo endomitosis, a unique variant of cell-cycle advancement where DNA replication occurs without the finalization of cell division. This results in significantly polyploid megakaryocytes characterized by increased cytoplasmic volume and elaborate membrane systems crucial for platelet synthesis. Following maturity, megakaryocytes deploy extended cytoplasmic projections known as proplatelets towards the bone marrow vasculature. These projections disintegrate and generate circulating platelets. Recent reviews underline the role of cytoskeletal organization, microtubules, membrane remodeling and the bone marrow vascular environment in affecting this final stage of thrombopoiesis [40]. Several transcription factors further influence megakaryocyte differentiation and platelet production. TPO/MPL signaling interacts with transcriptional networks that determine megakaryocyte lineage commitment and maturation. Factors such as GATA-1, FLI1, RUNX1 and NF-E2 contribute to the expression of genes required for megakaryocyte growth, cytoskeletal structure, granule formation and platelet release. Consequently, disturbance of these regulatory systems may hamper megakaryocyte proliferation and lead to thrombocytopenia or abnormal platelet formation.

In addition to TPO, additional cytokines and growth factors can alter thrombopoiesis. Interleukins, stem cell factor and other haematopoietic regulators can promote different stages of megakaryocyte growth, although their physiological impact is often less dominating than that of TPO. Inflammatory diseases can also influence platelet production. For example, inflammatory cytokines such as interleukin-6 (IL-6) might boost hepatic TPO synthesis and contribute to reactive thrombocytosis. Thus, thrombopoiesis can be altered in response not just to platelet demand but also to systemic inflammatory and physiological circumstances [40].

Functions of Platelets in Haemostasis

Platelets are the small anucleate cell fragments derived from the megakaryocytes in the bone marrow and are the essential components of the hemostatic system. The main function of platelets is to maintain vascular integrity and to prevent excessive blood loss after vascular injury [41]. Platelets do this by a coordinated sequence of adhesion, activation, secretion, aggregation and interaction with the coagulation system to finally produce a stable platelet–fibrin hemostatic plug (Table 3). Recent studies also indicate that platelets contribute to vessel integrity even in the absence of an overt rupture of the vessel [28].

Table 3: Major Functions of Platelets in Haemostasis

Platelet Function	Mechanism / Description	Importance in Haemostasis
Platelet adhesion	Platelets adhere to exposed subendothelial collagen at the site of vascular injury through von Willebrand factor (vWF) and platelet GPIb receptors.	Anchors platelets to the damaged vessel wall and initiates primary haemostasis.
Platelet activation	Adhesion causes platelets to change shape and release substances such as ADP, serotonin, calcium and thromboxane A_2 (TXA_2).	Recruits and activates additional platelets at the site of injury.
Platelet aggregation	Activated platelets express GPIIb/IIIa receptors, which bind fibrinogen and form bridges between adjacent platelets.	Produces the primary platelet plug, temporarily sealing the damaged vessel.
Vasoconstriction	Platelets release TXA_2 and serotonin, which promote constriction of the injured blood vessel.	Reduces local blood flow and limits blood loss.
Provision of a coagulation surface	Activated platelets expose negatively charged phospholipids, particularly phosphatidylserine, on their surface.	Provides a platform for coagulation-factor complexes, promoting thrombin and fibrin formation.
Clot stabilisation	Platelets interact with the developing fibrin network and help strengthen the platelet–fibrin clot.	Converts the temporary platelet plug into a more stable haemostatic clot.
Clot retraction	Platelet contractile proteins, including actin and myosin, generate forces that contract the clot.	Compacts and strengthens the clot and helps bring the edges of the injured vessel closer together.
Vascular and tissue repair	Platelets release growth factors such as PDGF and TGF-β.	Promotes repair of damaged blood vessels and surrounding tissues.

Source: Adapted from [28]

Thrombocytopenia

Definition Thrombocytopenia

Thrombocytopenia is a reduction in the number of platelets in circulation. The normal reference range is around 150,000 to 450,000/µL [31]. The most frequent cause of mucocutaneous bleeding is thrombocytopenia (platelet count <150,000/µL), which manifests as petechiae, purpura, ecchymoses, epistaxis, hematemesis, and menorrhagia [42]. Reduced platelet synthesis, rapid platelet breakdown, and aberrant platelet distribution or sequestration are the main pathophysiologic mechanisms in thrombocytopenia (Table 1).

Patients with platelet counts of 20,000/µL may not have many bleeding symptoms, and bleeding is uncommon when the platelet count is higher than 50,000/µL. Patients who have platelet counts below 10,000/µL are more likely to experience a severe episode of spontaneous bleeding [42].

Thrombocytopenia can be characterized along four intersecting axes: Severity, mechanism, acuity and aetiology.

Classification of thrombocytopenia

Classification by severity

Classification by severity is the most generally used clinical technique. In a worldwide inception cohort, thrombocytopenia was categorized as mild (100–149 × 10^9/L), moderate (50–99 × 10^9/L), severe (20–49 × 10^9/L) and very severe (< 20 × 10^9/L) Table 4, based on the platelet count upon admission and the nadir(lowest) count during the stay [43]. In oncology practice, thrombocytopenia is classified by severity from mild (Grade 1–2) to severe (Grade 3–4), and these grades often decide whether treatment must be modified, transfused or supported pharmacologically [44].

Classification by mechanism

Classification by mechanism follows the physiological scheme already outlined productive (decreased production), destructive (increased destruction), distributional (splenic sequestration), dilutional and artifactual and is useful because it directs the diagnostic search: Productive thrombocytopenia points toward bone marrow examination and myelotoxic exposure, whereas a destructive picture with increased marrow megakaryocytes points toward immune or consumptive processes [45].

Classification by acquity

Classification by acuity distinguishes acute from chronic thrombocytopenia, a distinction that carries direct management implications: Patients with acute thrombocytopenia may require hospitalisation, and common causes requiring emergency admission include heparin-induced thrombocytopenia, thrombotic microangiopathies and the haemolysis, elevated liver enzymes and low platelet count syndrome, whereas common non-emergency causes include drug-induced thrombocytopenia, immune thrombocytopenia and hepatic disease [46]. The illness course also effects bleeding symptoms, and the rate of bleeding-related events in newly diagnosed patients is much higher than in chronic cases [47].

Classification by aetiology

Classification by aetiology divides main or hereditary forms from secondary or acquired forms. Inherited thrombocytopenias today encompass 22 illnesses caused by mutations in 24 genes, marked by varied degrees of complexity and substantial diversity in outcome [48]. Because the clinical spectrum of congenital thrombocytopenia extends from severe bleeding diatheses to moderate disorders that may remain unnoticed even in adulthood, proper categorization is critical for appropriate follow-up, medication selection and counselling [48]. A final classification axis immune versus non-immune cuts across all of the above and is clinically decisive, since immune-mediated destruction is frequently corticosteroid- and splenectomy-responsive, whereas consumptive coagulopathies require treatment of the underlying trigger [49, 50].

Table 4: Classification according to severity

Category	Platelet count	Typical clinical correlate
Mild	100–149 × 10^9/L	Counts greater than 50 × 10^3/µL rarely produce symptoms
Moderate	50–99 × 10^9/L	Counts of 30–50 × 10^3/µL rarely manifest as purpura; 20–50 × 10^3/µL may produce mild skin manifestations such as petechiae, purpura or ecchymosis
Severe	20–49 × 10^9/L	Bleeding with minimal trauma may occur at 10–30 × 10^3/µL; bleeding without obvious trauma can appear when the count falls to 20–30 × 10^9/L
Very severe	< 20 × 10^9/L	Serious bleeding usually does not occur until the count is less than 10 × 10^3/µL; counts below 5 × 10^3/µL may cause spontaneous bleeding and constitute a haematologic emergency

Source: Adapted from [46]

Causes of Thrombocytopenia

Normally, about one third of all platelets are found in the spleen, the lifespan of platelets is 9 to 10 days, and approximately 15,000 to 45,000 platelets per microlitre have to be produced each day in order to maintain a steady state [51]. The cells responsible for platelet production, the megakaryocytes, are large, multinucleated cells that are located in the bone marrow, and thrombopoietin is the most important regulatory protein controlling this process; the messenger RNA for TPO is present in the kidney, the liver and smooth muscle cells and the TPO gene is situated on chromosome 3 (3q26-27) [49]. If TPO is absent, the megakaryocyte mass can be reduced by as much as 80 per cent, while platelet production can increase six to eight times within 10 days in response either to TPO or to the destruction of platelets [49]. Any disturbance of this closely regulated balance whether at the level of the stem cell, the megakaryocyte, the circulating platelet or in its distribution can lead to thrombocytopenia.

Thrombocytopenia is usually categorised according to the stage in platelet physiology at which the defect takes place. As noted in a thorough examination of the causes and clinical significance of thrombocytopenia, the condition can be due to decreased platelet production, increased peripheral destruction or abnormal distribution, or excessive consumption, and may be associated with anything from benign temporary conditions to life-threatening diseases; accurate interpretation requires an integrated understanding of platelet physiology, bone marrow function, immune regulation and haemostasis [52]. This approach is also reflected in diagnostic reviews, which list decreased bone

marrow production of platelets, increased peripheral destruction of platelets, increased splenic sequestration and dilution as the main mechanisms, and stress that investigation must take into account both the clinical history and the laboratory findings [53]. Another category spurious or artefactual thrombocytopenia has to be ruled out before any of these mechanisms is accepted [45].

Reduced platelets production

Low platelet production most often results from disorders that affect the bone marrow. It can happen due to bone marrow aplasia, because of abnormal cells replacing the marrow, as a result of chemical damage, or because of a congenital disease; marrow replacement takes place when large abnormal cells squeeze and push the normal megakaryocytes aside, a situation that is observed in leukaemias, lymphomas, myelofibrosis, granulomatous diseases and metastatic neoplasia, while chemical injuries involve exposure to toxic chemicals such as benzene and insecticides, to medications such as anticonvulsants, tranquilizers, thiazides and cancer chemotherapeutic agents, and also alcohol [54]. Ineffective thrombopoiesis; this being marked by a greater mass of megakaryocytes in the marrow together with a decrease in the formation of new platelets is another form of it, examples including hereditary disorders such as May-Hegglin anomaly, Wiskott-Aldrich syndrome and autosomal-dominant thrombocytopenia, as well as vitamin B12 and folate deficiency in individuals with a history of alcohol abuse or with defective folate metabolism [49]. Reviews of productive thrombocytopenia also link megakaryocyte depression with haematopoietic aplasia, various types of neoplasia and myelotoxic therapy [45].

Increased platelet destruction

The most common reason for thrombocytopenia in clinical practice is increased platelet destruction, this occurring when the rate of platelet destruction is greater than the rate of platelet production; the causes can be divided into immunological and non-immunological groups, the immunological ones comprising idiopathic autoimmune thrombocytopenic purpura, secondary autoimmune thrombocytopenic purpura and alloimmune thrombocytopenia, and the non-immunological ones including disseminated intravascular coagulation, thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome [49]. Autoantibodies promote platelet clearance by facilitating their removal through splenic macrophages and dendritic cells, by causing complement deposition and platelet apoptosis, or by inhibiting megakaryocytic platelet production [50].

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia is a separate and clinically serious type; over 100 drugs have been associated with it, such as quinine, sulfonamides, abciximab, carbamazepine and vancomycin, as well as herbal remedies and a number of non-prescription drugs, and drug-induced immune thrombocytopenia should be considered in any case of acute thrombocytopenia where the cause is unknown [55]. The drugs most frequently implicated in current practice are abciximab, carbamazepine, ceftriaxone, eptifibatide, heparin, ibuprofen, mirtazapine, oxaliplatin, penicillin, quinine, quinidine, rifampicin, suramin, tirofiban, trimethoprim-sulfamethoxazole and vancomycin [56].

Chemotherapy-induced thrombocytopenia (CIT)

Thrombocytopenia caused by chemotherapy is the type most relevant to exposure to cytotoxic agents. The frequency of CIT differs considerably according to the treatment employed, the highest rates being linked to regimens based on gemcitabine and platinum [57]. A comprehensive review of CIT in cancers of the gastrointestinal tract showed that the condition occurred in 20–25% of patients with solid tumours, the highest rates being seen in those given gemcitabine (64%), carboplatin (58%) and oxaliplatin (50%) [44]. The estimated 3-month incidence of thrombocytopenia at the population level is 13% in patients with solid tumours and 28% in those with haematological cancers [58].In a sample representative of the US population, 4% of patients with solid tumors and 16% of patients with hematological malignancies had grade 3 thrombocytopenia [59].

Consumptive and microangiopathic causes

In both disseminated intravascular coagulation (DIC) and thrombotic microangiopathy there is microvascular thrombosis going along with thrombocytopenia, a tendency to bleeding and organ failure; hyperfibrinolysis is seen in most patients with DIC, and markedly reduced A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif, member 13 (ADAMTS13) activity, the presence of Shiga-toxin-producing Escherichia coli and abnormalities of the complement system are helpful in diagnosing Thrombotic Thrombocytopenic Purpura (TTP), Shiga-Toxin-Producing *Escherichia coli*–Associated Haemolytic Uraemic Syndrome (STEC-HUS) and atypical Haemolytic Uraemic Syndrome (HUS) respectively [60]. The pathophysiology of these thrombotic microangiopathies can be described as a spectrum of different phenotypes TTP, consumptive DIC and non-consumptive secondary Thrombotic Microangiopathy (TMA) with platelet aggregation being the key mechanism in TTP and endothelial damage the characteristic feature of HUS [61].

Inherited causes

Inherited factors complete the picture of the cause. Inherited platelet disorders constitute a diverse group of rare diseases, the clinical severity of which varies, and are generally marked by mucocutaneous bleeding and by excessive blood loss following trauma or surgery; the molecular abnormalities may affect megakaryopoiesis and proplatelet production leading to an inherited thrombocytopenia or they may impact on the platelet ultrastructure, the granules and the responses to agonists, a condition known as inherited platelet function disorders [62]. At least 41 disorders caused by mutations in 42 different genes have now been identified [63]. Since inherited thrombocytopenias can range from severe bleeding tendencies that are recognised in the first weeks of life to mild forms which may go undetected until adulthood, it is essential to distinguish between inherited and acquired thrombocytopenia particularly between inherited and immune thrombocytopenic purpura in order to avoid unnecessary and possibly harmful treatments [64].

Mechanisms of Platelet Destruction and Reduced Production

Reduced platelet production

Reduced platelet production in the context of cytotoxic exposure begins at the level of the haematopoietic stem and progenitor cells. Acute bone marrow injury is mainly due to

apoptosis induced by chemotherapy in the rapidly proliferating haematopoietic progenitor cells; the haematopoietic system's homeostasis is then restored by haematopoietic stem cells undergoing self-renewal and differentiation to replenish progenitors and produce mature blood cells including platelets [58]. Haematopoietic stem cells are relatively more sensitive to oxidative stress partly because they reside in a hypoxic niche and maintain a quiescent state so that even a mild increase in reactive oxygen species can reduce their self-renewal capacity by triggering senescence, resulting in premature exhaustion and long-term bone marrow injury that may produce permanent thrombocytopenia; cisplatin has been shown to hinder normal haematopoiesis by generating oxidative stress in the bone marrow in an *in vivo* mouse model [58].

At the megakaryocyte level, the mechanisms are more specialized. Using a culture system that recapitulates human megakaryopoiesis, cytotoxic drugs were found to destroy predominantly megakaryocytic progenitors at early stages of differentiation; immature megakaryocytes could be protected by stem cell factor, which activated Akt, neutralised the mitochondrial apoptotic machinery and inhibited caspase activity, indicating apoptosis of megakaryocyte progenitors as a major cause of CIT [65]. Megakaryocytes possess an intrinsic apoptosis pathway whose key components are pro-survival Bcl-xL and pro-death Bak and Bax; loss of Bak and Bax significantly ameliorated both the thrombocytopenia and the anaemia triggered by carboplatin, confirming that this intrinsic pathway mediates megakaryocyte death in response to pro-apoptotic stimuli [66].

Signalling-level disruption adds a further layer. In carboplatin-induced CIT, expression of JAK2 was significantly reduced both *in vivo* and *in vitro*, and the JAK2/STAT3 pathway remained inactivated even when thrombopoietin was administered; carboplatin also caused prominent S-phase cell cycle arrest and markedly increased apoptosis in megakaryocytic cells [67]. This observation is essential because it explains why exogenous TPO supplementation alone may fail to restore thrombopoiesis under cytotoxic stress – the receptor-proximal signalling apparatus itself is inhibited [67]. The wider significance of this axis is evident from the genetic literature: Homeostatic platelet production is mainly regulated by TPO and the TPO receptor/JAK2 axis, and TPO regulates nearly all stages of megakaryocyte differentiation, so that numerous diseases characterised by altered megakaryocyte or platelet production are due to acquired or hereditary mutations in MPL, THPO or JAK2 [68]. TPO is the principal physiological regulator of thrombopoiesis, with blood and marrow levels inversely related to platelet count, and patients with aplastic anaemia or thrombocytopenia attributable to myelosuppressive medication have high levels of the hormone [69]. MPL expression on megakaryocytes and platelets is dispensable for thrombopoiesis itself but required to prevent megakaryocytosis and myeloproliferation by reducing the amount of TPO accessible to excite progenitor cells [70].

Different chemotherapeutic agents inhibit this pathway at different steps: Alkylating agents damage stem cells, cyclophosphamide affects later megakaryocyte progenitors, bortezomib limits platelet release from megakaryocytes, and certain treatments increase platelet apoptosis [57]. For cisplatin specifically, the main molecular mechanism of myelotoxicity is its ability to bind cellular DNA and render the cell incapable of replication, alongside its capacity to induce oxidative stress; reactive oxygen species are toxic to bone marrow cells and probably trigger apoptosis and affect the cell cycle, with platelet counts significantly decreased after 15 days of cisplatin treatment in rats, attributed to inhibition of bone marrow activity or to decreased production or increased consumption of platelets [71]. Free radicals are also generated by anthracycline drugs during metabolism, which leads to toxicity on normal hematopoietic cells, especially megakaryocytes in the bone marrow and decreases platelet formation [72].

Finally, reduced production may be ineffective rather than absent: Ineffective thrombopoiesis is characterised by an increase in the marrow megakaryocyte mass alongside a reduction in the formation of new platelets, as seen in certain hereditary thrombocytopenias and in vitamin B12 and folate deficiency [49]. Platelets, once released, have a limited life span, which is determined by a “platelet clock” that depends on Bcl-xL to inhibit the pro-apoptotic proteins Bax and Bak; when Bcl-xL declines, activity of Bax and Bak increases, leading to platelet apoptosis, and apoptotic platelets are removed by the reticuloendothelial system, probably in the liver [73]. Mechanisms of platelet destruction Antibody mediated clearance. The main mechanism of platelet clearance is the presence of autoantibodies against glycoproteins on the surface of platelets. About 70-80% of patients have autoantibodies against GPIIb/IIIa, 20-40% have autoantibodies against the GPIb complex, and some patients have autoantibodies against both or other glycoproteins [74, 75]. Autoantibodies can be found in around 50% of patients, and current hypothesis argues that antibodies against GPIIb/IIIa mediate platelet destruction in the spleen via macrophages through Fc–FcγR interactions [74]. The spleen is both the major location of antibody production and the dominating organ for clearance of IgG-coated platelets, however in a minority of cases hepatic clearance predominates [76]. Critically, a second, Fc-independent pathway has been identified: Antibodies against GPIbα, but not those against GPIIb/IIIa, can produce thrombocytopenia via their $F(ab)_2$ fragment, and most anti-GPIbα antibody-mediated thrombocytopenia is resistant to intravenous immunoglobulin [75]. This is explained by desialylation cytotoxic T lymphocytes and anti-GP autoantibodies can induce desialylation of platelet surface glycans, leading to premature platelet clearance, with desialylated platelets mainly cleared by liver Kupffer cells through the interaction of macrophage galactose lectin or Kupffer cell receptor with N-acetylgalactosamine, galactose and fucose on platelets [47]. Importantly, thrombopoiesis is decreased or normal in most patients with immune thrombocytopenia and absolute reticulated platelet counts are reduced, suggesting relatively insufficient platelet production; after binding to megakaryocytes, anti-GP autoantibodies can interfere with the differentiation, maturation and apoptosis of megakaryocytes [47]. In other words, immunological thrombocytopenia is not merely a destructive illness but a combination destructive and production-limited one a theory directly transferable to the understanding of cytotoxic thrombocytopenia [47].

Drug-dependent destruction proceeds through several distinct mechanisms: classic drug-dependent platelet antibodies (quinine-type), hapten-induced antibodies (e.g., penicillin), fiban-dependent antibodies (e.g., tirofiban), Fab-

binding monoclonal antibodies (e.g., abciximab), drug-induced autoantibody formation (e.g., gold), and immune complex formation (e.g., heparin) [77]. Quinine binds to platelet glycoproteins, allowing platelet-reactive antibodies to attach strongly to circulating platelets only when soluble drug is available, with targets commonly on GPIIbIIIa or GPIbIX [77]. Heparin-induced thrombocytopenia is a particular form of drug-induced immune thrombocytopenia caused in most cases by heparin-dependent antibodies specific for platelet factor 4, which strongly activate platelets *in vitro* and *in vivo*, explaining why affected patients usually have thrombotic rather than bleeding complications [56]. β-lactams work as haptens to produce antibodies that detect changed platelet proteins, whereas quinine promotes a conformational change in proteins that induces antibodies recognising the proteins only in the presence of soluble drug [78].

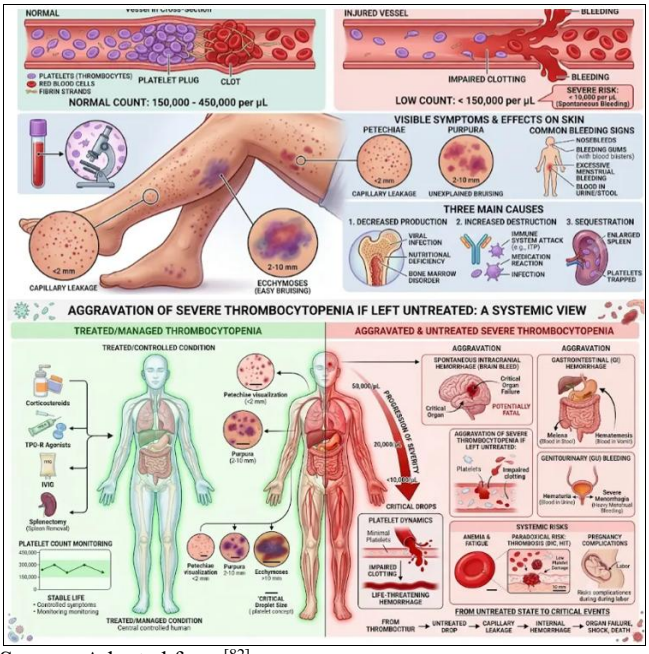
Consumptive destruction occurs in DIC and TMA, when microvascular thrombosis and platelet activation consume circulating platelets; all coagulation, fibrinolysis and platelet systems are activated in DIC, whereas only platelets are notably activated in TMA [60]. In sepsis-associated DIC the activation of coagulation is at the center of pathogenesis, while platelet aggregation is the fundamental mechanism in TTP and endothelial injury the hallmark of HUS [61]. Finally, anomalous distribution or pooling, splenic sequestration and dilution complete the mechanistic taxonomy, and both must be separated from genuine destruction because they demand for fundamentally different management [79].

Clinical Manifestations of Thrombocytopenia

The clinical presentation of thrombocytopenia is determined largely by the depth of the platelet count, although the severity of haemorrhagic symptoms is only approximately inverse to that count and is greatly influenced by concurrent variables [49]. Patients with a platelet count greater than 50 × 10^3/μL are generally asymptomatic; patients with counts between 20 and 50 × 10^3/μL may have mild skin manifestations such as petechiae, purpura or ecchymosis (Fig 4); and patients with counts below 10 × 10^3/μL have a high risk of serious bleeding [46]. Correspondingly, mild (100–150 × 10^9/L) and moderate (50–100 × 10^9/L) thrombocytopenia rarely are associated with clinical bleeding in the absence of trauma; bleeding without obvious trauma can appear when the count falls to 20–30 × 10^9/L, and serious bleeding usually does not occur until the count is below 10 × 10^9/L [80, 81].

If treatment is not administered, severe thrombocytopenia, or a low platelet count, can lead to potentially catastrophic consequences (Fig 6). These complications mostly entail uncontrolled internal and external bleeding. A lack of platelets seriously hinders the body's ability to stop bleeding from wounds or even on its own, since platelets are necessary for blood coagulation. The following are the primary issues and aggravations:

- In addition to gastrointestinal and urinary tracts, bleeding can occur in the brain (intracranial hemorrhage), which can be fatal.
- Excessive External Bleeding: Patients may experience bleeding gums, heavy, difficult-to-stop nosebleeds (epistaxis), and excessive bleeding from small cuts or from standard dental and medical treatments.
- Heavy Menstrual Bleeding: Menorrhagia, or exceptionally heavy and prolonged menstrual flow, can lead to anemia in women and menstruating individuals if left untreated due to insufficient platelets.
- A deficiency of clotting factors results in excessive bruising and petechiae, as blood accumulates beneath the epidermis. This causes a rash of petechiae, which are small, pinpoint red patches, as well as frequent, simple bruising.
- Pregnancy Complications: Individuals with thrombocytopenia are at an increased risk of experiencing fetal loss, premature birth, and excessive hemorrhage during delivery, and potentially life-threatening conditions such as preeclampsia.
- The progression of underlying conditions, such as autoimmune disorders (such as lupus), blood malignancies (such as leukemia), or bone marrow failure, may be indicated by thrombocytopenia. If a low platelet count is disregarded, the detection and treatment of these hazardous primary disorders will be postponed [82].



Source: Adopted from [82]

Fig 6: Clinical complications of thrombocytopenia

Cisplatin

Cisplatin, which is known as cis-diamminedichloroplatinum, is a platinum-based drug used in chemotherapy and continues to play a central role in contemporary oncology. It is employed in the treatment of a number of human cancers such as bladder, head and neck, lung, ovarian and testicular cancers, and is effective in the treatment of carcinomas, germ cell tumours, lymphomas and sarcomas [83]. The main reason for its anticancer action is its ability to bind to the purine bases in DNA, leading to the formation of intra-strand DNA adducts which prevent DNA repair and replication and thus cause apoptosis in cancer cells [83]. The cytotoxic effect is enhanced via both the intrinsic and extrinsic apoptotic pathways, as a result of reactive oxygen species being produced through lipid peroxidation, the activation of signal transduction pathways, the induction of p53 signalling and cell cycle arrest, the upregulation of pro-apoptotic genes and the downregulation of anti-apoptotic genes and proto-oncogenes [84].

Although cisplatin has a high clinical value, it is still limited by two ongoing problems: Its toxic effects and the development of resistance. The toxicity of cisplatin results from its interaction not only with DNA in tumour cells but also with proteins and nucleic acids in normal tissues, leading to nephrotoxicity, ototoxicity, neurotoxicity and gastrointestinal damage, permanent hearing loss being a particularly severe problem in children [83]. Other known side effects are nausea, cardiotoxicity, hepatotoxicity, allergic reactions, a reduced ability to resist infection, haemorrhage and suppression of the bone marrow [85, 86]. Resistance occurs due to reduced accumulation of the drug inside the cells, improved DNA repair, detoxification by thiol-containing molecules and changes in apoptotic signaling [83]. Since these limitations exist, combination therapies involving cisplatin and other drugs have been widely studied in order to overcome resistance and lower toxicity [87, 86]. Against this background given that the drug is highly effective but has a narrow therapeutic margin the haematological effects of cisplatin become important.

Cisplatin-Induced Haematological Toxicity

Haematological toxicity is a common and clinically important result of cisplatin exposure, with its mechanisms acting at various levels of the haematopoietic hierarchy. The rapid turnover of hematopoietic progenitor cells results in acute bone marrow injury shortly after the administration of chemotherapy due to apoptosis induced by the cytotoxic agents. However, the majority of hematopoietic stem cells are in a quiescent state and thus are relatively resistant to chemotherapy-induced apoptosis, and homeostasis is restored through the self-renewal and differentiation of stem cells, which replace the progenitors and lead to the production of mature blood cells [58]. Cisplatin causes damage to the normal hematopoiesis by reducing the production of colony-forming unit granulocytes/macrophages. Research conducted on rat models administered carboplatin has demonstrated an increase in DNA fragmentation in bone marrow cells which correlates to increased progenitor apoptosis [58].

At the molecular level, the primary way in which cisplatin causes myelotoxicity is by binding to cellular DNA and thus preventing the cell from replicating; another mechanism involves the induction of oxidative stress, since reactive oxygen species are toxic to the cells of the bone marrow and can cause apoptosis as well as affect the cell cycle, leading to anaemia and a reduction in the number of leukocytes [71]. It is described as a common and serious complication of cancer chemotherapy for myelosuppression to result in leukopenia and thrombocytopenia, and several authors have noted a decrease in white blood cell counts after cisplatin has been administered [71].

Anaemia is a significant haematological adverse effect linked with treatment using cisplatin. The occurrence of cisplatin-induced anaemia is due to a number of factors and can include both direct effects on erythropoiesis and, notably, renal injury leading to a decrease in the production of erythropoietin. Cisplatin builds up in the cells of the renal tubules and is capable of causing oxidative stress, DNA damage, inflammation and apoptosis, which in turn results in injury to the renal tubules and acute kidney injury [88, 89]. Since the kidneys are the main source of endogenous erythropoietin, renal dysfunction associated with cisplatin can lead to insufficient stimulation of erythroid progenitor cells by erythropoietin and thus to a reduced production of red blood cells. More generally, anaemia that develops during anticancer treatment can also be affected by inflammation, reduced availability of iron and the suppression of erythropoiesis caused by the treatment [90].

The link between renal toxicity and anaemia is especially important in the case of cisplatin since nephrotoxicity is one of its main dose-limiting side effects. Current evidence shows that renal injury caused by cisplatin results from a number of interacting mechanisms, such as oxidative stress, mitochondrial dysfunction, DNA damage, inflammatory signalling and programmed cell death [88, 91]. It is therefore not merely a consequence of direct toxicity to the bone marrow. Impairment of renal erythropoietin production and systemic effects of the cancer and chemotherapy are likely to make a substantial contribution to the decrease in erythropoiesis.

The tendency of platinum compounds to suppress bone marrow has been established through mathematical modelling. Drugs such as carboplatin, oxaliplatin and cisplatin can cause a significant reduction in platelet levels since these chemotherapy agents destroy the stem and progenitor cells in the bone marrow and this in turn results in a lower number of platelets in the blood; the model's parameters can determine which patients will have a strong reaction to the chemotherapy, this being marked by a quick fall in cell count followed by a small rebound [92]. As both chemotherapy and radiation act in a non-specific way and non-cancerous cells are affected as well, excessive treatment can lead to haematological toxicities and when the number of cells drops too low bleeding and infection can occur and treatment can be delayed [92].

Cisplatin-Induced Thrombocytopenia

Thrombocytopenia is one of the most clinically significant haematological toxic effects caused by platinum-based chemotherapy. In an experiment in which cisplatin was given to rats, the platelet count had been significantly lowered after 15 days of treatment when compared with that of the control group; the researchers explained this as being due to cisplatin inhibiting bone marrow activity, or alternatively as a result of reduced platelet production or increased platelet consumption, or because of increased platelet aggregation [71]. The threefold explanation suppressed production, accelerated consumption and enhanced aggregation reflects the ongoing mechanistic uncertainty surrounding platinum-induced thrombocytopenia and offers a helpful framework for studying it.

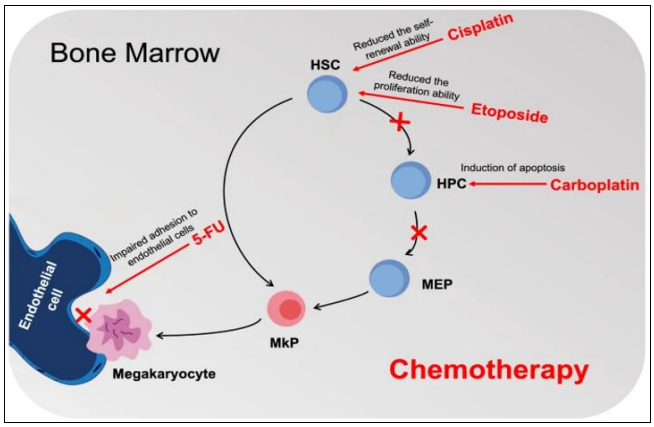
The evidence from other platinum-based agents is very informative since the same pathways are involved. Thrombocytopenia resulting from chemotherapy is mainly due to the selective death of megakaryocyte progenitors at early stages of their differentiation; in a culture system that mimics human megakaryopoiesis, cytotoxic drugs were seen to destroy mainly the megakaryocytic progenitors, and the immature megakaryocytes could be protected by stem cell factor, which activated Akt, neutralised the mitochondrial apoptotic machinery and inhibited caspase activity this showing that apoptosis of megakaryocyte progenitors is a major cause of CIT [65]. The intrinsic apoptotic pathway is controlled by the balance between the pro-survival protein Bcl-xL and the pro-death proteins Bak and Bax, and a loss of Bak and Bax greatly reduced both the thrombocytopenia

and the anaemia caused by carboplatin, thus confirming that death of megakaryocytes in response to pro-apoptotic stimuli occurs via this pathway [31].

There is another mechanism involved, namely disruption at the level of signalling. In the case of carboplatin-induced thrombocytopenia, expression of JAK2 was found to be significantly decreased both *in vivo* and *in vitro*, and the JAK2/STAT3 pathway stayed inactivated even though thrombopoietin was given; furthermore, carboplatin led to a marked S-phase cell cycle arrest and a substantial increase in apoptosis in megakaryocytic cells [67]. This is mechanistically significant since it explains why giving exogenous thrombopoietin alone may not be sufficient to restore thrombopoiesis during cytotoxic stress: The signalling machinery close to the receptor is itself suppressed. The broader importance of this pathway is clear from the genetic literature, which shows that homeostatic platelet production is primarily controlled by thrombopoietin and the thrombopoietin receptor/JAK2 axis, thrombopoietin regulating almost all the stages of megakaryocyte differentiation, so that many diseases involving altered megakaryocyte or platelet production result from acquired or inherited mutations in MPL, THPO or JAK2 [68]. Thrombopoietin is the main physiological regulator of platelet production, with blood and marrow levels being inversely related to platelet count, and patients with aplastic anaemia or thrombocytopenia resulting from myelosuppressive therapy have high levels of the hormone [93]. Although the expression of MPL on megakaryocytes and platelets is not necessary for thrombopoiesis itself, it is essential for preventing megakaryocytosis and myeloproliferation by limiting the amount of thrombopoietin that can act on progenitor cells [70].

This pathway can be blocked at different points by different chemotherapeutic agents. Alkylating agents affect stem cells, cyclophosphamide acts on the megakaryocyte progenitors at a later stage, bortezomib inhibits the release of platelets by megakaryocytes and some treatments induce apoptosis in platelets [72]. Similarly, anthracycline drugs produce free radicals during metabolism which are toxic to normal hematopoietic cells, particularly megakaryocytes in the bone marrow, resulting in a decrease in platelet production [72]. CIT is associated with a risk of suboptimal overall survival and bleeding, and it leads to a greater requirement for reducing chemotherapy doses, delaying treatment, needing platelet transfusions and involving higher incremental costs; yet, due to the influence of tumour types, chemotherapy protocols and individual differences, CIT does not always show a consistent pattern [94]. Most standard treatment schemes have relatively low rates of dose-limiting thrombocytopenia, and when thrombocytopenia does occur it is usually of short duration (4 to 6 days) and responds well to platelet transfusion [73]. Since platinum-induced thrombocytopenia results from a combination of suppressed megakaryopoiesis, oxidative bone marrow injury and impaired thrombopoietin signalling, it represents a logical target for agents that can preserve megakaryocyte viability which is exactly the reason for investigating plant-derived haematoprotectants such as Hibiscus sabdariffa.

Chemotherapy-induced thrombocytopenia (CIT) results primarily from impaired platelet production following chemotherapy-induced injury to haematopoietic stem and progenitor cells, megakaryocyte progenitors and mature megakaryocytes (Fig 7). Chemotherapeutic agents can reduce progenitor-cell proliferation and survival, induce apoptosis, impair megakaryocyte maturation and interfere with megakaryocyte interactions with the bone-marrow vascular niche, ultimately reducing platelet production. Cisplatin is among the chemotherapeutic agents capable of producing this type of bone-marrow toxicity.



Source: Adopted from [58].

Fig 7: Chemotherapy-induced thrombocytopenia

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