



REVIEW PAPER

## Drug-induced thrombocytopenia – etiology and alternative therapeutic approaches

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### ABSTRACT

**Introduction and aim.** The cumulative incidence of drug-induced thrombocytopenia (DIT) is 10 cases per one million people per year with a prevalence of approximately 25% in critically ill patients. This review provides a comprehensive view of drug-induced thrombocytopenia, diagnosis, underlying mechanisms, common strategies in therapeutics, and potential alternatives.

**Material and methods.** Databases such as “Google Scholar”, “PubMed”, “Medline” and “MDPI” was used for literature review with the keywords, “platelets”, “platelet disorders”, “thrombocytopenia”, “drug-induced”, “oxidative stress”, “plant extracts”, “phytochemicals”, “antioxidants”, for the articles published between 2013-2023 and written in the English language.

**Analysis of the literature.** Several antimicrobials, anti-cancer drugs, and antivirals are often reported to cause adverse effects during treatment, such as thrombocytopenia. A thorough understanding of the underlying pathophysiology is important for appropriate treatment. Even though an improvement in platelet count is observed after the discontinuation of the causative drug, there is a dire need for treatment in some cases due to associated complications. There are various pitfalls with conventional treatments which include clinical complications and lack of effectiveness.

**Conclusion.** Interventions in therapeutics through antioxidants can aid in faster recovery. Various plant extracts and phytochemicals have been employed as therapeutics in platelet disorders due to their exceptional antioxidant activity. It is imperative to explore the bioactive components of natural products and their influence on platelet efficacy. Also, it highlights how antioxidants can be used as a safe, yet effective option as therapeutics for treating a complicated disorder such as DIT or be used as supplements to prevent adverse effects of existing treatments involving antibiotics and chemotherapeutics.

**Keywords.** alternative therapeutics, drug-induced thrombocytopenia, phytochemicals, platelets

### Introduction

Platelets or thrombocytes are blood cells that are continuously produced from megakaryocytes in a process called Thrombopoiesis, mainly in the bone marrow. These anucleate cells range from ~150,000–450,000/ $\mu$ L in healthy individuals.<sup>1</sup> They are found circulating in the blood for 8-10 days and are eliminated in the spleen and liver.<sup>2</sup> The main function of the platelet is to react to vascular damage and form a blood clot at the site to stop bleeding.<sup>3</sup> Nonetheless, platelets are also involved in several other functions such as affecting tumor pro-

gression by stimulating angiogenesis, separating the lymphatic circulation during embryogenesis, and helping to close ductus arteriosus at the time of birth. They are a significant part of primary immunity and contribute inflammatory mediators.<sup>4</sup>

Platelet disorders are primarily due to following reasons: (i) an increase in platelet number, (ii) a decrease in platelet numbers, or (iii) platelet dysfunction.<sup>5</sup> These can lead to either defective hemostatic plug formation leading to bleeding or spontaneous clot formation leading to thrombosis.<sup>6</sup>

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Platelet disorders are classified into:

- i. Platelet function disorders: Inherited or acquired, due to loss or gain of platelet function, change in size and morphology of the platelets, and associated with clinically important bleeding defects.<sup>7</sup>
- ii. High platelet count conditions or Thrombocytosis: Abnormal accumulation of platelets in the blood is further classified into primary or essential and secondary or reactive thrombocytosis.<sup>8,9</sup>
- iii. Low platelet count conditions or Thrombocytopenia: Atypically low platelet levels (under 20,000 per mm<sup>3</sup>) due to an underlying cause.<sup>10</sup>

## Aim

This review provides a comprehensive view of drug-induced thrombocytopenia, its diagnosis, underlying mechanisms, common strategies in therapeutics, and potential alternatives such as phytochemicals.

## Material and methods

Databases such as “Google Scholar”, “PubMed”, “Medline” and “MDPI” was used for literature review with the keywords, “platelets”, “platelet disorders”, “thrombocytopenia”, “drug-induced”, “oxidative stress” “plant extracts”, “phytochemicals”, “antioxidants”, for the articles published between 2013-2023 and written in English language.

## Analysis of the literature

### *Thrombocytopenia*

Thrombocytopenia is characterized by a massive reduction in platelets in the peripheral blood, caused by a myriad of both congenital and acquired causes. Acute and severe decrease in platelet count exposes the individuals to an increased risk of developing spontaneous hemorrhage or thrombosis. Hemostasis entirely depends upon the functioning and the number of platelets in circulating blood and any deviation in the number can cause many complications.<sup>11</sup>

The major causes of thrombocytopenia can be summarized as follows:<sup>12,13</sup>

- a. Decrease in differentiation of hematopoietic stem cells in bone marrow
- b. Impairment of megakaryocyte maturation
- c. Disruption of endothelial adhesion of megakaryocytes
- d. Increase in peripheral platelet destruction due to immune and non-immune mediated pathways
- e. Increase in splenic sequestration
- f. Accelerated clearance from the circulation
- g. Oxidative Stress

### *Drug-induced thrombocytopenia (DIT)*

The main threat in any treatment procedure is the side effects caused by therapeutic drugs. Drugs administered

for the treatment of a clinical symptom are capable of causing a different disorder altogether, based on their mode of action at the molecular level. DIT is one such disorder with a cumulative incidence of about 10 cases per million population per year and a prevalence as high as 25% in critically ill patients.<sup>14</sup> DIT is often underdiagnosed and underreported and puts the patients at an increased risk of hemorrhage.

Studies have been conducted during the past two decades based on the types of drugs that specifically induce thrombocytopenia. Around 300 drugs have been clinically implicated in causing DIT as an adverse effect during the treatment procedure. Commonly reported drugs can be categorized into antibiotics, chemotherapeutic drugs, steroids and cardiovascular drugs. Chemotherapy regimens involving dexamethasone + cytarabine + cisplatin, isophosphamide + carboplatin + etoposide, gemcitabine + dexamethasone + cisplatin and gemcitabine + and oxaliplatin are most commonly reported to cause DIT in cancer patients.<sup>15</sup> Some of the glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors have also been reported in DIT cases.<sup>14,16</sup> Drug-related disorders are common in small molecules as well as biotherapeutics. Although they were believed to be safe due to their specific action, many biotherapeutic drugs have been reported to lead to adverse reactions leading to loss in blood cell count and functions.<sup>16</sup> Some of the clinically important cases of DIT are listed in Table 1.

A detailed history of the patient and timely diagnosis is necessary to understand the underlying etiology. However, DIT often manifests in two ways:

- a. One to two weeks after beginning a new drug or suddenly, after a single dose when the drug was previously taken intermittently.<sup>22</sup>
- b. Immediately after the first administration of anti-thrombotic agents that block fibrinogen binding to platelet GP IIb-IIIa.<sup>14,37</sup>

DIT varies extensively from case to case and is often misdiagnosed as immune thrombocytopenic purpura and patients receive inappropriate treatment, leading to several complications. There have been cases where patients may not consider that self-regulated medications, beverages, foods, or herbal remedies are relevant to their bleeding symptoms and may not report them.<sup>38</sup>

Thorough understanding of the underlying pathophysiology plays a crucial role in devising a treatment of DIT. Identification of the trigger for the sudden fall in platelet count is the first and foremost step in the diagnosis of DIT. Secondly, excluding pseudothrombocytopenia is critical which occurs due to *in vitro* factors such as anticoagulants used during blood collection. There is no gold standard for the diagnosis of DIT, however, following a certain protocol in diagnosis and treatment as outlined in Fig. 1 can be favourable.<sup>39-41</sup>

**Table 1.** Cases of drug-induced thrombocytopenia and treatments

Drug class	Drugs	Medical condition	Time of diagnosis	Plausible mechanisms	Treatments
Antibiotics	Acyclovir <sup>17</sup>	Systemic lupus erythematosus (SLE)	Day 5	Drug-dependent immune mechanism	Discontinued Acyclovir; started IVIG at 0.4 g per kg/day for 4 days
	Benznidazole <sup>18</sup>	Chagas disease	Day 15	Toxicity due to reactive metabolites (free radicals) formed during the bioactivation	Discontinued Benznidazole; Prednisone at 1.5 mg/kg for 4 days with subsequent tapering of dose
	Azithromycin <sup>19</sup>	Nonpruritic maculopapular rash	Day 5	Drug-dependent and drug-independent antibodies	Discontinued Azithromycin; administered dexamethasone 40 mg IV + intravenous immunoglobulin (IVIG) for 10 days
	Piperacillin-Tazobactam <sup>20</sup>	Sepsis	Day 1	Platelet destruction due to hapten-dependent antibodies	Replaced the drugs with imipenem on day 9
	Vancomycin; Ciprofloxacin <sup>21</sup>	Left total knee arthroplasty	Day 18	Drug-dependent platelet antibodies	Replaced vancomycin and rifampin with IV daptomycin
	Indinavir <sup>22</sup>	HIV infection	Month 15	Platelet destruction due to antibody-mediated lysis and decreased production in the bone marrow due to underlying infection	Switched to Stavudine + Didanosine + efavirenz.
	Nitrofurantoin <sup>23</sup>	Urinary tract infection	Week 3	Immune-mediated adverse reactions	Intravenous corticosteroids + intravenous immunoglobulin (IVIG) + 4-units of platelet transfusion
Antineoplastic drugs	Cisplatin <sup>24</sup>	Bladder tumor	Day 28	Myelosuppression	Prophylactic platelet transfusion
	Etoposide <sup>25</sup>	Metastatic rectal neuroendocrine carcinoma	Month 4	Immune-mediated adverse reactions	Platelet transfusion + Rituximab
	Carboplatin <sup>26</sup>	Glioblastoma multiforme	Week 5	Platelet destruction	Drug discontinuation + Platelet transfusions + Papaya leaf extract liquid supplementation
	Oxaliplatin <sup>27</sup>	Small Bowel Adenocarcinoma	24 h	Bone marrow suppression	Drug discontinuation + Platelet transfusions
Biotherapeutics	Trastuzumab <sup>28</sup>	Breast Cancer	Day 2	Platelet-reactive IgG and IgM targeting glycoprotein IIb/IIIa and Ib/V/IX complexes	Drug discontinuation + Oral prednisolone
	Durvalumab <sup>29</sup>	Non-small cell lung cancer	Week 6	Anti-human platelet antigen auto-antibodies	Drug discontinuation
	Atezolizumab <sup>30</sup>	Small cell lung cancer	Month 7	immune checkpoint inhibitor-induced	Methylprednisolone + platelet transfusion + thrombopoietin
Cardiovascular drugs	Abciximab <sup>31</sup>	Percutaneous coronary intervention of left anterior descending artery	Day 8	Formation of antibodies against its chimeric structural peptide sequence	Oral prednisone + intravenous immunoglobulin (IVIG) for 7 days
	Atorvastatin <sup>32</sup>	Hyperlipidemia	Week 10	Platelet apoptosis in vivo	Discontinued atorvastatin + IVIG for 2 days + Prednisone 80 mg for 5 days + Rituximab
	Tirofiban <sup>33</sup>	Percutaneous transluminal coronary angioplasty	<24 h	Drug-dependent antibody-mediated platelet destruction	Drug discontinuation
	Eptifibatid <sup>34</sup>	Acute coronary syndrome	Day 2	Platelet destruction	Drug discontinuation
	Carvedilol <sup>35</sup>	Hemodialysis	Week 2	Drug-dependent antibody-mediated destruction of platelets	Drug discontinuation
	Heparin <sup>36</sup>	COVID-19	Day 11	Anti-PF4/heparin antibody	Drug discontinuation
	Quinine <sup>37</sup>	Restless leg syndrome	48 h	Immune reactivation of drug specific antibodies	Platelet transfusion

### Mechanisms

Majorly, the mechanisms can be classified into (i) platelet destruction and (ii) platelet production.

i. Platelet destruction: Platelet clearance due to increase in platelet desialylation by NanA neuraminidase and the Ashwell-Morell receptor (AMR)-dependent pathway can be the major causes of DIT during infection.<sup>42</sup> Cross-Reaction of the drugs with endogenous thrombopoietin can lead to the neutralization of platelets in the blood stream.<sup>43</sup> Off-target platelet binding and activation due to the overloading of the therapeutic drug in blood can result in platelet acti-

vation and eventually destruction.<sup>44</sup> The immune system can also play a major role in platelet destruction by inducing antiplatelet antibodies against the murine sequences of the chimeric Fab molecule.<sup>31</sup>

ii. Platelet production: Low platelet levels may be due to the inhibition of thrombopoietin signaling in early megakaryokinesis leading to decreased platelet production.<sup>45</sup> Myelosuppression/toxicity by targeting the epidermal growth factor receptor pathway, vascular endothelial growth factor (VEGF) pathway, and BCR-ABL pathway can contribute to low platelet count as there is an abnormality at

the production level or induction of platelet apoptosis.<sup>37,46,47</sup> Bone marrow toxicity caused by some drugs can inhibit megakaryocyte differentiation and maturation which can impact platelet numbers.<sup>48</sup> Platelet consumption can also occur due to endothelial dysfunction from lack of VEGF or suppression of hematopoiesis.<sup>49</sup> Table 2 outlines various mechanisms that reduce platelet numbers based on different classes of drugs and their target pathways.

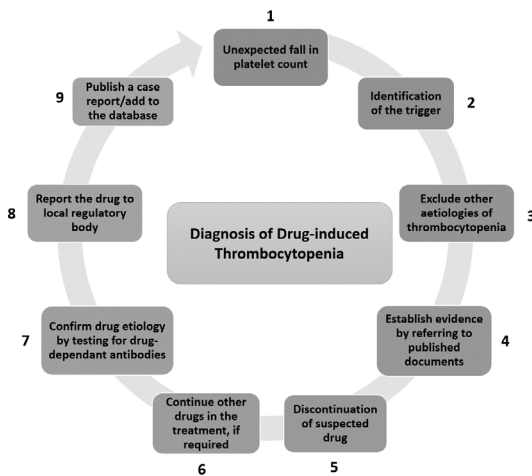


Fig. 1. Diagnosis of Drug-induced thrombocytopenia

Table 2. Mechanisms of the drugs inducing thrombocytopenia

Drugs	Mechanisms
Antimicrobials <sup>42</sup>	Increased platelet desialylation
Selinexor <sup>45</sup>	Inhibition of thrombopoietin signaling in early megakaryokinesis
Tyrosine and serine/threonine kinase inhibitors (KIs)- gefitinib and erlotinib <sup>46</sup>	Myelosuppression/toxicity by targeting epidermal growth factor receptor pathway
Tyrosine and serine/threonine kinase inhibitors (KIs)- sorafenib and sunitinib <sup>47</sup>	Myelosuppression/toxicity by targeting vascular endothelial growth factor pathway
Tyrosine and serine/threonine kinase inhibitors (KIs)- imatinib and dasatinib <sup>37</sup>	Myelosuppression/toxicity by targeting BCR-ABL pathway
Antibody-drug conjugates (ADCs)- brentuximab vedotin, trastuzumab emtansin; llotuzumab ozogamicin <sup>48</sup>	Bone marrow toxicity and inhibits megakaryocyte differentiation and maturation
Bevacizumab <sup>49</sup>	Platelet consumption due to endothelial dysfunction from lack of VEGF
Anti-CD40L mAbs <sup>50</sup>	Inhibits disaggregation of ADP-aggregated platelets
Abciximab <sup>51</sup>	Induction of antiplatelet antibodies directed against the murine sequences of chimeric Fab molecule
TNF- $\alpha$ inhibitors <sup>52,53</sup>	Induces autoantibodies including antiplatelet antibodies or suppression of hematopoiesis
AMG X and LY2541546 <sup>54,55</sup>	Platelet activation by direct binding to platelets and/or megakaryocytes causes the release of serotonin
Thrombopoietic agents- rHu-TPO or PEG-rHuMGDF <sup>43</sup>	Cross-React with endogenous thrombopoietin and neutralizes
CH12 humAb <sup>44</sup>	Off-target platelet binding and activation resulting in platelet destruction

Treatments

Treatment strategies for DIT focus primarily on the recovery of lost platelets. In most cases, physicians identify the drug responsible for the condition and take the first step by switching the suspected drug to an alternate drug. Cessation of administering a suspected drug generally reverses the condition of DIT in most cases.<sup>14</sup> However, treatment is required in cases where the therapeutic drug is crucial for the patient or when patients experience life-threatening bleeding. Conventional treatment is advised based on the following strategies outlined below.

Common approaches

The outline of commonly used strategies in the treatment of DIT is summarized in Fig. 2 and can be explained as follows:

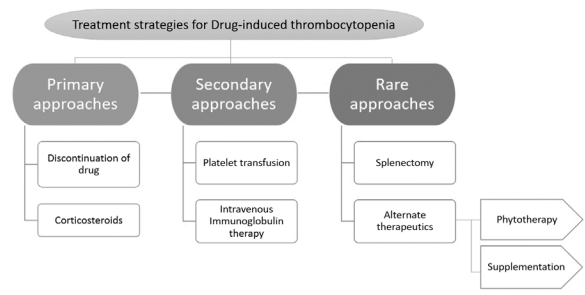


Fig. 2. Therapeutic strategies for Drug-induced thrombocytopenia

- i. Discontinuation of the suspected drug: The first approach of the treatment is by discontinuing the suspected causative agent. This can be done by establishing which of the patient’s medications is reported for causing DIT by referring to the available databases.<sup>56</sup>
- ii. Corticosteroids: Generally, corticosteroids like prednisone, dexamethasone, and methylprednisolone are used in the treatment of DIT. The mechanism of corticosteroids is primarily based on impairing the clearance of opsonized platelets in the bone marrow and peripheral organs. It also acts by reducing the autoantibody levels and preventing the immune-related platelet destruction, thereby increasing the platelet levels more rapidly than any other treatment.<sup>57,58</sup>
- iii. Intravenous (IV) immunoglobulin G (IgG) therapy: Another common approach is the use of IV IgG therapy to impair the clearance of opsonized platelets. IV IgG causes increased clearance of the antiplatelet antibodies by saturating the neonatal Fc salvage receptor for IgG. Even though it is more expensive than other treatments, it is beneficial due to rapid response ranging between 24-48 hours.<sup>59,60</sup>
- iv. Platelet transfusion: Transfusion can be attempted when the suspected drug is necessary for an extended duration. Transfusions can become ineffective in some cases, due to other related complications,

- making an individualized approach a necessity. Procurement of matched platelets by platelet apheresis are extremely difficult in emergency situations. Nonetheless, utilizing platelets stored in blood banks having limited shelf-life of up to 5 days can be ineffective due to the effect of storage lesions.<sup>61,62</sup>
- v. Surgical: Splenectomy is a surgical procedure that partially or completely removes the spleen to increase the platelet count. This procedure aids in the release of splenic sequestered platelets into circulation, thereby instantly elevating the platelets. However, the major drawback of the procedure is that it may adversely affect portal hypertension. Therefore, portal decompression is more preferred to improve thrombocytopenia. Nonetheless, surgical procedures are the least recommended for DIT as it is mostly unnecessary and may cause further damage during the procedure.<sup>63</sup>
  - vi. Other drugs: Thrombopoietin receptor (TPO-R) agonists are potential therapeutic drugs for DIT which stimulates the platelet production in the bone marrow. These act as replacement for thrombopoietin and elevate the platelet count. Spleen tyrosine kinase (SYK)-inhibitors are yet another approved class of drugs for DIT which can reduce antibody-mediated platelet destruction by immunosuppression mechanism.<sup>64,65</sup> Some of the examples for drugs include romiplostim, eltrombopag, imiglucerase, avatrombopag and fostamatinib.<sup>58</sup>

#### Alternative approaches

Oxidative stress in cells and tissues due to reactive oxygen species (ROS) is attributed as a primary causative agent in several disease conditions. Free radicals are highly unstable molecules and are highly reactive, thereby attacking the molecules in a biological system, causing metabolic malfunction, and cellular protein destruction, and can cause cell death.<sup>66,67</sup>

Antioxidants scavenge ROS and repair oxidative damage. Primary antioxidants scavenge ROS by hydrogen atom transfer (HAT) mechanism, by donating an H-atom, or act by single electron transfer (SET) mechanism. The secondary antioxidants neutralize the ROS using prooxidant catalysts by quenching free radicals and are thus exhausted.<sup>68</sup> Plant extracts and phytochemicals have excellent antioxidant capacity and are explored to reduce the possibility of the occurrence of disorders. There are reports that antioxidants alleviate the condition when used as an alternative therapeutic strategy or taken as a supplement or in numerous disease conditions.<sup>69,70</sup>

Studies have proven that various plant extracts can be used as therapeutic agents in the treatment of thrombocytopenic conditions. These plant extracts have been routinely tested in animal models for their effectiveness in stimulating the production of platelets in thrombo-

cytopenic condition. This ability of plant extracts is attributed to their antioxidant capacity. There are many studies dedicated to the identification of the bioactive compound in such extracts. Most bioactive components are phenolic acids, polyphenols, flavonoids or alkaloids in nature. The major challenge lies in identifying the specific bioactive compound in these extracts. Also, their influence on platelet functions is extremely under-reported. Nevertheless, specific antioxidants have been proven to be effective in improving platelet functions such as aggregation, granular secretion, activation and apoptosis and increasing the ability of endogenous antioxidant defense.<sup>71,72</sup> Our preliminary studies have indicated that antioxidants such as L-carnitine and vanillic acid are beneficial for platelet survival.<sup>73,74</sup> Table 3 and Table 4 provide details of plant extracts and antioxidants, respectively used under different thrombocytopenic conditions to improve platelet count. These studies are critical to categorize the antioxidants into either platelet agonists or anti-platelet agents as they are applied under rather entirely contrasting pathophysiological circumstances.

**Table 3.** Plant extracts as potential therapeutics

Plant	Condition	Effects
<i>Carica papaya</i> <sup>75</sup>	Cyclophosphamide induced-thrombocytopenia	Increase in platelet count
<i>Medicago sativa</i> <sup>76</sup>		Increase in platelet count
<i>Amaranthus spinosus</i> <sup>77</sup>	Ethanol-induced thrombocytopenia	Increase in platelet count and decrease in bleeding and clotting time
<i>Malus domestica</i> <sup>78</sup>	KBrO <sub>3</sub> induced thrombocytopenia	Increase in platelet count from 14.72 to 33.07 and from 11.08 to 32.90 (normal vs. thrombocytopenic) with apple fruit extract-enriched diet (AFE) and Apple seed extract-enriched diet (ASE), respectively
<i>Nigella sativa</i> <sup>79</sup>	Quinine-induced thrombocytopenia	Increase in platelet count by 1.59-fold
Ji-Xue-Teng (JXT, <i>Spatholobus suberectus</i> ) <sup>80</sup>	Radiation-induced hematopoietic alteration	Attenuates platelet decline on day 21
<i>Syzygium cumini</i> <sup>81</sup>	Hydroxyurea-induced thrombocytopenia	Increase in platelet counts
<i>Achyranthes aspera</i> <sup>82</sup>	Healthy	Increase in platelet count
<i>Annona muricata</i> ; <i>Fagara zanthoxyloide</i> <sup>83</sup>	Zidovudine-induced thrombocytopenia	Increase in platelet count by 49.56% (AM) and 51.32% (FZ), pronounced decrease in bleeding time
<i>Bauhinia monandra</i> <sup>84</sup>	Heparin-induced thrombocytopenia	Increased platelet counts and decreased bleeding and clotting time
<i>Psidium guajava</i> <sup>85</sup>	Busulfan induced-thrombocytopenia	Increase in platelet count and reversal of toxic effects
<i>Equisetum hyemale</i> and <i>Euphorbia hirta</i> <sup>86</sup>	Aspirin-induced thrombocytopenia	Both plant extracts possess platelet-increasing property in combination or alone

However, there are a few studies on using antioxidants and herbal products as supplements in human subjects with clinically significant thrombocytopenic conditions. These natural products have proven to improve patient's hematologic parameters and bleeding

score under different pathological conditions.<sup>92-94</sup> Effect of some antioxidants on platelet functions can be dose-dependent. They act as platelet agonists at higher concentration and can become anti-platelet at lower concentrations.<sup>95</sup> Hence, it is essential to evaluate such antioxidants and optimize the dose for use as supplements in alternate therapeutics.

**Table 4.** Antioxidants as potential therapeutics for thrombocytopenia

Antioxidant	Condition	Effects
Melatonin <sup>87</sup>	Luzindol-induced thrombocytopenia	Increased platelet count and plasma levels of platelet function markers, $\beta$ -thromboglobulin and PF 4
Mitoquinone <sup>88</sup>	Radiation-induced thrombocytopenia	Restored platelet count to normal levels, restored mitochondrial membrane potential and lowers superoxide production
$\gamma$ -Tocotrienol <sup>89</sup>		Decreased severity of thrombocytopenia
Carpaine <sup>90</sup>	Busulfan induced-thrombocytopenia	Platelet stimulating activity
Vanillic acid <sup>74</sup>	Hydroxyurea-induced thrombocytopenia	Improved platelet count
Quercetin-3-O- $\beta$ -D-glucuronide <sup>91</sup>	Cyclosporine A-induced bone marrow failure	Increased the number of platelets, inhibited the mitochondrial pathway-mediated platelet apoptosis and PI3K/AKT pathway

## Conclusion

Alternate therapies using phytochemicals can aid in faster recovery and reduce mortality due to their remarkable antioxidant properties. Plant extracts have shown promising results in increasing the number of platelets in patients with thrombocytopenia. Although these natural remedies are not a substitute for conventional therapies, they can be used a supplementary therapy to improve the effectiveness of treatments. Based on the studies conducted to this point, they can also be used as supplements to prevent adverse effects of existing treatments involving antibiotics and chemotherapeutics. Antioxidant therapies are currently followed for various clinical conditions and are a promising arena for further exploration. However, these therapies are still in its infancy, and have gained attention in the recent past due to the awareness and benefits of traditional approaches. Several scientific reports encourage using antioxidants as alternate therapeutic substances. Furthermore, antioxidants are investigated only in terms of enhancement of platelet count for DIT, but it is imperative to study their effect on platelet functions. Nonetheless, these antioxidants should be extensively studied for their mechanistic properties and physiological interactions to be regarded as one of the standard therapeutic strategies.

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## Declarations

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### Author contribution

Conceptualization, V.R.; Methodology, V.R. and A.B.A.; Validation, V.R.; Formal Analysis, V.R. and A.B.A.; Investigation, A.B.A.; Data Curation, A.B.A.; Writing – Original Draft Preparation, A.B.A.; Writing – Review & Editing, V.R.; Visualization, V.R.; Supervision, V.R.

### Conflicts of interests

The authors declare no competing interests.

### Data availability

All data generated or analyzed during this study are included in this published article.

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