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## New insights into anti-thrombotic effects of dietary bioactive components

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Thrombotic disorders pose a significant global health threat, prompting interest in dietary bioactive compounds for prevention and treatment. Some dietary compounds from plants, marine, and microbial-based sources, including polyphenols, omega-3 fatty acids, sulfur compounds, terpenoids, saponins, and emerging bioactive compounds like microalgal metabolites, probiotic-derived substances, and functional food peptides, show promise in mitigating thrombogenesis. These bioactive compounds can improve thrombotic disorders through various mechanisms, such as modulating platelet aggregation, inhibiting the coagulation cascade, enhancing fibrinolysis, and reducing oxidative stress and inflammation. The underlying action includes improving endothelial function, regulating thrombotic mediators like thrombin and fibrin, and suppressing inflammatory cytokines. Although preclinical and some clinical studies have shown encouraging results, there remains a need for larger, well-designed clinical trials to establish the efficacy, safety, and optimal dosage of these bioactive compounds in human populations. Future research should focus on understanding the precise molecular mechanisms involved, evaluating bioavailability, and investigating potential synergistic effects when combined with conventional anticoagulants. Thus, this review explores the mechanisms underlying thrombosis, highlighting how dietary bioactive substances might modify important processes to help prevent and manage thrombotic disorders.

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### 1. Introduction

Thrombosis, including venous thromboembolism, deep vein thrombosis (DVT), and pulmonary embolism, is a major global health concern with substantial morbidity and mortality. Globally, venous thromboembolism affects approximately 10 million individuals each year and is estimated to contribute to one in four deaths worldwide, underscoring its public health burden.<sup>1</sup> Thrombosis is a physiological process designed to prevent blood loss at sites of vascular injury; however, when dysregulated, clot formation occurs within intact blood vessels, obstructing blood flow and leading to severe complications.<sup>2</sup> Platelet aggregation, activation of the coagulation cascade, and inhibition of fibrinolysis are processes underlying thrombogenesis.<sup>3</sup> They are influenced by oxidative stress, inflammation, and endothelial dysfunction, which together create a pro-thrombotic environment.<sup>4,5</sup>

Current management of thrombosis relies heavily on anti-coagulant therapies, including warfarin, heparin, and newer direct oral anticoagulants. While effective, these drugs are associated with challenges such as bleeding risk, drug-drug

interactions, and the need for regular monitoring, which limit their long-term use.<sup>6</sup> This has led to growing interest in complementary or alternative strategies that may offer safer, more sustainable prevention and management options.

Dietary bioactive compounds have emerged as promising candidates due to their multi-targeted mechanisms of action and favorable safety profiles. Polyphenols and terpenoids from plants, omega-3 fatty acids from marine sources, and metabolites derived from microbial fermentation have been shown to mitigate oxidative stress, suppress inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin (IL)-6, improve endothelial function, and enhance fibrinolytic activity, thereby reducing thrombotic risk.<sup>7-10</sup> For instance, quercetin and catechins act on platelet aggregation and redox balance, omega-3 fatty acids modulate coagulation and inflammatory signaling, while probiotic-derived metabolites and bioactive peptides from functional foods also show unique anti-thrombotic potential.

This review discusses the mechanisms of thrombosis, emphasizing the role played by dietary bioactive compounds in modulating key pathways. It also explores emerging bioactive compounds and highlights the challenges and opportunities in adopting these compounds for thrombosis prevention and management. Through this, the review aims to provide insights into the potential of dietary interventions to reduce thrombotic risk and promote cardiovascular health.

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## 2. Thrombosis – pathophysiology and molecular mechanism

Thrombosis is a complex process including an interplay of platelet activation, the coagulation cascade, and fibrinolysis, all of which are essential for maintaining hemostasis. But it can contribute to pathological clot formation when dysregulated.<sup>3</sup> Fig. 1 shows a simplified representation of the mechanism of thrombosis.

### 2.1. Platelet aggregation

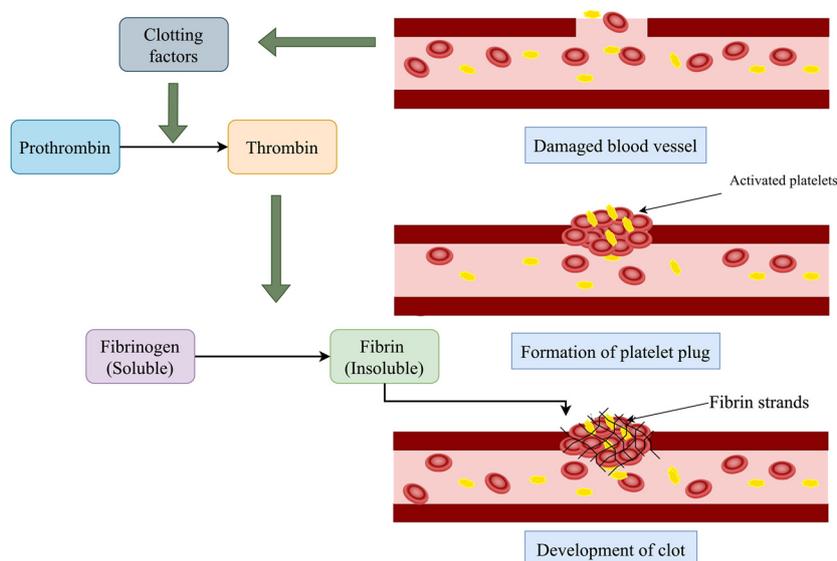
Platelets, small anucleate blood cells derived from megakaryocytes, are central players in thrombogenesis. When the vascular endothelium is damaged, platelets adhere to exposed sub-endothelial matrix proteins such as collagen and von Willebrand factor (vWF).<sup>11</sup> This triggers platelet activation, the interaction of receptors on the platelet surface with their respective ligands, initiating a cascade of signaling events.<sup>12</sup> The primary receptor, glycoprotein (GP) Ia/IIa complex, binds collagen, and the GP VI receptor also interacts with collagen and other matrix components. Furthermore, the vWF binds to the GP Ib/IX/V complex on the platelet surface, which is crucial for platelet adhesion under high shear conditions, such as in arteries.<sup>13</sup> Once activated, platelets release granules containing pro-thrombotic mediators such as ADP, serotonin, and thromboxane A<sub>2</sub> (TXA<sub>2</sub>). They act as autocrine and paracrine signaling molecules that further activate nearby platelets.<sup>14</sup> ADP binds to P<sub>2</sub>Y<sub>12</sub> receptors, while TXA<sub>2</sub> interacts with thromboxane-prostanoid receptors on the platelet surface, amplifying the activation signal and promoting aggrega-

tion. This leads to the activation of integrin receptors, primarily the  $\alpha$ IIb $\beta$ 3 integrin (also known as GPIIb/IIIa). It is the most abundant receptor on the platelet surface, which mediates platelet aggregation by binding fibrinogen, which is a critical step in the formation of a stable thrombus.<sup>15</sup> The final phase of platelet aggregation involves the cross-linking of platelets through fibrinogen bridges, which strengthens the platelet plug and leads to thrombus formation.<sup>16</sup> In addition to biochemical signals, the surrounding hemodynamic environment influences platelet aggregation. High shear stress (found in arterial circulation) enhances vWF-mediated platelet adhesion and aggregation.<sup>17</sup> Furthermore, activated platelets provide a catalytic surface for the coagulation cascade, linking primary hemostasis (platelet activity) with secondary hemostasis (fibrin formation).<sup>18</sup>

The regulation of platelet aggregation is critical to maintaining hemostatic balance. In order to prevent unnecessary platelet activation, endothelial cells release inhibitory molecules like prostacyclin (PGI<sub>2</sub>) and nitric oxide (NO). PGI<sub>2</sub> raises intracellular cyclic AMP levels in platelets, inhibiting activation, while NO enhances cyclic GMP levels, reducing platelet adhesion and aggregation.<sup>19</sup>

### 2.2. Coagulation cascade

The coagulation cascade is a finely regulated sequence of enzymatic reactions that is essential for blood clot formation. It ensures vascular integrity after injury. The coagulation cascade amplifies thrombus formation through a series of proteolytic reactions. Thrombin converts fibrinogen into insoluble fibrin, which polymerizes to form a stable network around the plate-



**Fig. 1** The mechanism of thrombosis: when a blood vessel is damaged, the endothelium gets disrupted, which triggers the release of clotting factors. Red blood cells, along with other components, start to gather at the location of the injury. At the location of the injury, platelets activate and aggregate to create a temporary plug. Vasoconstriction serves to restrict blood flow to the impacted region, while platelets aggregate to avert profuse bleeding. Through thrombin, the coagulation cascade transforms fibrinogen (which is soluble) into fibrin (which is insoluble). The platelet plug is reinforced and stabilized by fibrin strands, resulting in the creation of a stable blood clot. This stops additional bleeding and enables the repair of vessels.



let aggregate, stabilizing the clot. There are intrinsic and extrinsic pathways that operate this cascade. They converge at the activation of factor X. The intricate balance of this system ensures that clot formation is localized and controlled, yet dysregulation can lead to either uncontrolled bleeding or excessive clot formation.<sup>16</sup>

The extrinsic pathway is triggered by external trauma that exposes tissue factor (TF), a membrane-bound glycoprotein. TF binds to Factor VII, forming the TF–Factor VIIa complex, which activates Factor X to Xa. This pathway is rapid and serves as the primary initiator of coagulation *in vivo*. The intrinsic pathway, also known as the contact activation pathway, is initiated by damage to the vascular endothelium. It begins with the activation of Factor XII (Hageman factor) upon contact with negatively charged surfaces such as collagen. Activated Factor XII (XIIa) sequentially activates Factor XI to XIa, which then activates Factor IX. Factor IXa, in the presence of its cofactor Factor VIIIa and calcium ions, forms a complex that activates Factor X.<sup>20</sup> The common pathway begins with the activation of Factor X to Xa by either the intrinsic or extrinsic pathways. Factor Xa, in association with its cofactor Factor Va, calcium ions, and phospholipids, forms the prothrombinase complex. This complex converts prothrombin (Factor II) into thrombin (Factor IIa). Thrombin is a central enzyme in the coagulation cascade, as it performs several critical functions: It cleaves fibrinogen into fibrin monomers, which polymerize to form an insoluble fibrin mesh that stabilizes the platelet plug, activates Factor XIII to Factor XIIIa, which cross-links fibrin strands, enhancing clot strength, amplifies the cascade by activating cofactors Factor V and Factor VIII, as well as platelets, creating a positive feedback loop.<sup>21</sup>

The cascade is tightly regulated to prevent excessive clotting, with natural anticoagulants like antithrombin, protein C, and protein S playing crucial roles. Antithrombin inhibits thrombin and Factor Xa, while the protein C–protein S complex degrades Factors Va and VIIIa.<sup>22</sup> Dysregulation of the coagulation cascade, such as excessive thrombin generation or inadequate anticoagulant activity, can lead to pathological thrombosis, underscoring the importance of maintaining a delicate balance in hemostasis.

### 2.3. Fibrinolysis

Fibrinolysis represents the physiological process of degradation of formed blood clots, or fibrin, after vascular repair is complete, to ensure that clot formation does not block normal blood flow. Thus, it balances the clot formation. Plasmin, one of the major enzymes involved in fibrinolysis, degrades fibrin into soluble fragments called fibrin degradation products.<sup>23</sup> Plasminogen, the precursor of plasmin, is activated by tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). tPA is secreted by endothelial cells. It is most effective in activating plasminogen when bound to fibrin, ensuring localized fibrinolysis at the clot site. uPA is produced by a variety of cell types, including renal epithelium and immune cells, and plays a more systemic role in plasminogen activation. In turn, activated plasmin cleaves fibrin strands,

resulting in the degradation of the clot and restoring normal blood flow. The process is facilitated by cofactors such as fibrin itself, which enhances plasminogen activation by tPA.<sup>24</sup> This begets an efficient positive feedback mechanism in clot degradation.

Plasminogen activator inhibitor-1 (PAI-1) and PAI-2 inhibit fibrinolytic activity. Inhibiting both tPA and uPA activity will lead to the reduction of plasminogen modulation.  $\alpha$ 2-Antiplasmin directly binds to and inactivates plasmin, preventing fibrin degradation at inappropriate sites. Furthermore, thrombin-activatable fibrinolysis inhibitor modifies fibrin to make it less susceptible to plasmin-mediated degradation.<sup>25</sup> An imbalance in fibrinolysis can lead to pathological conditions. Excessive fibrinolytic activity may result in uncontrolled bleeding, while insufficient fibrinolysis can contribute to thrombosis by allowing clots to persist. Impairment of fibrinolysis might cause the thrombus to remain for prolonged periods and ultimately lead to the occlusion of vessels too.<sup>26</sup>

### 2.4. Mediators of thrombosis

Thrombosis and platelet aggregation involve a complex interplay of molecular mediators that regulate clot formation, stabilization, and inflammatory responses. Some of these, such as thrombin, fibrin, P-selectin, and various inflammatory cytokines, take on different roles in this context within a coordinated cascade to restore hemostasis and prevent pathological clotting.

Thrombin, a serine protease, is the central effector in the coagulation cascade, serving as a critical link between clot formation and platelet activation. It is generated from prothrombin through the action of the prothrombinase complex and performs several essential functions. Thrombin converts soluble fibrinogen into insoluble fibrin, creating a mesh that stabilizes the clot. It also amplifies the coagulation cascade by activating cofactors like Factor V, VIII, and XI, ensuring rapid clot formation. Moreover, thrombin directly activates platelets by binding to protease-activated receptors, triggering intracellular signaling cascades that enhance aggregation and shape changes.<sup>27</sup>

As the major structural component of blood clots, fibrin contributes to the stabilization of the platelet plug. Fibrinogen is cleaved by thrombin, forming the fibrin monomers that polymerize into a gel-like network. This network retains red blood cells, leukocytes, and plasma proteins, thus providing stability to the clot. Factor XIIIa cross-links fibrin chains, which further augments the mechanical strength of the clot and its resistance to degradation. Fibrin, besides being a structural protein, also serves as a matrix for cellular and molecular interactions that help to further stabilize the clot.<sup>16</sup>

P-selectin is an adhesion molecule associated with cell function. It is found in platelet alpha granules and endothelial Weibel–Palade bodies. Following its activation, P-selectin is moved to the cell membrane and thus is capable of interacting with P-selectin source glycoprotein ligand-1 (PSGL-1), to help activate leukocytes. This gives a chance for platelets and leukocytes to interact within the clot. Such action enhances inflam-



matory responses at the clot site. Besides, P-selectin is the pro-thrombotic factor that, through releasing TFs, stimulates monocytes, increases thrombin production, and upholds the thrombus through endothelial adhesion.<sup>28</sup>

Inflammatory cytokines such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$  link inflammation to thrombosis. They increase coagulation by inducing in monocytes and endothelial cells increased expression of TF and activation of the extrinsic coagulation pathway. In addition, they cause endothelial dysfunction by increasing the secretion of pro-thrombotic mediators such as vWF while reducing the availability of anti-thrombotic molecules such as NO.<sup>29</sup> Cytokines stimulate platelet activation and aggregation by inducing the release of pro-aggregatory mediators such as ADP and TXA2.<sup>30</sup>

Other mediators that include complement factors and vWF will further modulate thrombus formation.<sup>31</sup> Complement proteins, particularly C3a and C5a, promote the activation of platelets and recruitment of leukocytes. However, the membrane attack complex (MAC) compromises the integrity of the endothelium by exposing the underlying pro-thrombotic substrates.<sup>32</sup> Meanwhile, vWF serves to facilitate platelet aggregation and adhesion through binding to the glycoprotein receptors and fibrin. The endothelium-derived PGI2 and NO counteract these processes of inhibiting platelet activation and evoking vasodilation, thus indicating the importance of regulatory mechanisms in achieving hemostatic balance.<sup>33</sup>

Together, these mediators ensure a rapid and localized response to vascular injury while preventing excessive clot formation. However, their dysregulation can lead to pathological conditions, such as thrombosis or bleeding disorders. Understanding the roles and interactions of these mediators provides valuable insights for developing targeted therapies and dietary strategies to mitigate thrombotic risks.

### 2.5. Oxidative stress and inflammation: role in thrombogenesis

Oxidative stress and inflammation are critical contributors to the development of thrombosis. Their interaction plays a crucial role in the pathogenesis of cardiovascular diseases, such as stroke, heart attack, and DVT. Increased oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, promotes thrombogenesis by activating platelets, impairing endothelial function, and altering coagulation pathways. Under normal conditions, ROS plays a role in cellular signaling, but when produced in excess due to factors like hypertension, hyperglycemia, or smoking, they damage cellular structures, including lipids, proteins, and DNA.<sup>34</sup> In the context of thrombosis, excess ROS activates platelets by inducing integrins, receptors, and TXA2 synthesis, increasing adhesion, aggregation, and overall thrombotic risk.<sup>35</sup>

The endothelium plays a key role in regulating vascular tone and maintaining a non-thrombotic surface under normal conditions. However, oxidative stress induces endothelial dysfunction, characterized by reduced NO availability and increased endothelial permeability.<sup>36</sup> NO is a potent vasodila-

tor and inhibitor of platelet aggregation. Its depletion is due to oxidative stress, leading to impaired vascular relaxation and increased platelet aggregation.<sup>37</sup> Additionally, oxidative stress can trigger the expression of adhesion molecules, facilitating the recruitment of platelets and leukocytes to the site of injury. This inflammatory response further exacerbates the risk of clot formation.<sup>19</sup>

Proinflammatory cytokines TNF- $\alpha$ , IL-6, and IL-1 collectively induce inflammation and thus play a pathological role in the regulation of various aspects of coagulation and platelet behavior that promote thrombogenesis. These cytokines can increase the expression of TF on monocytes and endothelial cells, triggering the activation of the extrinsic coagulation pathway. This eventually enhances thrombin generation.<sup>38</sup> Moreover, thrombin induces platelet activation and fibrin formation, driving clot development. Inflammatory cytokines further promote the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), on endothelial cells. This further promotes leukocyte and platelet recruitment to sites of thrombus formation.<sup>39</sup> These inflammatory cytokines exacerbate oxidative stress. This results in aggravating endothelial injury and triggering chronic thrombotic conditions. Raised levels of IL-6 and TNF- $\alpha$ , for instance, have been associated with an elevated risk of arterial thrombosis, like myocardial infarction and ischemic stroke.<sup>38</sup>

Oxidative stress and inflammation synergistically support thrombogenesis. Oxidative stress and inflammatory cytokines, such as TNF- $\alpha$  and IL-6, create a positive feedback loop through ROS and NF- $\kappa$ B activation, amplifying platelet activation, endothelial dysfunction, and coagulation, thereby accelerating thrombus formation.<sup>40</sup> A deep understanding of oxidative stress and inflammation related to thrombus formation illuminates possible therapeutic options for the prevention of thrombotic incidents. Drugs that target oxidative stress or inflammation may avert platelet activation and endothelial damage. Dietary interventions that will thwart oxidative stress and inflammation, namely antioxidant-rich polyphenols (of fruits, vegetables, and tea), may be useful in a more natural, dietary approach for impacting thrombosis risk.

## 3. Dietary bioactive compounds with anti-thrombotic effects

Several dietary bioactive compounds have been identified for their potential anti-thrombotic effects, which can help prevent or mitigate the formation of harmful blood clots. These compounds, often derived from plant-based foods and marine sources, exert their effects through various mechanisms, including the inhibition of platelet aggregation, modulation of inflammatory pathways, reduction of oxidative stress, and improvement of endothelial function (Fig. 2). Among plant-based bioactives, polyphenols such as quercetin and catechins, terpenoids, and saponins have been widely studied for their ability to inhibit platelet activation and reduce endothelial dys-



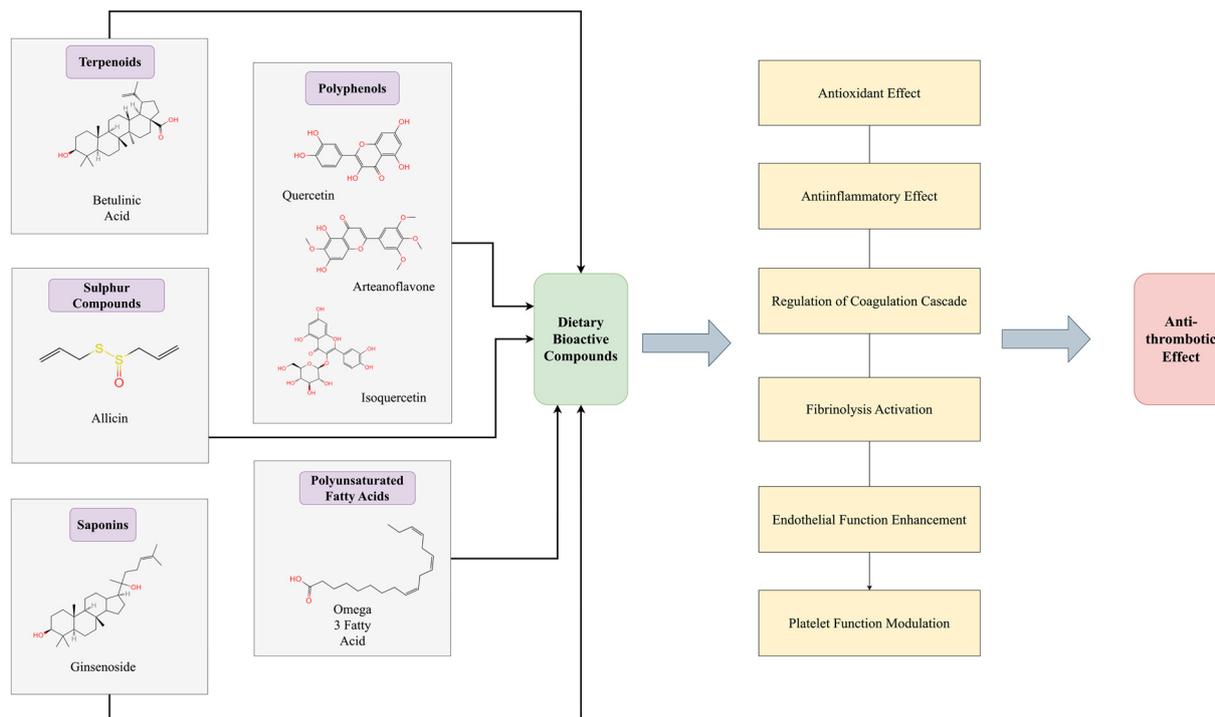


Fig. 2 Dietary bioactive compounds affecting thrombosis.

function. Marine-derived bioactives, including omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), marine peptides, and carotenoids such as astaxanthin, exhibit anti-inflammatory and anticoagulant properties that contribute to thrombus prevention. Microbial-derived compounds, such as short-chain fatty acids (SCFAs) (butyrate, propionate), fermentation-derived peptides, and exopolysaccharides, modulate platelet function, reduce vascular inflammation, and influence coagulation through receptor-mediated pathways such as GPR41/43 (FFARs). Table 1 summarizes the effects of these dietary bioactive compounds on thrombosis. By targeting different stages and molecular mediators of thrombus formation, bioactives from these diverse dietary sources offer promising strategies for both the prevention and management of thrombotic disorders.

### 3.1. Polyphenols

Polyphenols are a vast group of compounds found abundantly in fruits, vegetables, tea, and red wine. They serve well-known antioxidant purposes to diminish oxidative stress and the inflammatory response that leads to the development of thrombosis. Polyphenols, especially flavonoids and phenolic compounds, have been shown in many studies to inhibit platelet aggregation by modulating platelet functions.<sup>44–46,55</sup> Additionally, polyphenols improve endothelial function by increasing the bioavailability of NO. These effects not only contribute to a decreased risk of thrombosis but also support vascular health by reducing inflammation and promoting blood vessel relaxation. They also inhibit thrombin-activated platelets

to fibrinogen.<sup>56</sup> The *in vivo* finding of *Rosa roxburghii* fruit flavonoids revealed that it had more platelet aggregation activity and the above-mentioned regulation on coagulation, oxidative stress, and inflammatory cytokines as described by Pu *et al.*<sup>46</sup> *Camellia osmantha* flavonoids, polyphenols, and saponins, among other chemical compounds described by Yang *et al.*,<sup>45</sup> showed anti-thrombotic action. They prevented blood clotting by modulating the fibrinolytic system in Wistar rats. The anti-thrombotic activity of quercetin from *Flaveria bidentis* was evaluated by Guglielmone *et al.*<sup>43</sup> They found that quercetin possesses important anticoagulant, antiplatelet, and profibrinolytic activities. It activates heparin cofactor II and increases the thrombin inhibition rate while inhibiting the expression of TFs. In another *in vivo* study, isoquercetin, a quercetin metabolite, was dosed twice per day by oral gavage, with 200 mg kg<sup>-1</sup> over 48 hours. The results showed that isoquercetin inhibited platelet function and thrombus formation through effects on early activatory processes, including calcium mobilization, granule secretion, and integrin activation. Other than that, Arteanoflavone from *Artemisia iwayomogi* elevates cAMP/cGMP levels, reduces intracellular Ca<sup>2+</sup>, suppresses integrin  $\alpha$ Ib/ $\beta$ <sub>3</sub>, and reduces TXA<sub>2</sub> production and granule release in human platelets.

### 3.2. Omega-3 fatty acids

Omega-3 fatty acids, primarily found in fatty fish, flaxseeds, and walnuts, have well-documented cardiovascular benefits, including their anti-thrombotic effects. Omega-3s, especially EPA and DHA, help prevent thrombosis by reducing platelet





Table 1 Effects of dietary bioactive compounds on thrombosis

Classification	Compound	Source	Model	Effect	Ref.
Phenolic acids	Diethyl phthalate, ( <i>E</i> )-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenol, 7,9-di- <i>tert</i> -butyl-1-oxaspiro (4,5) deca-6,9-diene-2,8-dione	<i>Ficus benghalensis</i>	Laboratory-bred male and female Sprague-Dawley rats, 12–14 weeks old	Inhibits collagen-induced platelet aggregation, exhibits anti-thrombotic action, downtime clot formation	41
	Arteanoflavone	<i>Artemisia iwajomogi</i>	Human platelets	Elevate cAMP/cGMP levels, reduce intracellular Ca <sup>2+</sup> , suppressing integrin αIIb/β <sub>3</sub> , reduce TXA <sub>2</sub> production and granule release	42
Flavonoids	Quercetin	<i>Flavaria bidentis</i>	C57BL/6 mice male, <i>n</i> = 30	Possesses important anticoagulant, antiplatelet and profibrinolytic activities, activates heparin cofactor II, increasing thrombin inhibition rate. Inhibits the expression of TF	43
	Quercetin metabolites	Apples, onions, and red wine	Human whole blood	Increased antiplatelet effect	44
Quercetin metabolites – isoquercetin	Quercetin metabolites		C57/BL6 mice, 4 weeks old	Inhibit platelet function and thrombus formation through effects on early activatory processes including calcium mobilization, granule secretion, and integrin activation	44
	Flavonoids	<i>Camellia osmantha</i>	Wistar rats	Inhibit platelet aggregation prevent blood coagulation by affecting the fibrinolytic system	45
Flavonoids	Flavonoids	<i>Rosa roxburghii</i> fruit	Kunming mice, male, 4 weeks old, <i>n</i> = 8	Regulated coagulation, platelet aggregation, oxidative stress, and inflammatory cytokines	46
	Quercetin, apigenin and kaempferol	<i>Premna foetida</i>		Stronger inhibition towards AA-induced platelet aggregation. Apigenin exhibiting the strongest effect IC <sub>50</sub> 52.3 and 127.4 μM	47
Polyunsaturated fatty acids	Omega-3 fatty acids	Antarctic krill oil	Male ICR mice, 6 weeks old, <i>n</i> = 8	Decrease the secretion of proinflammatory cytokines inhibition of adhesion molecules and adhesion of monocytes to endothelial cells	48
	Omega-3 fatty acids	Plant-derived α-linolenic acid	C57BL/6J mice, 8–12 weeks or old (>18 months), <i>n</i> =8	Regulate inflammatory cytokines, procoagulant factors TF and PAI-1 reverses age-associated platelet hyperactivity and heightened thrombotic potential	49
Saponins	Panax ginseng ginsenoside	Panax ginseng ginsenoside	Male Sprague-Dawley (SD) rats, C57BL/6J male mice, 7 weeks old	Inhibit ADP-induced platelet aggregation inhibit [Ca <sup>2+</sup> ] elevation in platelets inhibit fibrinogen binding	50
		<i>Glechoma longituba</i> , <i>Glechomanolides A–E</i>	Normal mice and rabbits (PRP)	Glechomanolides A–E antithrombotic activity, Glechomanolides C and D anticoagulant effect	51
Peptides		<i>Panax notoginseng</i> flower	Male SD rats, 5–6 weeks old, <i>n</i> = 5	Restore thrombin induced platelet aggregation inhibit activation of PLCγ2 cascade	52
		<i>Delonix regia</i> seeds	Adult male C57BL/6J mice	Decrease in platelet aggregation	53
Terpens		<i>Melaleuca bracteata</i>	Sprague-Dawley rats <i>n</i> = 4	Possess antithrombotic, antiplatelet aggregations and anticoagulants potential	54
		Betulnic acid			

aggregation and promoting fibrinolysis. These fatty acids inhibit the production of pro-inflammatory cytokines and the release of platelet-activating factors, thus reducing the activation of platelets.<sup>57</sup> Omega-3 fatty acids also modulate the lipid composition of cell membranes, making platelets less likely to become activated in response to injury.<sup>58</sup> Moreover, omega-3s reduce triglyceride levels and promote a more favorable balance between pro-thrombotic and anti-thrombotic factors in the body.<sup>59</sup> In an *in vivo* study, Omega-3 fatty acids from Antarctic krill oil showed a decrease in the secretion of proinflammatory cytokines along with an inhibition of adhesion molecules and adhesion of monocytes to endothelial cells, which resulted in anti-thrombotic effects.<sup>48</sup> The study of Saravi *et al.*<sup>49</sup> found further support for vascular health and reduced risk of clot formation. According to their study, plant-derived  $\alpha$ -linolenic acid possesses the ability to regulate inflammatory cytokines, procoagulant factors TF and PAI-1, and reverses age-associated platelet hyperreactivity and heightened thrombotic potential.

### 3.3. Saponin

Saponins, naturally occurring glycosides found in legumes, soybeans, and certain herbs, have also been associated with anti-thrombotic effects. Saponins possess antioxidant and anti-inflammatory properties.<sup>60</sup> Studies have shown that saponins can inhibit platelet aggregation by interfering with the activation of the clotting cascade and the expression of surface markers involved in platelet adhesion. They also promote the dissolution of fibrin clots by enhancing fibrinolytic activity. In an *in vivo* study, *Panax ginseng* ginsenoside exhibited high activity in the inhibition of ADP-induced platelet aggregation and inhibition of  $[Ca^{2+}]$  elevation in platelets and inhibition of fibrinogen binding, resulting in an anti-thrombotic effect.<sup>50</sup> Ouyang *et al.*<sup>51</sup> studied the anti-thrombotic effects of saponins from *Glechoma longituba*. They discovered that Glechomanosides A–E possessed antithrombotic activity, while C and D showed significant anticoagulant effects. Alternatively, saponins can modulate lipid metabolism, which helps reduce cholesterol levels and prevent the accumulation of fatty deposits in blood vessels, thereby reducing the risk of thrombosis.<sup>61</sup>

### 3.4. Sulfur compounds

The sulfur compounds have been known for ages to possess cardiovascular benefits, which include their anti-thrombotic effects. Such compounds can be found in garlic, onions, and other cruciferous vegetables. It has been found that allicin, the active sulfur compound of garlic, decreased platelet aggregation and inhibited the activity of thrombin, which is a key enzyme in the coagulation cascade. Moreover, allicin and other sulfur compounds promote vasodilation and reduce platelet adhesion to the endothelium. Furthermore, sulfur compounds carry anti-inflammatory properties, which are further actions in reducing activation of pro-thrombotic pathways. All these mechanisms together could support a

reduction in thrombus formation and contribute to better cardiovascular health from the dietary sources of sulfur.<sup>62</sup>

### 3.5. Terpenoids

Generally, terpenoids comprise a large class of natural compounds obtained from various plants, herbs, and fruits. Some classes, such as carotenoids and essential oils (like limonene and pinene), displayed the anti-thrombotic effect by modulating the platelet function and by reducing inflammation. Terpenoids from *Melaleuca bracteata* are antithrombotic, anti-platelet aggregating, and showed anticoagulant potential in Sprague-Dawley rats.<sup>54</sup> Terpenoids are also antioxidants and scavengers of ROS, which are known to promote oxidative stress and cause endothelial dysfunction. These compounds also reduce the production of inflammatory cytokines and thrombotic mediators to prevent excessive formation of clots.<sup>63</sup>

## 4. Emerging bio-actives with potential anti-thrombotic effects

Bioactive compounds are being explored for their potential significance in the prevention of thrombosis. Bioactive compounds under research possess the functionality to modulate thrombotic pathways and subdue blood clots through food, microalgae, probiotics, and dietary fiber. They usually work through the inhibition of platelet aggregation, modifying inflammation, increasing fibrinolysis, and supporting endothelial function. More specifically, the emerging bioactive compounds, say peptides from functional food sources, compounds from microalgae, metabolites from probiotics, and dietary fibers, are proving their utility as natural agents for the prevention of thrombus formation. The continued exploration of these emerging bioactives highlights the potential of functional foods, probiotics, and dietary modifications in the prevention and management of thrombosis-related diseases.

### 4.1. Peptides from functional foods

Lately, it has been revealed that peptides originating from regular nutritional sources, like dairy, eggs, pulses, and fish, have beneficial effects for cardiovascular health, such as an anti-thrombotic nature. These are bioactive peptides frequently released during food fermentation or digestion. They, in turn, show potent multi-effects, such as inhibiting platelet aggregation and reducing blood coagulation. For instance, milk protein, casein, and whey peptides have been shown to have an anti-thrombotic nature by modulating platelet receptor activation and thrombin generation.<sup>64</sup> Certain fish peptides, especially those in tuna and salmon, can reduce the expression of prothrombotic molecules such as P-selectin and TXA2. Hence, these functional food-derived peptides may be regarded as a promising approach for fighting thrombosis as they alter various aspects of the coagulation cascade and platelet activation.<sup>8</sup>



## 4.2. Microalgal compounds

Microalgae are invaluable sources of bioactive agents with numerous benefits with regard to health and a possible anti-thrombotic effect. These include polysaccharides, polyunsaturated fatty acids (PUFA), carotenoids, and peptides, and many of them show action on thrombotic pathways. For example, some microalgal polysaccharide types, including those derived from *Spirulina* and *Chlorella*, have demonstrated anticoagulant properties through inhibition of thrombin and other clotting factors.<sup>65</sup> According to Koukouraki *et al.*,<sup>66</sup> lipid, polysaccharide, and protein extracts derived from *Spirulina* have shown strong antithrombotic properties against objective platelet aggregation induced by inflammatory and thrombotic mediators such as PAF and thrombin. Microalgal omega-3 fatty acids, including EPA and DHA, are also effective at preventing thrombosis, similar to what fish oils do in reducing platelet aggregation, lowering triglycerides, and improving endothelial function. Furthermore, certain microalgae also synthesize astaxanthin, which is a carotenoid with antioxidant properties that help prevent oxidative stress-induced platelet activation and endothelial injury and inhibit thrombosis.<sup>67</sup>

## 4.3. Probiotic-derived metabolites

Probiotics, beneficial bacteria found in fermented foods and supplements, are increasingly recognized for the modulatory role they play on many health fronts, from their involvement in thrombosis prevention. Probiotics produce many types of bioactive metabolites, including SCFAs and peptides, which affect platelet function, inflammation, and blood coagulation. SCFAs such as acetate, propionate, and butyrate are produced in the gut by the fermentation of dietary fiber and shown to exert anti-thrombotic effects by decreasing platelet aggregation and increasing fibrinolytic activity.<sup>68</sup> On the other hand, probiotic-derived peptides, mainly produced by *Lactobacillus* and *Bifidobacterium* species, have been stated to inhibit the activation of platelets and diminish the adhesion molecules on endothelial cells to prevent thrombus formation. The ability to link metabolites with systemic inflammation and coagulation through the gut microbiome serves as a novel and natural approach for managing thrombosis risk.<sup>69</sup>

## 4.4. Dietary fiber

Soluble dietary fiber is linked to gastrointestinal functioning and the risk of cardiovascular diseases in humans. Recently, it has also been determined that dietary fiber could play a role in an anti-thrombotic effect due to its influence on the gut microbiome and bioactive metabolites such as SCFAs. Soluble dietary fibers, such as those from oats, lentils, cereals, fruits, and vegetables, are known to inhibit platelet aggregation and reduce blood cholesterol levels, thereby reducing the risk of thrombosis.<sup>70</sup> SCFAs that result from the fermentation of soluble fiber in the gut were demonstrated to reduce the expression of pro-thrombotic markers, enhance endothelial function, and inhibit activation of platelets. In addition, dietary fiber has been linked to controlling blood sugar levels

and reducing systemic inflammation, which affects thrombosis, thus acting as a protective barrier against its development. Dietary fiber serves as a potential player in the area of cardiovascular health through maintaining a healthy gut microbiome and reducing risks relating to thrombosis.<sup>71</sup>

## 5. Molecular mechanisms of action of dietary bioactive compounds in thrombosis

Dietary bioactive compounds exert their anti-thrombotic effects through multiple interconnected mechanisms that target different stages of thrombus formation and resolution. These include antioxidant activity, modulation of platelet function, anti-inflammatory actions, regulation of adhesion molecules, improvement of endothelial function *via* nitric oxide (NO) production, modulation of the coagulation cascade, activation of fibrinolysis, and the influence of microbial metabolites. To provide a clearer understanding of these complex and overlapping pathways, Fig. 3 summarizes the major mechanisms discussed in the following subsections.

### 5.1. Antioxidant effects

The role played by oxidative stress in thrombosis has been widely recognized, with oxidative damage to endothelial cells being a crucial factor in the initiation and progression of thrombus formation. As shown in Fig. 4, free radicals, particularly ROS, such as superoxide anions, hydrogen peroxide, and hydroxyl radicals, are known to contribute to endothelial dysfunction, platelet activation, and the formation of thrombi. Antioxidants, whether endogenously produced or derived from dietary sources, can mitigate these effects by scavenging ROS and modulating oxidative stress pathways, thus preventing excessive thrombus formation. The antioxidant effects of dietary bioactive compounds have been studied in specific models of thrombus formation, shedding light on how they protect endothelial cells and inhibit the various processes involved in thrombogenesis.<sup>72</sup>

#### 5.1.1. Scavenging free radicals in thrombus formation.

Free radicals, particularly ROS, are generated during various stages of thrombus formation, including platelet activation and the coagulation cascade. Endothelial cells, compared with other cells, can be highly susceptible to oxidative damage because blood flows through them and may activate prothrombotic pathways.<sup>4</sup> ROS directly interferes with endothelial function by increasing the expression of adhesion molecules such as P-selectin and vWF, thus promoting the aggregation of platelets and the adhesion of inflammatory cells to the vessel wall. In this context, antioxidants may counteract the harmful effects of ROS by scavenging free radicals before they cause damage to the endothelium or activate the thrombotic process.<sup>73</sup>

Polyphenols, a well-studied class of antioxidants, have been shown to effectively scavenge ROS. For instance, flavonoids



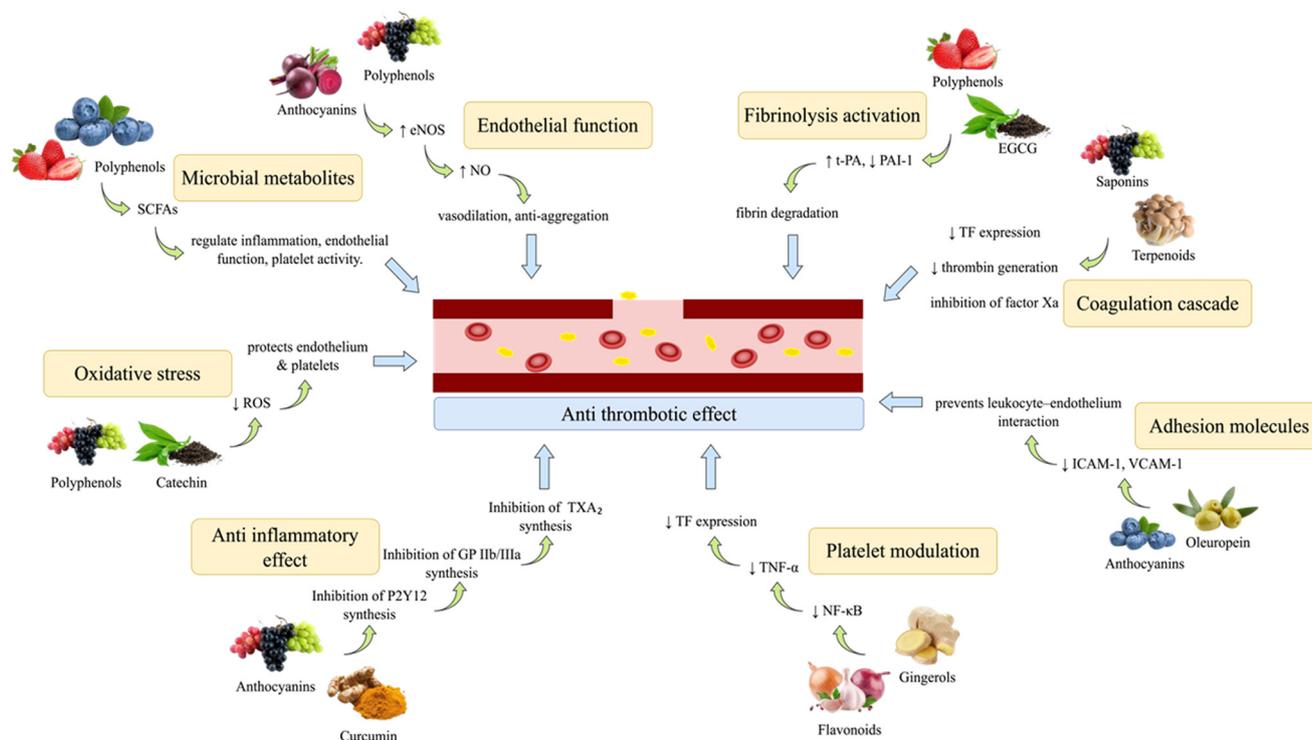


Fig. 3 Key molecular targets of dietary bioactives in thrombotic regulation.

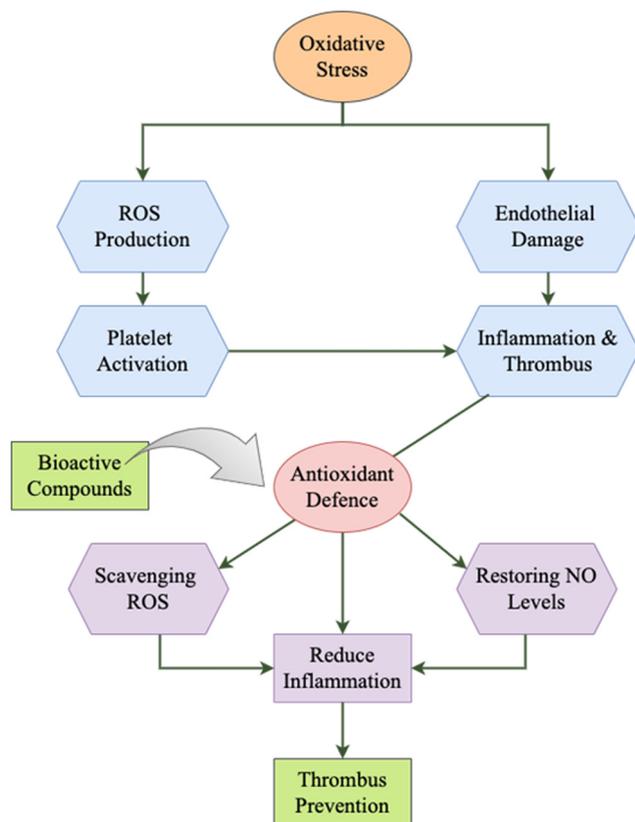


Fig. 4 Antioxidant effects of bioactive compounds in thrombosis.

like quercetin,<sup>74</sup> epicatechin, and resveratrol<sup>75</sup> have been shown to neutralize free radicals, preventing the oxidative modification of low-density lipoproteins (LDL), a critical factor in atherogenesis and thrombosis. By direct scavenging of ROS, these polyphenols can counteract oxidative stress, thereby impeding endothelial dysfunction and platelet aggregation. Also, omega-3 fatty acids like EPA and DHA have been proved to be strong antioxidants, with studies indicating that they decrease ROS generation and thus diminish oxidative damage to the endothelial lining, resulting in a lower chance of thrombus formation.<sup>76</sup>

**5.1.2. Reducing oxidative stress in endothelial cells.** The dysfunction of endothelial cells is a central reason for thrombosis. Under oxidative stress conditions, endothelial damage occurs, leading to greater permeability in blood vessels and platelet adhesion–aggregation. All these functionalities cause the production of ROS, which can disturb the activity of endothelial nitric oxide synthase (eNOS). This results in reduced bioavailability of NO and impairment of vasodilation.<sup>77</sup> Consequently, the endothelial cells would be pre-activated, leading to thrombus formation initiation.

Antioxidants eradicate oxidative stress among endothelial cells through the regulation of prevailing pathways that help in maintaining endothelial function.<sup>78</sup> One of the most important effects of antioxidants is the restoration of the bioavailability of NO. NO prevents platelet aggregation and proliferation of smooth muscle cells by suppressing the expression of adhesion molecules and reducing the adhesion of platelets to the vessel walls.<sup>79</sup> Numerous antioxidants, like



polyphenolic antioxidants found in fruits, vegetables, and tea, are known to exhibit increased activity of eNOS and increase the release of NO, thus leading to vasodilation and inhibition of thrombus formation. Resveratrol and quercetin are, for instance, known to elevate eNOS activity, leading to increased levels of NO, thus creating a protective effect on the endothelial lining against thrombosis.<sup>80,81</sup>

Additionally, antioxidants can modulate the expression of pro-inflammatory genes in endothelial cells. Oxidative stress activates various signaling pathways, including the nuclear factor-kappa B (NF- $\kappa$ B) pathway, in which the generation of inflammatory cytokines and the expression of adhesion molecules like ICAM-1 and VCAM-1 occur. These molecules further recruit inflammatory cells and platelets to the site of injury of the vascular wall, aggravating thrombus formation. From this, antioxidants prevent the initiation of thrombosis through the scavenging of ROS in the inhibition of the NF- $\kappa$ B pathway, with a consequent reduction in the expression of these pro-inflammatory adhesion molecules.<sup>82</sup>

### 5.1.3. Specific models of thrombus and antioxidant effects.

Antioxidants, in both *in vitro* and *in vivo* models of thrombus formation, have been shown to directly influence various stages of thrombus development. In an animal model of DVT, the antioxidant vitamins E and C have been implicated in decreasing thrombus size by decreasing the ROS levels and subsequent endothelial damage.<sup>83,84</sup> In these models, oxidative stress was linked with increased thrombin activity, platelet aggregation, and increased fibrin formation. Antioxidants can counteract these effects by preventing the initiation of clotting factor-dependent thrombus-forming reactions, thus sustaining the generation and increasing the risk of thrombus formation and propagation.

The involvement of antioxidants in the mitigation of oxidative stress in the arterial walls has been well investigated using models of thrombosis due to atherosclerosis. By promoting oxidative modification of lipoproteins, the generation of ROS is implicated in plaque formation and platelet activation.<sup>35</sup> In that regard, studies indicated that antioxidants such as resveratrol from red wine and catechins from green tea diminish oxidative modification of LDL, inhibit platelet aggregation, and protect the endothelium, thereby reducing the risk of thrombus formation associated with atherosclerosis.<sup>85,86</sup>

## 5.2. Modulation of platelet function

A primary event in thrombus formation is the activation and aggregation of platelets. The inhibition of these processes is essential to prevent undesirable clot formation, such as that found in arterial thrombosis, leading to stroke or myocardial infarction. When there is vascular injury, platelet activation and shape change, granule release, adhesion to the exposed subendothelial matrix, aggregation, and formation of a primary hemostatic plug ensue. A complex signaling pathway regulates this process.<sup>87</sup> Inhibition of platelet activation and aggregation, therefore, constitutes an important strategy for controlling thrombosis, and a variety of dietary and pharmaco-

logical bioactive compounds serve as potent modulators of these pathways.

**5.2.1. Inhibition of platelet activation pathways.** Inhibition of platelet activation can theoretically be achieved by targeting numerous receptors, enzymes, and signaling pathways involved in activation. Various bioactive substances can inhibit key molecules and enzymes that mediate platelet activation. Several bioactive compounds have been identified for their ability to inhibit key molecules and enzymes that mediate platelet activation. One of the best-known mechanisms is through the inhibition of cyclooxygenase (COX), an enzyme responsible for the production of the potent platelet activator TXA<sub>2</sub>.<sup>88</sup> The non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, inhibit COX-1 and thereby lessen the production of TXA<sub>2</sub> and, by extension, the activation of platelets.<sup>89</sup> This strategy is one of the most applied for the prevention of cardiovascular events.

Flavonoids, polyphenols, and omega-3 fatty acids have been well documented to inhibit platelet activation. For example, flavonoids such as quercetin and catechins from tea have been shown to inhibit activation of GPVI and associated signaling pathways, resulting in a decrease in platelet aggregation.<sup>90</sup> Likewise, omega-3 fatty acids, including EPA and DHA, inhibit platelet activation by regulating TXA<sub>2</sub> generation and down-regulating activation markers like P-selectin.<sup>91</sup> These compounds may also inhibit the expression of adhesion molecules on platelets and thus inhibit their adhesion to the vascular wall, thereby reducing thrombus formation.

**5.2.2. Inhibition of platelet aggregation pathways.** Platelet aggregation is mediated primarily by  $\alpha$ IIb $\beta$ 3 integrin that binds to fibrinogen to help make a platelet plug.<sup>92</sup> Several inhibitors of this action include antiplatelet agents such as clopidogrel and ticagrelor, which inhibit ADP receptors P2Y<sub>12</sub> on the platelets, thereby inhibiting  $\alpha$ IIb $\beta$ 3 integrin activation. These drugs work to inhibit platelet aggregation and thrombus formation by interfering with fibrinogen binding.<sup>93</sup> Additionally, a range of natural products has demonstrated the ability to inhibit platelet aggregation through different mechanisms.

For instance, there are compounds in garlic, like allicin, that are found to inhibit platelet aggregation by enhancing NO levels, which decreases platelet activation and aggregation. Allicin could inhibit the enzyme activity associated with thrombin generation and subsequently prevent the activation of platelets further in the cascade.<sup>94</sup> In a similar fashion, the polyphenolic compound in turmeric, curcumin, has been documented to inhibit platelet aggregation by modulating the function of multiple signaling pathways, which include the inhibition of COX-2 and the NF- $\kappa$ B pathway involved in platelet activation.<sup>95</sup>

Another class of bioactive components, flavonoids, inhibits platelet aggregation by intervening in multiple platelet-activation mechanisms. For example, rutin and quercetin can reduce platelet aggregation by promoting the release of ADP from platelet granules, thereby inhibiting its activation of the P2Y<sub>12</sub> receptor.<sup>96</sup> Additionally, resveratrol, which is found in grapes and red wine, inhibits platelet aggregation by enhan-



cing the bioavailability of NO and suppressing pro-aggregatory molecules such as TXA2 and P-selectin.<sup>97</sup>

### 5.2.3. Other mechanisms of platelet function modulation.

Besides inhibiting platelet activation and aggregation, some bioactive substances affect other functions of platelets, such as adhesion, signaling, and interaction with the endothelial cells. For example, compounds like PUFAs and antioxidants downregulate the expression of adhesion molecules present on platelet surfaces, including P-selectin and integrins, thereby reducing platelet adhesion to vascular endothelium and finally causing inhibition of thrombus formation.<sup>98</sup> Additionally, antioxidants such as vitamin E and flavonoids have been found to decrease oxidative stress in platelets, preventing activation and the formation of reactive oxygen species that may enhance thrombosis.<sup>99</sup>

Some bioactive substances also affect platelet microtubule stability, which is crucial for maintaining shape and enabling the aggregation process. Resveratrol, for instance, has been shown to interfere with microtubule polymerization within platelets, thus attenuating their ability to aggregate.<sup>100</sup> Furthermore, green tea polyphenols such as epigallocatechin gallate (EGCG) interfere with the activation of platelet signaling pathways mediated by thrombin receptor and GPVI, thereby preventing platelet activation and aggregation.<sup>101</sup>

### 5.3. Anti-inflammatory effect of dietary bioactive compounds

Inflammation plays a major role in the development of thrombosis; this includes not just platelet activation but also hastening of the clotting cascade and inhibiting fibrinolysis. The chronic inflammatory response can lead to endothelial dysfunction, an increased expression of adhesion molecules, and the release of pro-inflammatory cytokines, all of which contribute to thrombus formation.<sup>4</sup> Hence, targeting cytokines and adhesion molecules in the inflammatory pathway is one of the key approaches for therapeutic prevention of thrombotic events, particularly heart attacks and strokes. Many bioactive compounds, especially those derived from the diet, have shown promise in this regard.

#### 5.3.1. Inflammatory cytokines and thrombogenesis.

Inflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6, IL-8, and interferon-gamma (IFN- $\gamma$ ) play critical roles in regulating immune responses and inflammation.<sup>102</sup> In the context of thrombosis, these cytokines are involved in the activation of endothelial cells, increased expression of adhesion molecules, stimulation of platelet aggregation, and coagulation cascade initiation. For example, TNF- $\alpha$  and IL-6 are potent activators of the endothelial cells, leading to the upregulation of adhesion molecules like P-selectin, E-selectin, and ICAM-1, which facilitate the attachment and rolling of leukocytes and platelets on the endothelial surface.<sup>39</sup>

Moreover, IL-1 and TNF- $\alpha$  enhance the production of ROS, which further activate platelets and endothelial cells, creating a pro-thrombotic environment.<sup>103</sup> Inflammation also leads to the increased production of TF, which activates the coagulation cascade and promotes thrombus formation. The link between inflammation and coagulation is evident in various

inflammatory conditions, such as atherosclerosis, where elevated levels of IL-6 and TNF- $\alpha$  are correlated with increased thrombosis risk.

Emerging evidence highlights the role played by the gut microbiota in modulating this inflammatory coagulation axis. Microbial-derived metabolites, including SCFAs and lipopolysaccharides (LPS), can act on G-protein-coupled receptors GPR41/43 (FFAR3/FFAR2) expressed on endothelial cells, platelets, and immune cells, leading to suppression of pro-inflammatory cytokines and attenuation of platelet aggregation.<sup>104</sup> Conversely, microbial dysbiosis and elevated LPS levels can enhance TNF- $\alpha$  and IL-6 production, amplifying endothelial activation and coagulation, thereby increasing thrombotic risk.<sup>105</sup> This highlights a direct microbiota-cytokine-coagulation crosstalk, linking dietary and microbial influences on thrombogenesis.

**5.3.2. Suppression of inflammatory cytokines by dietary bioactive compounds.** Various bioactive compounds of dietary origin may modulate inflammatory cytokines, thereby preventing the pro-thrombotic effects associated with their over-expression. Polyphenols, for instance, have a well-established history of action against inflammation. Flavonoids such as quercetin, kaempferol, and catechins have been shown to inhibit TNF- $\alpha$ , IL-6, and IL-1 $\beta$  in several *in vitro* and *in vivo* models.<sup>106</sup> This inhibition occurs by modulating transcription factors NF- $\kappa$ B and activator protein-1 (AP-1), which promote pro-inflammatory gene expression. These bioactive compounds suppress inflammatory cytokines and adhesion molecules by inhibiting NF- $\kappa$ B activation, hence inhibiting platelet aggregation and thrombus formation.<sup>106</sup>

Omega-3 fatty acids, especially EPA and DHA, have strong anti-inflammatory effects. These fatty acids modulate inflammatory cytokine-producing signals by inhibiting the pro-inflammatory transcription factors NF- $\kappa$ B and stimulating the anti-inflammatory mediators such as resolvins and protectins, which promote inflammation resolution and establish homeostasis. Omega-3 fatty acids have been shown to reduce the levels of TNF- $\alpha$  and IL-6 in the presence of stimulants in macrophages and endothelial cells, consequently tempering the pro-inflammatory milieu responsible for thrombus formation.<sup>107</sup>

Compounds containing sulfur, such as in garlic (*e.g.*, allicin), have been reported to exert prominent anti-inflammatory action. Allicin has been demonstrated to inhibit pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , because it blocks their activation pathway of NF- $\kappa$ B, that induces inflammation,<sup>94</sup> at the onset. Similarly, curcumin is another polyphenolic compound that prevents the expression of those pro-inflammatory cytokines by depressing the NF- $\kappa$ B pathways, reducing endothelial activation and platelet aggregation.<sup>108</sup> Moreover, in ApoE<sup>-/-</sup> mice, a standard model for atherosclerosis, soyasaponins (A1 and A2) reduced aortic and innominate artery plaque formation by alleviating hypercholesterolemia and inflammation.<sup>109</sup> These compounds create an anti-inflammatory setting, which is essential for bringing about successful removal of thrombi by modification of pathways.



#### 5.4. Adhesion molecules and thrombosis

Adhesion molecules are fundamentally important in the movement of platelets and leukocytes to the site of vascular injury, thereby initiating thrombus formation. These include P-selectin and E-selectin, as well as adhesion molecules such as ICAM-1 and VCAM-1, which are induced by inflammatory cytokines. They promote the adhesion of platelets and leukocytes onto the endothelium. Once platelets adhere to the endothelial surface, they release more pro-inflammatory cytokines and recruit further platelets to amplify the thrombotic response.<sup>110</sup>

P-selectin, which is strongly expressed on the surface of activated platelets and endothelial cells, plays an important role in mediating platelet-leukocyte interactions and platelet aggregation. Increased levels of P-selectin correspond to enhancement of thrombotic events, whereas its inhibition has been shown to prevent thrombosis.<sup>111</sup> Other adhesion molecules, such as E-selectin and ICAM-1, promote interactions between the platelets and leukocytes, further enhancing thrombus formation.<sup>112</sup>

**5.4.1. Inhibition of adhesion molecules by dietary bioactives.** Adhesion molecules are also modulated by bioactive dietary compounds, which lower platelet aggregation and thrombus formation. Flavonoids such as quercetin and resveratrol inhibit adhesion molecule expression in activated endothelial cells and platelets, especially P-selectin and ICAM-1. These compounds inhibit the activation of NF- $\kappa$ B, a key transcription factor controlling the expression of adhesion molecules. By preventing the upregulation of adhesion molecules, these bioactive compounds limit the recruitment of platelets and leukocytes at the site of vascular injury, thereby limiting thrombus formation.<sup>113,114</sup>

Omega-3 fatty acids also exert their anti-thrombotic effects by modulating the expression of adhesion molecules. EPA and DHA have been shown to decrease the expression of P-selectin, E-selectin, and ICAM-1, thereby reducing platelet-endothelial interactions and leukocyte infiltration. Additionally, omega-3 fatty acids help to preserve endothelial integrity and function, making them a powerful tool in the prevention of thrombosis.<sup>115</sup> Moreover, saponins from *Tribulus terrestris* L. decreased the expression of ICAM-1, VCAM-1, and E-selectin in human endothelial cells, indicating anti-inflammatory and anti-atherosclerotic effects.<sup>116</sup>

#### 5.5. Endothelial function: enhancement of NO production and reduction of endothelial dysfunction

Endothelial cells line the interior surface of blood vessels and play a crucial role in maintaining vascular homeostasis. The endothelium regulates vascular tone, blood flow, and hemostasis through a series of bioactive molecules, among them NO. Endothelial dysfunction is the condition where the endothelium loses its ability to regulate vascular tone and maintain a non-thrombotic surface. This is usually characterized by low bioavailability of vaso-protective NO. NO is an important key molecule in maintaining the integrity of the vasculature. In a

normal endothelium, NO is produced *via* the action of endothelial eNOS in catalyzing the conversion of L-arginine to NO. Then, NO acts to cause vasodilation, prevention of platelet aggregation, and inhibition of the proliferation of smooth muscle cells, which contribute to a stable and non-thrombogenic vascular environment.<sup>36</sup>

Endothelium becomes dysfunctional, often due to factors such as oxidative stress, inflammation, or hyperglycemia. This results in impaired NO production. Reduced NO bioavailability results in vasoconstriction, platelet activation, and increased leukocyte adhesion, all of which favor thrombosis. Endothelial dysfunction is associated with increased expression of adhesion molecules such as P-selectin and ICAM-1, which enhance the adhesion of platelets and leukocytes to the endothelium, thus aggravating thrombus formation.<sup>39</sup>

Several dietary bioactive compounds have been shown to improve endothelial function by enhancing NO production and attenuating endothelial dysfunction. These bioactive compounds have been shown to inhibit oxidative stress and inflammatory responses that limit NO bioavailability and contribute to the incidence of thrombosis. Flavonoids and other polyphenols have been found to enhance NO production *via* eNOS activation and improve endothelium function, such as quercetin.<sup>6</sup> Other flavonoids such as hesperidin, naringin,<sup>117</sup> and curcumin<sup>118</sup> have also been associated with such action. Punicalagin and anthocyanins from pomegranate<sup>119</sup> are reported to enhance NO production through eNOS activation and improve endothelial function. These compounds act as antioxidants, thus reducing damage to eNOS activity by oxidative stress. Polyphenols, on the other hand, can enhance endothelial eNOS activity by controlling specific intra- and extracellular signaling pathways, for instance, AMP-activated protein kinase (AMPK) and phosphoinositide 3-kinase (PI3K) involved in the activation of eNOS as a result of polyphenols improving vascular reactivity, decreasing platelet aggregation, and the risk of thrombosis.<sup>120</sup> Omega-3 fatty acids were also known to enhance NO production in improving eNOS activity and decreasing oxidative stress. These fatty acids are seen to promote endothelin eNOS expression while inhibiting the production of ROS, which is known to inhibit bioavailability.<sup>121</sup> Omega-3 fatty acids also have anti-inflammatory potential, as given by their reduction of levels of pro-inflammatory cytokines. Allicin is a sulfur-containing compound found in garlic that increases the production of NO and enhances endothelial function. Allicin stimulates eNOS activity because of the activation of the PI3K/Akt signaling pathway, leading to increased bioavailability of NO.<sup>122</sup> Moreover, trimethylamine *N*-oxide is linked to endothelial dysfunction, whereas compounds like glycyrrhizin may protect endothelial function by enhancing NO production and maintaining cell junction integrity.<sup>123</sup>

#### 5.6. Regulation of the coagulation cascade

The coagulation cascade is an enzymatically controlled and regulated process of coagulation and the formation of clots to stop bleeding following blood vessel damage. Thrombosis adds to DVT, stroke, and myocardial infarction, which occur



due to the formation of a thrombus by uncontrolled or wrong initiation of activation of clotting factors. Thus, appropriate control of the coagulation cascade is essential to stop the formation of pathological thrombi. Several regulatory systems are in place to control players in the coagulation cascade, like thrombin, TF, and fibrin polymerization, in order to avoid over-coagulation.

**5.6.1. Thrombin inhibition.** Thrombin is one of the fundamental enzymes of coagulation and is synthesized by the activation of prothrombin. Besides, it has an anticoagulant effect, it effectively intervenes in the process of the conversion of fibrinogen to fibrin, activates platelets, and enhances the cascade effect. Thrombin has several pathways by which its action is regulated and the rate of clot formation is limited. There are some ways in which thrombin can be inhibited, and natural bioactive compounds have been shown to modulate these pathways.

Flavonoids, such as quercetin, catechins, and polyphenols, present in crude drugs are known to have direct anti-thrombin action. These compounds bind at the active site of thrombin and thus inhibit its action upon fibrinogen to produce fibrin. This direct inhibition can be useful to prevent clotting when there is a hypercoagulable state.<sup>124</sup> Antithrombin III (ATIII) is an inhibitor of thrombin and other serine proteases of the coagulation cascade. Garlic, having allicin, diallyl disulfide (DADS), and fish oil containing omega-3 fatty acids can augment ATIII activity. Both the increasing concentrations of ATIII and its enhanced activity oppose the effects of thrombin and minimize clot formation.<sup>125</sup> Thrombomodulin is also a membrane-bound glycoprotein on the endothelial cell surface. It participates in the binding of thrombin and the change of thrombin from procoagulant to an anticoagulating protein. Thrombin activates protein C when it binds to thrombomodulin; *via* protein C activation, it inactivates factor Va and factor VIIIa to prevent the formation of another thrombin molecule. The authors also highlighted that natural compounds, such as ferulic acid,<sup>126</sup> resveratrol,<sup>127</sup> and curcumin,<sup>128</sup> might increase the thrombomodulin expression on endothelial cells, therefore increasing thrombin inactivation and reducing coagulation.

**5.6.2. Inhibition of tissue factor (TF).** TF, also known as coagulation factor III, is a key initiator of the extrinsic pathway of coagulation. TF binds to factor VIIa, which activates factor IX and factor X, leading to thrombin generation and fibrin clot formation. Inhibition of TF activity is another important strategy for regulating coagulation.

Studies have demonstrated that polyphenols, particularly those found in green tea (*e.g.*, EGCG), can downregulate the expression of TF. By inhibiting the transcription of the TF gene, these compounds prevent the initiation of the extrinsic coagulation pathway. This reduces the activation of factor VIIa, subsequently limiting thrombin generation and clot formation.

Omega-3 fatty acids, found in fish oils, certain plant-based sources like flaxseeds,<sup>129</sup> and curcumin<sup>130</sup> have been shown to reduce the expression of TF in endothelial cells. The anti-inflammatory properties of omega-3s likely contribute to this

effect, as inflammation can induce TF expression. By inhibiting TF, omega-3s help to reduce the activation of the coagulation cascade, thus limiting the potential for thrombus formation. Gypenoside XLIX, a saponin from *Gynostemma pentaphyllum*, inhibits LPS-induced tissue factor expression in monocytes *via* PPAR- $\alpha$  activation, reducing procoagulant activity and potentially lowering thrombotic risk.<sup>131</sup>

Furthermore, the interplay between inflammatory cytokines and coagulation pathways underscores the importance of targeting both aspects in thrombotic disorders. Inflammatory cytokines such as TNF- $\alpha$  and IL-6 can upregulate TF expression, linking inflammation to coagulation. Dietary bioactive compounds that modulate these cytokines may, therefore, offer therapeutic potential in preventing thrombosis by inhibiting TF expression and activity.<sup>132</sup>

**5.6.3. Inhibition of fibrin polymerization.** Fibrinogen is a plasma protein that, during coagulation, is converted into fibrin by the action of thrombin. The fibrin monomers then solidify to give a structure of fibrin that arrests the clot. Because of that, the regulation of fibrin polymerization is another important parameter that is necessary to maintain appropriate clot formation. A number of bioactive agents have been reported to be able to prevent fibrin polymerization and decrease the stability of thrombi.

For instance, quercetin,<sup>133</sup> kaempferol,<sup>134</sup> and anthocyanins<sup>124</sup> have been observed to suppress the polymerization of fibrin or act on fibrinogen or fibrin directly. These compounds could hinder the ability of the fibrin monomers to link to form long fibers and thus weaken and destabilize the clot. Therefore, when an anticoagulant is present, the clot may dissolve quickly or may not entirely form, hence greatly decreasing the chances of thrombus-associated diseases. Heparin, a naturally occurring sulfated polysaccharide, acts synergistically with ATIII and has an antithrombin effect on thrombin.<sup>135</sup> Besides that, saponins drawn from foods such as beans, legumes, and some herbs can also impact fibrin polymerization.<sup>106</sup> This can also assist in decreasing the formation and, to some extent, the stability of clots.

## 5.7. Fibrinolysis activation

The dissolution of the fibrin clot, which has formed at a particular site once that clot is no longer required, is called fibrinolysis. Self-activation of fibrinolysis plays an essential role in the regulation of hemostasis as it opposes the coagulation cascade. The fibrinolysis process involves plasminogen, plasminogen activators (for instance, tPA), and plasmin, which, on acting on the fibrin clots, degrade the clots into some preformed fragments. Activation of plasminogen into plasmin and fibrin degradation is fundamental for the prevention of abnormal thrombus formation.<sup>23</sup>

The effect was observed for polyphenolic compounds, which include green tea (EGCG),<sup>136</sup> grapes, resveratrol, and berries, and anthocyanin<sup>137</sup> on the tPA gene. These compounds may also act by altering different signal transduction pathways that contain MAPK and PI3K/Akt, that is, which are responsible for the regulation of the tPA gene. High levels of



tPA promote the conversion of plasminogen into plasmin with the purpose of dissolving the clot.<sup>137</sup> Omega-3 fatty acids, particularly fish oil-derived fatty acids (EPA, DHA) have been documented to improve fibrinolytic activity by augmenting the conversion of plasminogen to plasmin. These fatty acids can raise tPA and uPA levels, promoting the transformation of plasminogen to plasmin.<sup>138</sup> Curcumin<sup>130</sup> and ginger root, which contain gingerols and shogaols, showed efficacy in fibrin degradation through an increase of plasminogen activation and the level of plasmin.<sup>80</sup> In another study, it has been proved that they can cause fibrinolysis by increasing plasminogen activation. Both curcumin and omega-3 fatty acids' anti-inflammatory effects can enhance the effects of fibrinolysis by inhibiting the levels of inflammatory cytokines that are known to suppress the activity of fibrinolytic enzymes.<sup>138</sup>

### 5.8. Microbial metabolites and thrombosis

SCFAs, primarily acetate, propionate, and butyrate, are microbial metabolites produced through the fermentation of dietary fibers by the gut microbiota. These metabolites influence thrombosis by modulating vascular inflammation, endothelial function, and platelet activity *via* multiple mechanisms.<sup>139,140</sup>

SCFAs activate G-protein-coupled receptors GPR41 (FFAR3) and GPR43 (FFAR2), which are expressed on endothelial cells, immune cells, and platelets.<sup>141</sup> Activation of these receptors has been shown to reduce pro-inflammatory cytokine production, including TNF- $\alpha$  and IL-6, thereby attenuating endothelial activation and the expression of adhesion molecules such as ICAM-1 and VCAM-1. This reduces leukocyte and platelet adhesion to the vascular wall and limits the pro-thrombotic environment. SCFAs also directly modulate platelet function by reducing aggregation and thrombus formation through intracellular signaling pathways such as cAMP and calcium mobilization.<sup>105</sup>

SCFAs, particularly butyrate, inhibit histone deacetylases, leading to increased histone acetylation and altered gene expression.<sup>142</sup> This inhibition promotes the differentiation of regulatory T cells (Tregs). The modulation of Tregs by SCFAs contributes to the attenuation of vascular inflammation and reduced thrombosis risk. SCFAs can influence the NLRP3 inflammasome, a key component of the innate immune system involved in inflammatory responses.<sup>105</sup> By modulating NLRP3 activity, SCFAs reduce the production of pro-inflammatory cytokines, thereby decreasing vascular inflammation and thrombosis risk. SCFAs enhance the integrity of the endothelial barrier by upregulating the expression of tight junction proteins such as ZO-1 and claudin-5, reducing vascular permeability, and preventing infiltration of inflammatory cells and molecules.<sup>140</sup> This protects against vascular inflammation and thrombus formation. In addition to SCFAs, microbial-derived LPS can activate endothelial cells and platelets, increasing adhesion molecule expression and platelet aggregation. The balance between SCFAs and LPS, shaped by gut microbiota composition, is therefore critical in regulating vascular inflammation and thrombosis.<sup>141</sup>

Dietary bioactive compounds are essential modulators of microbial metabolism and can enhance SCFA production. Dietary fibers (*e.g.*, inulin,  $\beta$ -glucans, resistant starch) are fermented by gut bacteria to generate SCFAs, contributing to reduced platelet reactivity and improved vascular health.<sup>143</sup> Polyphenols, such as quercetin, catechins, and anthocyanins, have been shown to alter gut microbiota composition, promoting SCFA-producing taxa.<sup>144</sup> For example, omega-3 fatty acids not only exert direct anti-inflammatory effects but also reshape the gut microbiota, favoring SCFA-producing genera.<sup>145</sup> Glycyrrhizin, a pentacyclic triterpenoid saponin abundant in *Glycyrrhiza*, was reported in the Chinese herb XinNaoKang to alleviate atherosclerosis in mice by modulating the cecal microbiota and improving lipid metabolism.<sup>146</sup> Together, these findings suggest that dietary bioactive compounds can modulate thrombosis not only through direct molecular interactions with host targets but also indirectly by shaping microbial metabolic outputs, particularly SCFAs. These metabolites, acting through GPR41/43, HDAC inhibition, and secondary bile acid or indole signaling, provide a mechanistic link between diet, microbiota, and thrombosis regulation.

## 6. Human studies on the anti-thrombotic effects of bioactive compounds

### 6.1. Evidence from clinical studies

Clinical studies have provided valuable insights into the potential of dietary bioactive compounds as anti-thrombotic agents. The clinical evidence supporting the anti-thrombotic effects of bioactive compounds is summarized in Table 2, highlighting key studies, target compounds, and mechanisms of action.

Flavonoids have been evaluated in clinical settings for their anti-thrombotic properties. Quercetin and catechins, commonly found in fruits, vegetables, and tea, have been shown to inhibit platelet activation and aggregation in human studies. A clinical trial involving patients with metabolic syndrome demonstrated that supplementation with flavonoid-rich extracts significantly reduced markers of platelet activation, including P-selectin and thromboxane B<sub>2</sub>.<sup>146</sup> In studies that used human blood with different flavonoid types and concentrations, flavonoids showed antiplatelet activity by binding to the GPIIb/IIIa platelet receptors,<sup>147</sup> inhibiting the response of thrombin-activated platelets to fibrinogen, and inhibiting the response of ADP-activated platelets to fibrinogen.<sup>56</sup> Ravishankar *et al.*<sup>55</sup> used blood platelets from three aspirin-free, healthy volunteers, with an incubation time of 5 min,  $4 \times 10^8$  cells per mL, with different tested flavonoids. They observed an inhibition of platelet aggregation stimulated by collagen. These findings underscore the potential of flavonoids as natural modulators of platelet function and thrombotic risk.

Several bioactive compounds have demonstrated significant anti-thrombotic effects through diverse mechanisms in clinical



**Table 2** Evidence supporting the anti-thrombotic effects of bioactive compounds

Bioactive compounds	Design of the trial	Dosage	Effect	Ref.
Isoquercetin	Patients with advanced cancer, age, $\geq 18$ years, $n = 64$	500 mg day <sup>-1</sup>	Reduce markers of platelet activation, including P-selectin and thromboxane B2	147
Quercetin, Rutin, Diosmetin	Blood from healthy, non-smokers donors, age $21.1 \pm 0.9$ [mean $\pm$ SD] years, $n = 20$	0.5 mM	Bind to the GPIIb/IIIa platelet receptors, show antiplatelet activity	148
<i>Lens culinaris</i> Medik. quercetin and kaempferol	Fresh human blood and plasma from healthy, non-smoking, drug-free volunteers of both sexes	5 and 50 $\mu\text{g mL}^{-1}$	Inhibit thrombin-activated platelets to fibrinogen, inhibit ADP-activated platelets to fibrinogen	56
Different flavonoids	Blood platelets from three aspirin-free, healthy volunteers.	3.125–100 $\mu\text{M}$	Inhibition of platelet aggregation stimulated by collagen	55
Pterostilbene	Healthy, aspirin-free individuals	1–100 $\mu\text{mol L}^{-1}$	Repressed platelet activation by hindering the PLC $\gamma$ 2–PKC cascade, Inhibition of activation of PI3K–Akt and MAPK	149
3,5,2',4'-Tetramethoxystilbene	Health human volunteers who had not taken any supplements or drugs in last two weeks		Inhibits PAR4-mediated platelet aggregation and secretion, reduce thrombus formation under whole blood flow conditions	150
Isorhapontigenin	Healthy, aspirin-free individuals		Inhibited integrin $\alpha\text{IIb}\beta$ 3-mediated inside-out and outside-in signalling and dense granule secretion in ADP-induced platelet activation	55
Omega-3 and acetylsalicylic acid	Healthy volunteers, male, aged 21–29, $n = 10$	1260 mg day <sup>-1</sup> for 5 days	Induced platelet aggregation	151
Omega-3 PUFAs	Blood of healthy volunteers		Enhanced antiplatelet effect	91
<i>Panax ginseng</i> ginsenoside saponins	Blood of healthy volunteers		Increases cAMP in human platelets, induces IP3R and VASP phosphorylation, reducing TXA <sub>2</sub> production and granule release, inhibits the formation of thrombin-induced fibrin clots	152
<i>Panax ginseng</i> ginsenoside	Normal healthy human volunteers		Inhibit ADP-induced platelet aggregation, inhibit [Ca <sup>2+</sup> ] elevation in platelets, inhibit fibrinogen binding	50
<i>Delonix regia</i> seed peptides	Blood from healthy volunteers		Decrease in platelet aggregation	53

or preclinical settings. Pterostilbene, tested with the blood from healthy, aspirin-free individuals, was found to repress platelet activation by inhibiting the PLC $\gamma$ 2–PKC cascade, which subsequently reduced the activation of PI3K–Akt and MAPK pathways, calcium ion release, and platelet aggregation.<sup>148</sup> Similarly, 3,5,2',4'-Tetramethoxystilbene inhibited PAR4-mediated platelet aggregation and secretion while reducing thrombus formation under whole blood flow conditions in healthy human volunteers who had abstained from supplements or drugs.<sup>149</sup> Isorhapontigenin showed potent inhibition of ADP-induced platelet aggregation, with an IC<sub>50</sub> of 1.85  $\mu\text{M}$ , and disrupted integrin  $\alpha\text{IIb}\beta$ 3-mediated inside-out and outside-in signaling in aspirin-free healthy participants.<sup>153</sup> Omega-3 fatty acids demonstrated synergistic platelet inhibitory effects when combined with acetylsalicylic acid in healthy male volunteers,<sup>151</sup> and their combination with antiplatelet drugs enhanced the overall antiplatelet efficacy compared with the drugs alone.<sup>91</sup>

Saponins from *Panax ginseng*, particularly ginsenosides like G-Rk3, inhibited platelet aggregation by increasing cAMP, inducing IP3R and VASP phosphorylation, and reducing calcium recruitment and cytoplasmic activation of integrin  $\alpha\text{IIb}\beta$ 3. G-Rk3 further inhibited thrombin-induced fibrin clot formation by controlling PI3K/Akt and MAPK phosphorylation.<sup>152</sup> Furthermore, ginsenosides are known to lower the impedance of platelet aggregation, decrease platelet calcium signaling, and lessen fibrinogen binding of healthy human platelets aggregated by ADP.<sup>50</sup> Protein peptides isolated from

the seeds of *Delonix regia* were also found to exhibit antiplatelet activity in blood samples of healthy adults.<sup>53</sup>

These outcomes provide evidence of multiple routes by which bioactive compounds may reduce platelet activation and thrombosis and serve as potential ideas for further treatment. However, current evidence on dietary bioactive compounds and anti-thrombotic effects remains weak and inconsistent. Most studies are small-scale *in vitro* or *ex vivo* investigations in young, healthy, aspirin-free volunteers, using hyperphysiological concentrations unlikely to be achieved through diet. Only one clinical trial<sup>146</sup> assessed patient outcomes, while others remain limited to surrogate mechanistic endpoints such as signaling pathways (PI3K–Akt, MAPK) or receptor binding. Moreover, the majority of these trials remain small in sample size, short in duration, and often restricted to healthy volunteers. Populations most vulnerable to thrombosis, such as elderly individuals or those with metabolic disorders, are notably absent. Heterogeneity in study design, doses, and platelet activation markers further hampers comparability. Importantly, large-scale, long-term, outcome-driven randomized controlled trials (RCTs) are still lacking. Overall, the field is dominated by preliminary mechanistic data with poor clinical translatability, underscoring an urgent need for standardized, physiologically relevant, and well-powered RCTs in at-risk groups. Future well-designed RCTs with clinically relevant endpoints are needed to validate and translate these promising findings into evidence-based recommendations.



## 6.2. Evidence from systematic reviews/meta-analyses

In recent years, systematic reviews and meta-analyses have synthesized evidence from RCTs to evaluate the anti-thrombotic efficacy of diverse dietary bioactive compounds. These comprehensive analyses provide higher-level evidence compared with individual studies and help in clarifying clinical relevance, safety, and potential therapeutic applications. Curcumin has been the focus of multiple systematic reviews. Evidence indicates that curcumin supplementation significantly reduces platelet aggregation, thromboxane B2 levels, and fibrinogen concentrations, highlighting its potential to modulate platelet function and coagulation pathways in cardiovascular disease prevention and management.<sup>154,155</sup> Similarly, quercetin was reported to inhibit platelet aggregation, improve endothelial function, and lower blood pressure, thereby contributing to an overall anti-thrombotic profile.<sup>156</sup> Furthermore, a meta-analysis of RCTs (841 participants) demonstrated that quercetin significantly lowers both systolic and diastolic blood pressure in normotensive and (pre)hypertensive individuals.<sup>157</sup> Since hypertension is a key risk factor for thrombosis, these findings highlight quercetin's indirect contribution to thrombosis prevention. Moreover, another meta-analysis of nine RCTs (730 patients) assessed traditional Chinese medicine (TCM) combined with Rivaroxaban for lower extremity DVT. The combination therapy significantly enhanced anti-thrombotic effects by reducing coagulation markers, D-dimer, and inflammation, while also alleviating limb swelling and pain compared with Rivaroxaban alone. Overall, TCM plus Rivaroxaban appears safer and more effective in preventing thrombosis, though further high-quality studies are needed.<sup>158</sup> A meta-analysis of 20 RCTs (2216 patients) evaluated *Panax notoginseng* preparations (PNP) combined with aspirin *versus* aspirin alone in coronary heart disease and ischemic stroke. The combination therapy enhanced anti-thrombotic effects by stronger inhibition of platelet aggregation and improved coagulation markers, without increasing bleeding risk or other adverse effects. Overall, PNP plus aspirin appears more effective and safer for preventing thrombosis compared with aspirin alone.<sup>159</sup>

Taken together, these systematic reviews and meta-analyses highlight that bioactive compounds from plant and dietary sources exert measurable anti-thrombotic effects through diverse mechanisms. Importantly, most were shown to be safe and well-tolerated, with no significant increase in bleeding risk in the clinical studies analyzed. These findings underscore the translational potential of dietary bioactives as complementary approaches for thrombosis prevention and cardiovascular disease management.

## 7. Challenges and limitations

Despite the promising potential of dietary bioactive compounds in preventing and managing thrombotic events, several challenges and limitations must be addressed to fully realize their therapeutic applications. These challenges pri-

marily involve bioavailability, dose–response relationships, and interindividual variability. Each of these factors can influence the efficacy and safety of dietary bioactives, presenting significant hurdles for their clinical use.

### 7.1. Bioavailability and metabolism

One of the inherent drawbacks when using dietary bioactive compounds mainly for therapeutic purposes is the compound's bioavailability. That is the ratio of the portion of a compound that actually gains access to systemic circulation and reaches the various tissues when ingested. Bioactive compounds such as polyphenols, terpenoids, and many peptides have poor bioavailability owing to poor absorption, rapid rate of metabolism, and first-pass metabolism in the liver.<sup>160</sup> This frequently leads to only a small part of the active compound actually entering the bloodstream, thus sharply restricting its curative effectiveness. For example, quercetin and catechins are rich in polyphenols; their bioavailability is low because their absorption by the gastrointestinal tract is low, and they are rapidly metabolized by the gut microbiota and liver.<sup>161</sup> However, even omega-3 fatty acids, which have several advantages, can be either oxidized or respond to enzymatic conversion that leads to their decrease in circulation.<sup>162</sup> To overcome these bioavailability barriers, approaches including the use of encapsulation techniques, nanoparticles, and co-administration with absorption enhancers (*e.g.*, piperine) have been explored.<sup>163</sup> These approaches seek to reduce the degradation of bioactive compounds, increase their permeability, and increase their bioavailability. For instance, platelet-membrane-coated curcumin nanoplateforms enable thrombus targeting and ultrasound-triggered release, enhancing thrombolysis and vessel repair *versus* non-targeted curcumin formulations.<sup>164</sup> Lipid systems also improve polyphenol performance. In a study by Stainer *et al.*,<sup>44</sup> quercetin metabolites show potent antiplatelet/antithrombotic activity and synergy with aspirin. Moreover, rutin delivered in lipid-based nano-formulations reduces thrombus formation in mice.<sup>165</sup> Similarly, nano-emulsions/liposomes enhance the bioavailability of hydrophobic compounds such as curcumin, translating to stronger inhibition of platelet activation, aggregation, and favorable coagulation profiles in preclinical and *ex vivo* human models.<sup>95</sup> For lipids, omega-3 PUFA nano-emulsions and related nano-materials stabilize EPA/DHA and modulate platelet function, supporting antithrombotic effects and potential combination with standard antiplatelet drugs.<sup>91,166</sup> Collectively, nanoparticles, emulsions/nanoemulsions, and bioactive-enhancer conjugates represent viable routes to increase systemic exposure and enable thrombus-site delivery actions for translating dietary bioactive compounds into adjunct anti-thrombotic therapy.

### 7.2. Dose–response relationship

Another concern of the clinical application of dietary bioactive compounds in thrombosis prevention is the dose–response relation. However, it is quite challenging to define an effective dose because of varying compound potency, diverse adminis-



tration forms, and different metabolism rates from one subject to another. Mechanistically, the doses investigated in human clinical trials can greatly differ from the concentrations used *in vitro*. Moreover, the outcomes obtained primarily depend not only on the dose of the bioactive compound but also on the period of supplementation. The form of the bioactive, whether as a whole food, extract, or individual bioactive compound, may also exert great influence. For example, the research about polyphenols reveals such information that polyphenols with doses of 100–500 mg day<sup>-1</sup> may denote positive outcomes, but at the same time, higher doses of polyphenols may be needed for further results.<sup>167</sup> However, as was noted, the dose–response curve may not be a straight line, and higher concentration does not always equal improved results. However, taking polyphenols may lead to more serious harm in larger doses. Additional studies are therefore warranted to determine the optimal therapeutic dosage ranges of polyphenols to achieve maximum therapeutic benefits while minimizing toxic effects.

### 7.3. Interindividual variability

Interindividual variability is a critical factor in determining the effectiveness of dietary bioactive compounds. Variations in how different people absorb, metabolize, and respond to these compounds depend on factors such as genetics, age, sex, diet, health status, and gut microbiota composition. These individual differences can significantly influence how well dietary bioactives work to prevent thrombotic events. Genetic factors, for example, can affect the activity of enzymes involved in metabolizing bioactive compounds, such as cytochrome P450 enzymes or UDP-glucuronosyltransferases, which can result in different responses to the same compound.<sup>168</sup> Additionally, the gut microbiota plays a key role in the bioactivation of certain bioactives, such as polyphenols and omega-3 fatty acids. Variations in the gut microbiota composition from person to person can influence how well these compounds are converted into their active forms, affecting their anti-thrombotic efficacy.<sup>169</sup> Age and underlying health conditions, such as diabetes or liver disease, also contribute to variability in bioactive metabolism. These factors can alter the pharmacokinetics of dietary compounds, impacting both their absorption and effectiveness. Therefore, personalized approaches that account for genetic, microbial, and health differences may offer more tailored strategies to optimize the anti-thrombotic benefits of bioactive compounds.

## 8. Future directions

This section identifies specific challenges and future opportunities for advancing research on dietary bioactives and their anti-thrombotic impact. Increasing the biological availabilities of bioactives through enhanced delivery technologies such as nanoencapsulation, liposomes, and microbiome engagement remain vital in improving the therapeutic potential of the bioactives. Genetic and metabolomics, microbiome, and other

individuality-driven protocols, including Precision Nutrition, demonstrate how extant evidence can be implemented more selectively and safely.

Investigating the synergistic effects of combining bioactives, such as polyphenols and omega-3 fatty acids, could unveil multi-target strategies to prevent thrombosis. Long-term clinical trials involving diverse populations and randomized controlled designs are essential to confirm safety and efficacy. Mechanistic studies should focus on elucidating the pathways influenced by bioactives, such as platelet aggregation, oxidative stress, and inflammation, while identifying biomarkers to track their effects *in vivo*.

Standardization and regulatory frameworks must be established for consistent extraction, formulation, and dosing of bioactives, ensuring quality and safety for therapeutic use. The addition of bioactive-enriched functional foods for supplementation in public health campaigns could be strategic alongside and in parallel to the use of drugs for cardiovascular diseases, especially in high-risk groups. These will enhance evolution and improve the translation of bioactives from the laboratory to clinical and health practice.

## 9. Conclusion

Dietary bioactive compounds from plant-based, marine-based and microbial-based sources offer a promising, natural approach for the prevention and management of thrombotic disorders, addressing key pathways such as platelet aggregation, oxidative stress, inflammation, and the coagulation cascade. Evidence from *in vitro*, *in vivo*, and clinical studies highlights the potential of polyphenols, omega-3 fatty acids, sulfur compounds, terpenoids, saponins, and emerging bioactive compounds like microalgal compounds and probiotic-derived metabolites in mitigating thrombogenesis. These compounds act through diverse mechanisms, including scavenging free radicals, modulating platelet function, enhancing fibrinolysis, and improving endothelial health. Despite their promise, challenges such as poor bioavailability, interindividual variability, and limited clinical data remain barriers to their widespread use. Addressing these limitations requires focused research on bioavailability enhancement, dose optimization, and long-term clinical trials. Furthermore, advancing precision nutrition approaches and understanding the synergistic effects of bioactive combinations could revolutionize their application in personalized thrombosis-prevention strategies.

Future work should incorporate dietary bioactives into population health programs, packaging them with functional foods and eating plans. They will also need some regulatory progress as well as protocol harmonization for safe and effective utilization. In overcoming the existing gaps and barriers to current knowledge, dietary bioactives are poised to provide synergistic supplementation to standard treatments as a means of greatly alleviating the global burden of thrombotic disorders. This holistic and sustainable approach aligns with



the growing emphasis on preventive healthcare and offers hope for improved cardiovascular health outcomes.

## Author contributions

NR: design study, investigation, data analysis, software, writing – original draft preparation. JL: investigation, data analysis, software, writing – original draft preparation. BX: conceptualization, funding acquisition, methodology, supervision, writing – reviewing and editing.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

## Abbreviations

ATIII	Antithrombin III
COX	Cyclooxygenase
DHA	Docosahexaenoic acid
DVT	Deep vein thrombosis
EGCG	Epigallocatechin gallate
eNOS	Nitric oxide synthase
EPA	Eicosapentaenoic acid
ICAM-1	Intercellular adhesion molecule 1
IL	Interleukin
LPS	Lipopolysaccharides
NF- $\kappa$ B	Nuclear factor-kappa B
NO	Nitric oxide
PAI	Plasminogen activator inhibitor
PGI <sub>2</sub>	Prostacyclin
PI3K	Phosphoinositide 3-kinase
PUFAs	Polyunsaturated fatty acids
RCTs	Randomized controlled trials
ROS	Reactive oxygen species
SCFAs	Short-chain fatty acids
TCM	Traditional Chinese medicine
TF	Tissue factor
TNF- $\alpha$	Tumor necrosis factor-alpha
tPA	Tissue plasminogen activator
TXA <sub>2</sub>	Thromboxane A <sub>2</sub>
uPA	Urokinase-type plasminogen activator
VCAM-1	Vascular cell adhesion molecule 1
vWF	Von Willebrand factor

## Data availability

The current manuscript is a review manuscript. All data are summarized in the tables based on the original research papers. Therefore, there are no original data newly generated in this review manuscript.

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