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Non-hemostatic functions of human blood platelets: Effects of bioactive compounds

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Abstract

Platelets have long been associated with sustaining the balance between hemostasis and thrombosis. Platelets, however, are also involved in a wide range of biological activities, including inflammation, infection, immunology, wound healing, cancer biology, and angiogenesis. Platelets' diverse roles are mediated by the expression of various adhesive and immune receptors and the secretion of a diverse array of bioactive proteins, ions stored in granules, and several mediators. The challenge for therapeutic intervention in non-hemostatic disease is identifying the factors that primarily inhibit specific targets implicated in platelets' complicated contribution to inflammation or tumor growth while leaving their hemostatic function intact. Anti-platelet drugs/bioactive compounds are developed based on their platelet anti-aggregatory properties; however, very little information is available on their effects on non-hemostatic function. In this review, a comprehensive overview of platelet multifunctional roles in CVD and other diseases and dietary factors' modulatory effects are described.

Keywords: Aspirin, COVID-19, Human blood platelets, Angiogenesis, Fatty acids, Immunity, Inflammation, Non-hemostatic function, Atherosclerosis, Cancer, Diabetes, Obesity, Hypertension, Bioactive compounds, Water-soluble tomato extract, Kiwi fruit, Papaya leaf extract, Polyphenols, Evodiamine, Polyphenols

Abbreviations: ARA, Arachidonic acid,20:4n-6; CVD, Cardiovascular Disease; COX, cyclooxygenase; GP, glycoprotein; DHA, ICAM , Intercellular adhesion molecule; PDI, protein disulfide isomerase; PDGF, Platelet-derived growth factor; LCPUFA, Long-chain polyunsaturated fatty acids; Platelet-derived endothelial cell growth factor: vWF von Willebrand factor; VSMC, vascular smooth muscle cells; TLRs, toll-like receptors; $TxA_{2,}$ thromboxane $A_{2;}$ vascular cell adhesion molecules, VCAM; VEGF, Vascular endothelial growth factor, chemokine receptor 4, CXCR4; MIP1α (macrophage inflammatory protein 1 alpha), RANTES, regulated on activation, normal T cell expressed and secreted, MCP3 monocyte-chemotactic protein 3, GRO-α (growth-regulated protein alpha), Epithelial-neutrophil activating peptide 78 (ENA-78); platelet microbicidal proteins (PMPs); Src-family kinases (SFKs); PTK2 (proline-rich tyrosine kinase-2); P-selectin glycoprotein ligand-1 (PSGL1); Platelet-derived endothelial cell growth factor (PD-ECGF); mitochondrial antiviral-signaling (MAVS); Toll-like receptor 7 (TLR7)

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1. Introduction

Platelets are the essential components of human blood that play a critical role in penultimate acute thrombotic events [1]. During normal conditions, platelets reside quiescently. But platelets form a plug whenever any disruption happens in the vascular endothelial cell layer [2,3]. At the vascular injury site, adhesion of platelets occurs, followed by platelet activation and aggregation, which is a crucial step in forming the platelet plug [4]. In addition to their involvement in hemostasis and thrombosis, platelets also develop several diseases involving processes such as inflammation, immunity, angiogenesis, atherosclerosis, and cancers [5-8].

Furthermore, these activated platelets are involved in the activation of the complement system, which is also involved in the coagulation cascade[9]. Activated platelets produce the potent platelet agonist known as thrombin, adenosine diphosphate (ADP), collagen and thromboxane (Tx)A_2, fibrinogen and factor V, and several others [10]. Maintaining physiological platelet activity is crucial for overall hemostasis and other physiological activities [3]. Inefficient activation of platelets compromises hemostasis and can result in excessive clinical bleeding. In contrast, excessive platelet activation is associated with arterial thrombotic conditions such as myocardial infarction and stroke. Therefore, blood platelets are a primary target for preventing recurrent cardiovascular events.

Platelets showed increased sensitivity at baseline for the platelet plug formation to those persons with diabetes, obesity, insulin resistance, hypertension, maintaining sedentary lifestyle and regular smoking, etc. [1]. Platelet hyperactivity is associated with the release of different components and the shedding of membrane particles that play essential roles in developing atherosclerosis, blood flow, inflammation, cancer metastasis, and hypertension. Hyperactive platelets engage with the secretion of various sticky growth factors and the release of macro-particles and inflammatory agents, reducing blood flow within the vessel and creating a prothrombic condition [11]. Platelet microparticles are also involved in the atherosclerosis process; in thrombus and foam cells formation, cancer metastasis, and inflammation. Platelet membrane glycoprotein (GP), GPIbα, GPV, GPVI, amyloid βA4, TLT-1 (TREM-like transcript-1), P-selectin (CD40L), amyloid-like protein 2, and semaphorin 4D are the most abundantly shed platelet proteins[12]. This eventually leads to platelet hyperactivity and endothelial dysfunction [1,13-15]. Also, platelets have several mediators that modulate the functions of platelets and different neighboring cells in the circulation and vascular bed endothelium [15,16].

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Apart from hemostasis, platelets play several roles in inflammatory processes[17]; wound healing processes [18]; host defense mechanism against microbes [19]; generation of innate immune responses [20]; tumor growth and malignancies [17]; angiogenesis [21]; development of lymphatic vessel [22]; and also atherosclerosis processes. Blood platelets can also influence innate and adaptive immune responses [18,23,24]. A complex hemostatic mechanism participates in the pathophysiology of various diseases, including cardiovascular disorders, diabetes, hypertension, inflammation, and infections. Among these factors, platelet dysregulation is associated with atherosclerosis and mainly involves the aggregation of platelets and a reduction in blood flow in the vascular endothelium. Blood platelets also act through multiple time-dependent activities, including signal-dependent pre-mRNA splicing and constitutively expressed mRNA translation, in addition to producing instantaneous messengers.

Aspirin, the key inhibitor of COX-1 mediated platelet synthesis of TxA_2, has several side effects which make it inappropriate for primary CVD prevention [25,26]. In addition, 25-30% people are aspirin resistant [25]. However, aspirin has multifactorial or pleiotropic effects, including inhibition of uncoupling of oxidative phosphorylation, inhibition of activation of nuclear factor binding kappa-B (NFκ-B), inhibition or stimulation of mitogen-activated protein kinases (MAPK), inhibition of nitric oxide (NO) synthetase activity, decrease ATP level and increase the level of adenosine in the extracellular medium thereby it causes suppression of platelet aggregation in the prevention of cardiovascular events [27].

Nowadays, there is rising interest in searching for naturally occurring anti-platelet bioactive compounds that may not have the same adverse effects as many anti-platelet drugs have [16,28]. Many studies have reported the anti-platelet compounds present in fruits and vegetables [1,16,29-34]. However, their actions on non-hemostatic functions of platelet are not well investigated. Achieving a better understanding of the roles and mechanisms of activity of these bioactive compounds on platelet functions in non-hemostatic processes may prevent several diseases, including cardiovascular disease (CVD). Since the role of platelets in the development and severity of a variety of illnesses other than thrombosis is now well known, the roles of bioactive compounds in these processes deserve more attention[17]. However, the hemostatic and inflammatory functions of platelets overlap; therefore, anti-platelet agents, depending on their mechanism of action, may also impact platelets' non-hemostatic activities. This review describes the non-hemostatic functions of human blood platelets and the roles of anti-platelet bioactive compounds in these processes.

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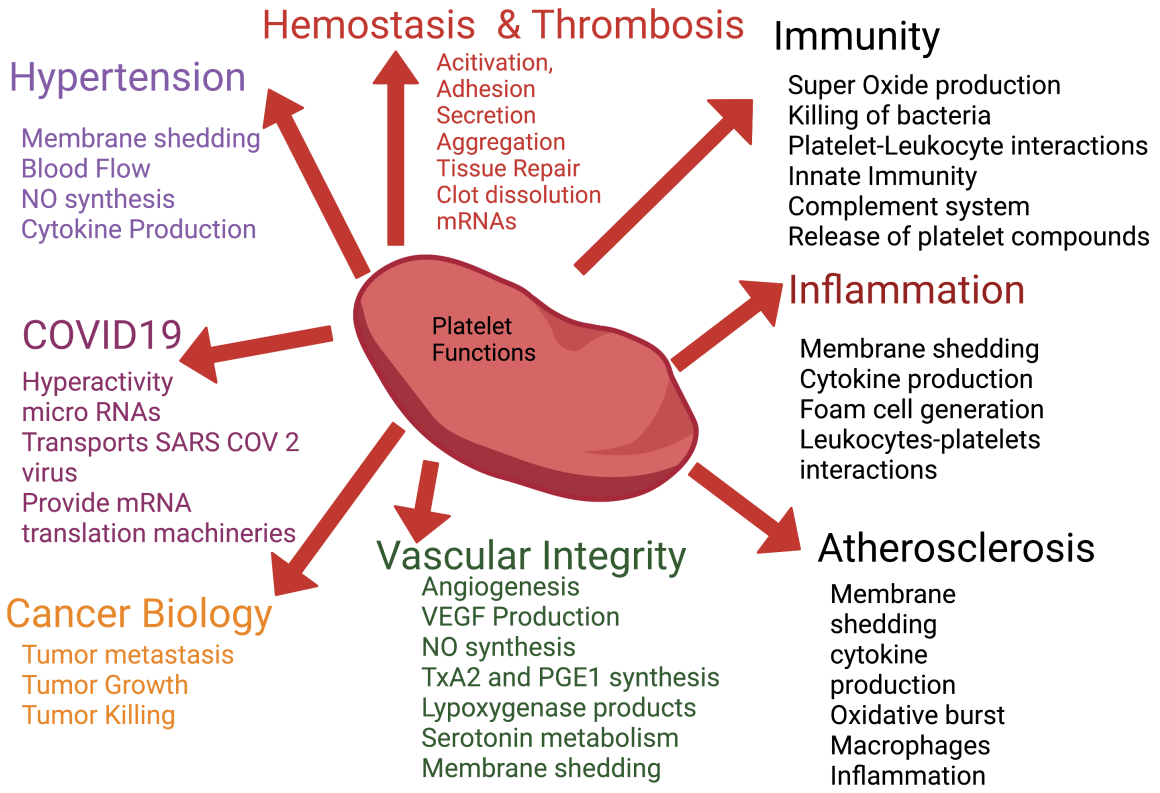
2. Non-hemostatic properties of human blood platelets

Human blood platelets have retained many functions of the primitive multi-functional hemocyte. Platelets have a more expansive repertoire of physiological roles and therefore are implicated in more pathological conditions other than thrombosis. They are active participants in several non-hemostatic processes such as an immune function to tumor biology, atherosclerosis, infection, diabetes. The challenge for therapeutic intervention in these diseases is to identify bioactive compounds/drugs that preferentially block or prevent specific targets involved in the complex contribution of platelets to these pathological processes while leaving hemostatic functions at least partially intact. **Figure-1** describes the overview of the various roles of blood platelets in multiple diseases.



2.1 Human blood platelets and vessel walls interactions

Endothelial dysfunction is a significant feature in metabolic syndrome, atherosclerosis, hypertension, diabetes, hyperlipidemia, and cardiovascular disorders [35,36]. The critical importance of platelets for maintaining vascular integrity was shown first by Gimbrone et al. 2016 [37]. The molecular mechanisms of forming a hemostatic plug formation are relatively well understood. When the subendothelial matrix proteins are exposed, platelets either interact directly with matrix proteins and integrin α2β1 to subendothelial collagen or bind to von

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Willebrand factor (vWF) at the site of injury[38]. Expressed GPIIa-IIIb receptors on platelet surface involve in aggregation of platelets. Thrombin, TxA_2, and ADP generate an activation signal and promote thrombus propagation via G protein-coupled receptors (GPRs) [9,39].

On the other hand, the vascular endothelium uses three different pathways for controlling of reactivity of platelets, (a) arachidonic acid, 20:4n-6 (ARA)–prostacyclin (PGI_2) pathway, (b) the L-arginine–NO pathway, and (c), the endothelial ecto-adenosine diphosphatase (ecto-ADPase) pathway[12,40,41]. PGI_2 is derived from ARA in endothelial cells by COXs and PGI_2 synthase [42,43]. PGI_2 inhibits platelet aggregation by increasing cyclic AMP (cAMP) levels in the platelets [41,42,44]. Increased cAMP levels in platelets cause phosphorylation of proteins that restrict GPIIb/IIIa activation from the inside out by inhibiting cytoskeletal re-arrangement [45].

Endothelial nitric oxide synthase (eNOS) produces NO that mediates several anti-platelet effects. No is diffused into blood platelets to inhibit their adhesion, activation, and aggregation via cGMP-mediated pathways [46,47]. Ecto-ADPase of the endothelial cell also inhibits platelet aggregation by metabolizing ADP released from activated platelets. By this mechanism, ecto-ADPase regulates the plasma levels of ADP and ATP [48]. GPVI and C-type lectin-like 2 (CLEC-2) are immunoreceptor tyrosine-based activation motif (ITAM) receptors of platelets membrane protect vascular integrity at the site of inflammation[49].

The pathogenesis of atherosclerosis is believed to be initiated by endothelial dysfunction. Endothelium produces angiotensin II (Ang II), endothelin-1 (ET-1), prostaglandin $(PG)H_2$, NO, PGI_2, Bradykinin, etc., and thus contribute to vasoconstriction and vasodilation of the blood vessel [50]. In the absence of a functional endothelium, atherosclerosis and thrombosis are initiated by leukocyte adhesion, activation of platelets, pro-oxidation of mitogens, dysregulation of the synthesis of PGI_2, NO, and endothelium-derived hyperpolarizing factor (EDHF), as well as other vasoconstriction factors such as Ang II and PGH_2 [51]. Vasoconstrictors (TxA_2, PGH_2, ET-1) and vasodilator (NO, EDHF, PGI_2) determine vascular tone. Atherosclerosis is also influenced by endothelium expression of adhesion molecules such as selectins, intracellular adhesive molecules (ICAMs), and vascular adhesive molecules (VCAM-1). Trans-endothelial cell migration is promoted by platelet lysophosphatidic acid, including invasion by tumor cells[52]. **Figure-2** describes the impacts of anti-platelet bioactive and aspirin targeting platelet-vessel wall interactions.

2.2 Human blood platelets and atherosclerosis process

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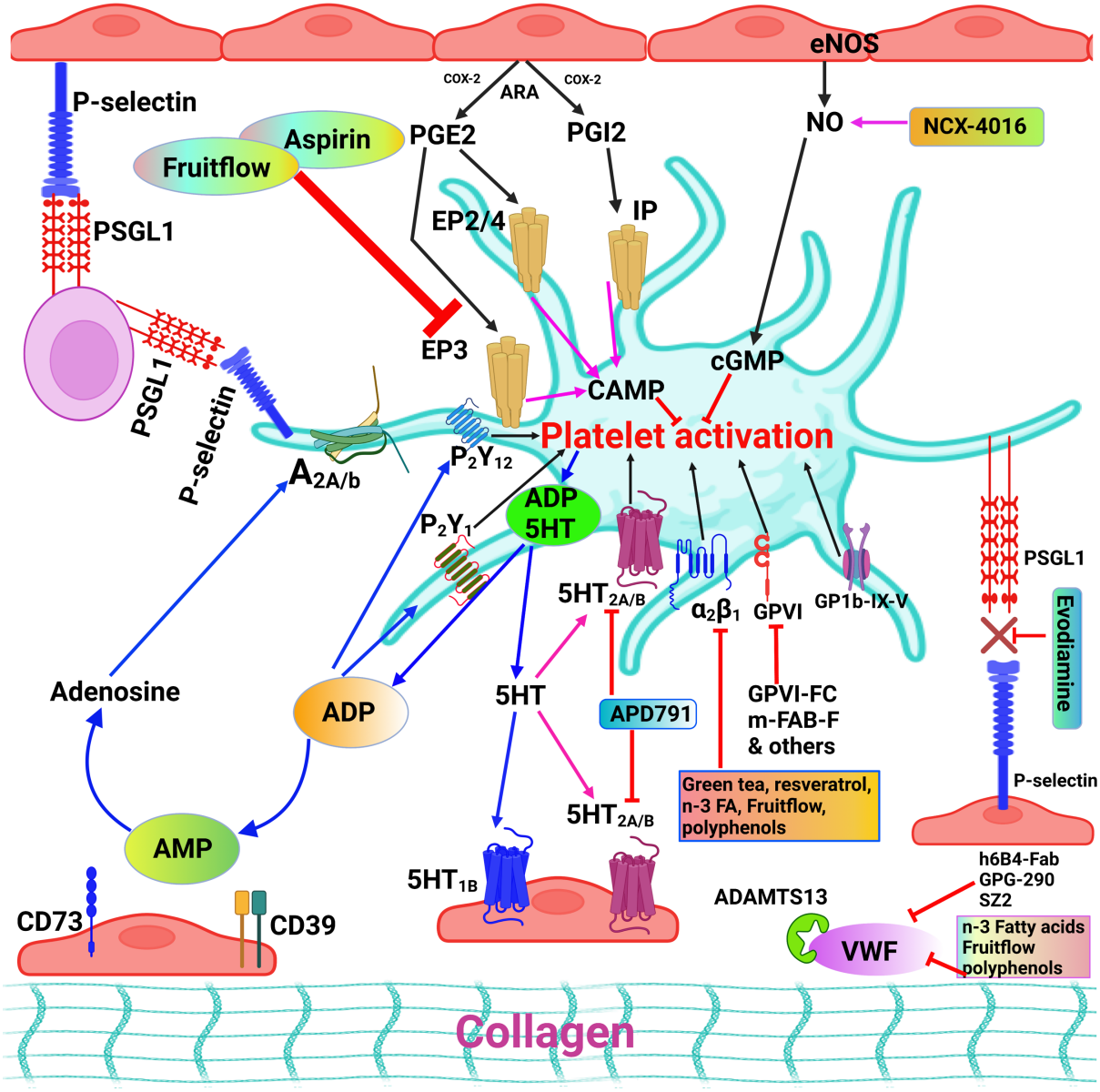
Physiological vascular integrity, vascular repair, and pathological derangements of the cardiovascular system depend on the cellular determinants of blood platelets. Activation of blood platelet accelerates the atherosclerotic processes by forming a link between various metabolic and hemodynamic abnormalities. Platelets become activated at the sites of atherosclerotic lesions and promote angiogenesis by releasing some modulators to endothelial progenitors and monocytes [53]. Platelet hyperactivity is associated with various physio-pathological conditions, including hypertension, diabetes mellitus, insulin resistance, smoking, obesity, hypercholesterolemia, and sedentary lifestyle [54], plays a crucial role in the progression of atherosclerosis and thereby promotes CVD[1,55].



Blood platelets of diabetic and hypertensive patients show spontaneous aggregation [56]. Hyperactive platelets are involved in inflammatory and atherosclerosis processes by secreting several inflammatory and agonists.

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Indeed, compounds present in the granules of platelet contribute to the cross-talk between platelets and inflammatory cells during vascular inflammation. Activated platelets produce platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), thus promoting atherosclerosis by increased proliferation of vascular smooth muscle cells (VSMCs) [57]. Activated platelets also produce serotonin, ADP, ATP, and lysophosphatidic acid that raise the intracellular Ca^{2+} concentration in VSMCs, thus enhancing vasoconstriction of a blood vessel and enhancing catecholamine response. Isoprenaline and Ang II are the two important agonists of β–adrenoceptors that raise [Ca^{2+}] levels and stimulate VSMC contraction, platelet activation, and aggregation. Furthermore, AngII can also increase pH in platelets in hypertensive patients, which possibly contributes to platelet hyperactivity. Platelets also have increased intracellular Ca^{2+} levels and release more β-thrombomodulin and P-selectin. Hypertensive individuals have increased reactive oxygen species (ROS) levels in their platelets, which promote platelet activity by inhibiting NO bioavailability and increasing [Ca^{2+}], among many other cellular effects.

Obesity is associated with increased platelet activation, elevated surface expression of P-selectin, and increased shedding of platelet microparticles. By stimulating the production of monocyte chemoattractant protein, activated platelets modulate the chemotactic characteristics of endothelial cells. Activated platelet α-granules also produce TGF-β, which can facilitate type-1 plasminogen activator inhibitor secretion from adipose tissue. Activated platelets, adipose tissue, and the endothelium of blood vessels form a feedback loop, leading to an atherothrombotic vascular environment.

vWF is a determinant of atherosclerotic plaque development and mediates platelet recruitment at the site of vascular damage. As endothelial cells release inflammatory stimuli, platelets can be drawn to the area when they interact with vWF. By rolling on endothelial cells, platelets release vWF, modulating the blood flow. In addition, activated platelets express P-selectin involved in platelet–endothelium interactions and thus influence plaque development. P-selectin induces monocytes and macrophages to create chemoattractants and growth factors. In apoE-/- mice, activated platelets aggravate atherosclerosis in a P-selectin–dependent way [58].

It is necessary to find new approaches to bridge the gap between the large body of evidence supporting blood platelet involvement in atherogenesis and the relatively modest number of diseases associated with the condition. Several platelet inhibitors from dietary sources or functional foods may represent an effective primary prevention solution, given that CVD is becoming more prevalent due to obesity, diabetes, sedentary lifestyles, smoking, bad diets, and pollution.

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2.3 Human blood platelets and the immune system

Human blood platelets act similarly to classic immune cells like macrophages and mast cells, engulf bacteria, secrete chemokines, and remove invading pathogens from the circulation. Many of the underlying mechanisms platelets employ in their immunological response are analogous to hemostatic activities. Blood platelets contribute to pathological lesions in inflammatory disease and tumor growth due to incorrect reactions at the wrong location and wrong time.

Platelets internalize pathogens, microbes, bacteria, and viruses and kill various internalized pathogens to promote their clearance from the bloodstream and tissues [23,59]. Platelets exhibit different immunoreceptor attributes and antimicrobial properties against microbial pathogens [59-61]. Apart from the primary agonist, chemokines of platelets play a crucial role in the activation of platelets. The low agonist level induces the secretion of various chemokines from the alpha granule of platelets[62]. After interacting with chemokine receptor, 4, such as CXCR4, chemokines such as CCL4 and CCL17 bind to chemokine receptor 4 (CXCR4/CCR4) and cause platelet aggregation. The chemokines PF4 and SDF-1 also cause platelet aggregation, whereas CCL17 and TARC cause plaque adhesion through CXCR4/CCR4 [63,64]. Several other chemokines are also released from alpha granules that help attract the leukocytes and activate platelets at the injury site. These chemokines are CCL3, also known as MIP1α, CCL5, also known as RANTES, CCL7 initially called MCP3, CXCL1 initially known as GRO-α, CXCL5 also known as ENA-78 and CXCL8 (IL-8), etc. [64,65]. Platelets release the chemokines from alpha granules to combat microbes by trapping and engulfing them[7,19,66-70]. Chemokines and cytokines released by immune cells or activated platelets strictly regulate inflammatory processes. CCL2/MCP-1, CCL3/MIP-1, and CCL4/MIP-1 recruit monocytes, essential in the innate immune response. CCL5/RANTES and CXCL10/IP-10 chemo-attract activated T cells, implicated in the adaptive immune response. CXCL8/IL-8 chemokine is involved in attracting neutrophils [71]. Platelet stores and releases various molecules, including chemokines, and express functional immunoreceptor, which modulates the immune system[7,69]. Platelets also influence the development and activation of neutrophils, macrophages, and dendritic cells by expressing immunological receptors and modulating innate and adaptive immune responses[70,72].

Interactions between platelets and bacteria induce platelets adhesion, degranulation, shape change, and aggregation. The platelet-bacteria interaction is a complex process in which bacteria uses a wide range of receptors, including complement receptors like Fc gamma receptor type 2a (FcγRIIa), GPIIb-IIIa, GPIb and pattern recognition receptors (PRRs) including toll-like receptors (TLRs), nod-like receptors (NLRs), and C-type

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lectin receptors (CLRs) families to interact with platelets[6]. TLRs regulate the release of various cytokines from platelets in response to bacterial lipopolysaccharide[23,73,74]. TLRs cause inflammation when they come into contact with microbial products or inflammatory tissue products. The presence of TLRs on platelets may be responsible for the direct engulfment of pathogens similar to leukocytes. PAMPs of various cellular compartments, like plasma membrane, endosomes, endolysosomes, and lysosomes, are recognized by TLRs expressed on platelets[75]. There are multiple signaling pathways through which TLRs affect platelet function, including ERK1/2, PI3K/AKT, and NF-kB [76].

Human blood platelets are also involved in innate immune response with the help of TLRs present on the platelet membrane against invaded microbial pathogens [20,23,77]. TLR1, TLR2, and TLR6 are the predominantly expressed TLRs on platelet surfaces [78]. Human blood platelets also express TLR4, TLR8, and TLR9, but TLR2 and TLR9 are highly expressed on platelets at the time of activation[74,78,79]. Different biological reactions are triggered when TLRs are activated on platelets [23,80] , leading to the release of TNFα [81] and interleukin (IL)-1[82]. Platelets also recognize different isoforms of LPS, resulting in a varied reaction and the release of certain chemokine and cytokine types [83].

Human platelet release platelet microbicidal proteins (PMPs), or platelet kinocidins and PF4, have antimicrobial activity. Plasma PF4 showed antimicrobial activity against various pathogenic bacteria and fungi, and its levels significantly increased in *Plasmodium falciparum-induced* malarial disease conditions. Platelets also release CXCL4, CXCL7, and CCL5, defensins, human β defensin 2, thymosin β4, and some derivatives, thrombocidins, and fibrinopeptide A and B [84,85]. These chemokines and kinocidins ensure the process of platelet recruitment and accumulation at the infection site [24,84]. Moreover, platelets can also modulate other immune cells to release chemokines, kinocidins, and RANTES (CCL5) [84]. Platelet-derived RANTES modulates immune function by increasing the cytotoxic ability of T cells and the production of cytokines. Platelet-derived PF4 can kill erythrocytes infected with parasites. Platelets also play a role in innate immunity because thrombocidins contain antibacterial and antifungal characteristics. Even non-specifically, the constituents of platelet lysosomal granules, such as cathepsin, degrade the microbes [7,86]. Indeed, platelets and neutrophils can combine to form a neutrophil extracellular trap (NET) [87]. Neutrophils use a NET to trap and destroy pathogens, and the development of NET is a crucial mechanism of neutrophil death, and inhibiting this process can lead to a rise in infections [87]. A small antimicrobial cationic peptide β-defensin released from the platelet also can create a NET. The case of a gram-

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positive bacterial infection causes the activation of platelets. These activated platelets then surrounded and trapped them and limited their proliferation with the use of β-defensin 1.

P-selectin is an essential component of the alternative pathway complement system acts as a C3b binding protein on the platelet surface to induce complement activation [9]. Leukocytes can roll on a template of adhering platelets, firmly adhere, and subsequently transmigrate through the adherent platelets, similar to how they interact with inflammatory endothelium [88,89]. Adhesive receptors, cellular shape, and, probably most importantly, shear forces created inside moving blood regulate leukocyte rolling and adherence on platelets or endothelial cells [90]. The selectin family of sticky receptors mediates the first stage of cellular rolling.

Endothelial cells expressed both P-selectin and E-selectin, which have a role in endothelial cell–leukocyte interactions. P-selectin glycoprotein ligand-1 (PSGL1) is the best-characterized leukocyte ligand for P-selectin; it can bind directly with all subtypes of selectin molecules. Furthermore, PSGL1, with the help of their cytoplasmic domain, causes the activation of leukocyte 2 integrins [91]. Firm leukocyte adhesion and arrest require both immobilized and released chemokines. Immobilized chemokines induce leukocytes to be arrested in reconstituted systems [113,114], primarily due to the activation of GPRs. Platelet-generated chemokines such as PF4/CXCL4, CCL5/, and CXCL1/GRO- can modulate leukocyte activity and platelet–leukocyte interactions [24,92].

The PSGL-1 and GPRs direct leukocytes to produce transcription factors, cytokines, and chemokines [93,94]. Integrin αMβ2 (Mac-1) found on neutrophils plays a key role in integrin adherence by binding to GPIb and/or other ligands, notably, fibrinogen, which also interacts with integrin αIIbβ3 of platelets proline-rich tyrosine kinase-2 is a type of tyrosine kinase that occurs in the phosphorylated condition in leukocytes when they attach to platelets. Pyk2 played an essential role in maintaining the adhesion of platelet–neutrophil in murine and human cells, which could be a critical downstream modulator of Src-family kinase-dependent signaling [95].

Platelets promote wound healing by secreting thrombin and a range of growth factors, cytokines, and chemokines [96,97]. Thrombin also acts as a chemoattractant, bringing macrophages, stromal cells, and endothelial cells, as a growth factor mitogenic activity, and as an angiogenesis promoter [98]. Platelet CD154 has a role in the modulation of adaptive immunity and modulates innate immunity. In a murine model, platelet CD154 induces CD8+ T-cell responses to regulate adaptive immunity and is necessary for the production of different antibodies such as IgG, IgM, and IgA by interacting with CD40 found on antigen-presenting cells [99]. Furthermore,

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alloantibodies can activate complement pathways, causing endothelial damage and the subsequent recruitment of platelets [100].

2.4 Human blood platelets and inflammation

Platelets play a larger role vascular inflammation[101]. Platelets contribute to the progression of a chronic inflammatory disease such as atherosclerosis by inducing chemokine deposition, aggregation of inflammatory cells, and recruitment of leukocytes at the vascular wall [53]. Activated platelet causes the alteration of chemotactic, adhesive, and proteolytic properties of endothelial cells by releasing inflammatory mediators and mitogenic molecules and the local circulatory microenvironment[92,102]. As a result, these altered endothelial cells help in supporting the chemotaxis, adhesion, and transmigration of monocytes to the site of inflammation[103]. This sequence encourages monocyte migration and adherence to the location, which further leads to an increase in the formation of atherosclerotic plaques [104]. The involvement of platelet in inflammation is evident by anti-platelet drugs' effectiveness in inflammatory conditions [105,106].

Human platelets store, express, and release various inflammatory mediators, predominantly stored in α-granules[7]. Eicosanoids, serotonin, fibrinogen, vWF, PDGF, platelet-derived angiogenesis mediators such as VEGF, FGF, and other plasma proteins protease inhibitors[107,108]. Platelets play a role in inflammation by allowing these mediators to adhere to other cells via immunoreceptors or by enabling them to produce chemokines. Platelets interact with leukocytes, neutrophils, monocytes, endothelial cells, lymphocytes, dendritic cells, erythrocytes, and cancer cells [17,108,109].

PF4 also contributes to atherosclerosis by stimulating atherogenesis and causing vascular inflammation [110]. PF4 prevents the degradation of LDL by inhibiting the interaction between LDL and its receptors [11]. PF4 also promotes neutrophil granule release and endothelial cell adhesion, inhibits monocyte apoptosis, and increases monocyte differentiation into macrophages and ROS generation [85]. Platelet-derived CD154 (CD40L) produces inflammatory reactions in the vascular endothelium layer by associating with CD40 expressed on vascular endothelium [104]. Platelet CD40L, in turn, can cause endothelial E-selectin, VCAM1, and ICAM1 expression, as well as MCP1 and IL-8 secretion from endothelial cells [104]. In addition, endothelial cells can be induced to create ROS, adhesion molecules, chemokines, and tissue factors by platelet-derived CD40L, all of which contribute to inflammatory and atherosclerotic processes [104]. In LDL-receptor-/- mice, blocking the CD40-CD40L signaling pathway dramatically reduces atherosclerotic plaque formation and arterial lipid

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316 deposition[111]. Furthermore, in various types of CVD, cigarette smoking and type 2 diabetes mellitus act as
317 significant risk factors by releasing the increased amount of CD40L [112].

318 IL-1 causes active platelets to produce more chemokines and increases neutrophils adhering to the endothelium.
319 IL-1 increases platelet binding to collagen and fibrinogen as well as promotes aggregation of platelets [113]. The
320 P-selectin expression on activated endothelial cells or platelets encourages the migration of platelet microparticles
321 harboring the PSGL-1 and tissue factor to regions of vascular damage [114].

322 Platelet microparticles account for 60 percent to 90 percent of all microparticles in circulation. Platelet
323 microparticles are similar to exosomes and apoptotic bodies, extracellular vesicles. Platelet microparticles contain
324 GPIIb/IIIa, P-selectin, and vWf, all of which are involved in primary homeostasis. Since platelet microparticles
325 include procoagulant factors, nucleic acid, mitochondria, chemokines, and cytokines, they can influence the
326 inflammatory pathway, atheosclerotic plaque development, and thrombosis [114].

327 Platelet microparticles increase COX-2 mediated prostaglandins synthesis in monocytes and endothelial cells
328 [115]. Chemokines of platelet microparticles act as a chemoattractant for monocytes or encourage them to
329 differentiate into macrophages. PF4 causes endothelial cells to produce E-selectin [116] and release matrix
330 metalloproteinases-2 and -9, which cause atherosclerosis by degrading the extracellular matrix component[117].

331 O2 is a critical NO scavenger that regulates redox-sensitive ectonucleotidases on platelet and endothelial cell
332 membranes [2]. ROS prevents NO-mediated late disaggregation of thrombus as it scavenges NO. The COX-1
333 enzyme involves forming ROS by active platelets by metabolizing ARA. The different isoforms of NADPH
334 oxidase in platelets are activated by agonists that promote platelet activity. The synthesis of O_2- by platelets via
335 the route dependent on these oxidases aids in the recruitment of platelets to a developing thrombus.

336 Furthermore, NO can be removed more quickly by reacting with COX-1 products. ROS causes the peroxidation
337 of membrane phospholipids and LDL, resulting in enhanced production of F2-isoprostanes. F2-isoprostanes can
338 modify the adhesive responses and platelet activity. The synthesis of F2-isoprostanes and thromboxane has a
339 continuous link, suggesting that thromboxane-dependent platelet activation may be triggered by a low-grade
340 inflammatory state and associated metabolic diseases.

341 Thrombocytopenia is a condition in which platelet count decreases, which can reduce inflammation-induced
342 permeability of endothelial and extravasation of leukocytes without producing hemorrhage; platelet inflammatory

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functions are more responsive to platelet count reductions than inflammation-associated hemostasis [118]. Diverse platelet concentration threshold requirements for different platelet functions during inflammation suggest that it might have a role in targeting separately to discover innovative therapeutic strategies for platelet dependent diseases. ADP, TxA_2, or thrombin allow more platelets to be attracted and aggregated by activating GPIIb-IIIa on the platelet surface. In an animal model, platelet GPRs were shown to have a role in inflammation-related hemostasis [3].

In inflammation-related scenarios, platelets can prevent bleeding without the use of GPIIb/IIIa-mediated aggregation [3]. Platelets GPVI and CLEC-2 is one type of CLR, used ITAM for signal transduction which has a role in antigen and Fc receptors mediated signaling to their signaling on the mouse and human platelets, may be important for platelets' functions in tumor vascular protection[3]. The ability of platelets to prevent bleeding without aggregation has gotten a lot of attention in recent years because it explains why selective can effectively prevent the formation of occlusive thrombus without a significant risk of bleeding in homeostasis [119].

2.5 Human blood platelets and cancers

Human blood platelets have a role in cancer metastasis and angiogenesis in various malignancies, including colon cancer, breast cancer, lung cancer, ovarian carcinomas, and melanoma. In cancer patients, hypercoagulable states are associated with hemostatic and platelet abnormalities [120]. Tumors express several membrane receptors that bind and activate platelets [121], thus, inducing platelet activation or aggregation. The activated platelets mediated coagulation system helps in the pathophysiology of cancer by promoting tumor development and progression. Adhesion, activation, and aggregation of blood platelets influence cancer patients' coagulation cascade and thrombus formation. Platelet membrane proteins such as integrins, glycoproteins, and many other signaling receptors are involved in these processes. Within the circulatory system, platelets not only help in the spreading of cancer via angiogenesis but also help in immune evasion by providing physical and mechanical support, promoting their attachments on endothelium, and also helping in extravasations to the secondary organ to generate secondary lesions. Because of such contributions of platelets to tumor cell survival and spread, it is now recognized as a new target for therapy[122]. Different types of cells present in bloodstreams such as endothelial cells, platelets, lymphocytes, macrophages, mast cells, fibroblasts, bone marrow-derived progenitor cells, and hypercoagulable state forming components also help in metastasis processes.

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Diverse set receptors of platelet surface are implicated in cancer, and cancer cells [123]. Platelets have a vast range of pro-and anti-angiogenic substances that have a role in physiological and pathological angiogenesis and tumor formation [8,124]. Platelets contain anti-angiogenic inhibitors such as endostatin, TSP-1, PF4, plasminogen activation inhibitor-1, and TGFβ proteins, as well as pro-angiogenic activators such as VEGF, PDGF, FGF-2, and MMP-9 [124-126]. In cancer patients, the amount of VEGF generated by platelets and released into the blood is high, and it is an essential prognosis of numerous malignancies. Platelet-derived endothelial cell growth factor (PD-ECGF) is another pro-angiogenic factor found in platelets. Platelet activation and the coagulation system are essential in cancer metastatic development. The GPIb-IX-V knockout mice had a 15-fold reduced melanoma cell metastasis [127]. Other platelet membrane receptors such as GPVI and GPI-Ib-IIIa have a role in cancer progression [128]. PDGF signaling pathway is involved in the growth of ovarian cancer, prostate cancer, and gliomas cell lines. In addition, PDGF is involved in activating cancer cells [129]. Since platelets play pro-tumorigenic roles predominantly in various cancers, these are a possible target in anti-cancer therapy research. It is extremely challenging to design optimum anti-cancer therapy in patients with active tumor malignancy. As a result, before these drugs are administered, future trials, including anti-platelet medications into standard anti-cancer therapy, must carefully analyze various parameters, including cancer type, degree of malignancy, sex, age, bleeding profile, and other risk factors to patients.

3. Effects of anti-platelet compounds on the non-hemostatic function of human blood platelets

Despite the fact that hyperactive platelets have a role in the pathophysiology of CVD and other disorders, the processes by which platelets become hyperactive are not entirely understood. Many bioactive compounds may affect blood platelet function in various ways [16,130]. New dietary regimens for a long-term strategy to modify human blood platelet activity favorably are being developed [1,16,32,130,131].

Dietary long-chain polyunsaturated fatty acids (LCPUFAs) are beneficial in CVD [16,132]. These LCPUFAs modulate several CVD risk factors, inflammation, cancers, and platelet hyperactivity[16,130,133,134]. N-3 PUFAs inhibit platelet aggregation by decreasing the level of platelet TXA_2 and increasing NO production in vascular endothelial cells[135]. Several lines of evidence suggest that polyphenols reduce CVD by different mechanisms, including suppressing platelet activity [16,130,133,134]. In addition, tomato, garlic, ginkgo biloba, zinc, and other bioactive compounds inhibit platelet aggregation [16,136]. Curcumin, quercetin, capsaicin, piperine, eugenol, and allyl sulfide have anti-platelet activity[137]. The phenolic compounds, which include flavonoids and non-flavonoids, also affect blood vessels. Natural phytochemicals have complementary and

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overlapping functions, such as antioxidant properties, immune system activation, and anti-inflammatory reactions. Studies have shown that polyphenols reduce atherosclerosis processes by inducing anti-platelet activity via modulation of GPVI–collagen, COX-1–thromboxane, protease-activated receptor 1 (PAR1)–thrombin, and P2Y1/P2Y12–ADP mediated pathway of platelet activation[138].

Aqueous extracts of various fruits have anti-aggregatory effects on human blood platelets [31-34]. The water-soluble and heat-stable tomato extract, later named Fruitflow®, is the most studied anti-platelet agent used worldwide [1,139]. Fruitflow® can inhibit ADP-induced platelet activation via several mechanisms, including inhibiting protein disulfide isomerase (PDI) and lowering the P-selectin level [1,30]. Kiwifruit extract (KFE) also showed anti-platelet activity *in vitro* and *ex vivo*[33]. Fruitflow®, KFE, and polyphenols from other sources also lower blood pressure by inhibiting angiotensin-converting enzyme and by increasing vasodilation [32,137,140].

3.1 Effects of anti-platelet compounds on platelet-vessel wall interactions

As previously stated, the platelet-vessel wall interaction is critical in the early and late phases of atherosclerosis and atherothrombotic events and hemostasis and vascular healing. Numerous medicines not initially intended for antiplatelet treatment change platelet–vessel wall interactions. Aspirin and receptor antagonists of the P2Y12 and GPIIb-IIIa integrins influence platelet-vessel wall interaction. Aspirin has other pharmacological effects, apart from inhibiting platelet aggregation[141]. Inhibitors of platelet synthesis of TXA_2 may also affect the cross-talk between platelets and vascular endothelium as it influences vessel wall constriction and vascular cell proliferation[142]. Aspirin reduces the development of atherosclerosis in mice lacking the thromboxane receptor, suggesting that it may act as an anti-atherosclerotic agent[143]. In addition, aspirin's antitumor activity is to be mediated via platelet-vessel wall interaction[144].

The N-3 and n-6 LCPUFAs and their eicosanoid derivatives play a variety of physiologic functions in cell growth and development, inflammation, and the cardiovascular system [135]. The eicosanoid-mediated depends on the ratio of n-6 and n-3 fatty acids-derived eicosanoids. PGE_2 and TxA_2 play an essential role in maintaining vascular homeostasis[145]. PGI_2 is a vasodilator and a platelet inhibitor [44], whereas TxA_2 is a vasoconstrictor and activator/aggregator of platelets[97,146]. Therefore, an imbalance in PGI_2 and TxA_2 production is implicated in the pathophysiology of many cardiovascular disorders[145,147]. NO affects vasorelaxation and platelet inhibition by activating intracellular guanylyl cyclase, leading to cGMP formation[148]. The vasoprotective function of endothelial cells is associated, among others, with biosynthesis and release of NO, PGI_2, PGE_2, and tissue

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plasminogen activator (tPA)[135]. Platelet activation is counteracted by PGI_2 and PGE_2, produced from ARA by the endothelium after various vasoactive agents, including thrombin. NO produced by eNOS enhance the effect of PGI2. The endogenous fibrinolytic system, responsible for the dissolution of the thrombus, is regulated by the endothelium-derived profibrinolytic factor, tissue plasminogen activator (tPA), and its inhibitor, plasminogen activator inhibitor type-1 (PAI-1)[149]. Depending on their structure, fatty acids regulate PAI-1 and tPA activity; however, the definitive conclusions are yet to be reached [150-152]. These endothelium-derived compounds can inhibit activation of platelets and leukocytes, promote fibrinolysis, maintain tissue perfusion and protect the vascular wall against acute damage and chronic remodeling. Endothelial dysfunction is associated not only with suppression in the release of these compounds but also with the secretion of deleterious compounds such as PGH_2, PGG_2, TxA_2, superoxide anions (O_2-, peroxynitrite (ONOO-), and PAI-1.

Circulating non-activated blood platelets do not interact with the negatively charged surface of the endothelium. However, the activated platelets can bind GpIbα to either P-selectin or vWF of the endothelium, indirectly via a fibrin bridge that joins GpIIb/IIIa and ICAM-1. In contrast, NO decreases the intracellular level of Ca^{2+}, the transformation of the GPIIb/IIIa platelet receptor, and suppresses the integrin's binding to fibrinogen[153,154]. The ecto-ADPase (CD-39), on the surface of endothelial cells, hydrolyzes both ATP and ADP to generate AMP, thus decreasing platelet aggregation/activation [44,153]. TxA_2 aggregates platelets and expresses adhesive co-factors for platelets such as vWF, fibronectin, and factor V [97,155].

3.2 Immune modulatory activities of anti-platelet compounds

Lymphocytes, monocytes/macrophages, and neutrophils modulate immune response via different mechanisms. Circulating monocytes respond to activation cues (such as PAMPs and TLRs) by enhanced production of multiple cytokines and chemokines. Monocytes move via ligands in the endothelial cell layers to develop into tissue-resident macrophages. Anti-platelet Fruitflow® reduces CCL4/MIP-1 production in vitro while increasing CXCL8/IL-8 production[156]. Fruitflow® affects cell trafficking, activation of the classical or alternative pathway, and cellular differentiation in diverse immune system compartments by modulating various cytokines, chemokines, and adhesion molecules. However, the modulatory roles of Fruitflow® in the immune and inflammation response of platelets are yet to be known.

Fruitflow® inhibited platelet activation by lowering phosphorylation of Akt, which is a downstream molecule of the PI3K signaling pathway; GSK3; ERK, JNK, and p38 MAPK, which are downstream molecules of the MAPK

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signaling pathway; and Hsp27 [157]. Fruitflow® also affected a variety of platelet proteins[158]. PDI is highly expressed on the activated platelet membrane and isomerizes disulfide bonds on the platelet membrane to help in the aggregation of platelets, secretion from platelets granules, and fibrinogen binding GPIIb-IIIa. PDI do all these functions by targeting thiol-containing protein expressed on platelet membrane, and all these functions will be inhibited if PDI is blocked using inhibitory antibodies [159,160]. Blocking cell-surface thiol isomerases inhibited platelet function [161]. In addition, PDI interacts with quercetin-related glycosides, of which several are present in Fruitflow® [162,163]. The interaction of polyphenols with PDI revealed a mechanism through which Fruitflow® components may suppress platelet aggregation in various pathways.

Aspirin can inhibit experimental vascular inflammation with a reduction in inflammatory molecules (CRP, M-CSF, MCP-1), as well as pro-inflammatory factors (TXA_2, S1P, sICAM-1, IL-6)[164]. Eicosanoids synthesized from n-6 LCPUFAs promote inflammatory responses[165], whereas n-3 LCPUFAs produce anti-inflammatory or neutral eicosanoids. N-6 eicosanoids modulate cellular growth, inflammation, coagulation, and vascular homeostasis[166,167]. Also, n-6 eicosanoids increase the synthesis of cytokines and adipokines that play a vital role in metabolism and inflammation [168]. Linoleic acid,18:2 (LA) induces inflammation by increasing the levels of TNF-α, MCP-1, VCAM-1, and ICAM-1 through the activation of NF-κB and activator protein 1 [169].

Fruitflow® lowered the inflammatory responses by inhibiting the production of NO, PGE_2, TNFα, IL1β, IL6, IL12 from macrophages involved in chronic inflammatory processes[1]. In addition, fruitflow® increases cellular awareness and senses altered immunological homeostasis in the vascular-endothelial compartment during acute inflammation, according to these *in vitro* findings. Furthermore, Fruitflow® influenced the production and expression of different inflammatory mediators by modulating the transcription factors of the NF-κB signaling pathway [170].

3.3 Effects of fatty acids on blood-vessel-platelet interactions

PUFAs influence adhesion molecules of endothelial cells and modulate leukocyte-endothelial adhesion [171]. Endothelial cells express adhesion molecules such as selectins and immunoglobulin superfamily members such as ICAM-1, ICAM-2, and ICAM-3 and vascular cell adhesion molecules (VCAM) 1 and 2. In addition, a number of adhesion molecules, including integrins and selectins (e.g., P-selectin glycoprotein-1 (PSGL-1), which bind to E, L, and P-selectin), is expressed on leukocytes to function as counter-receptors to those expressed on endothelial cells[172].

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N-3 LCPUFAs can reduce the ARA content of platelet cell membrane phospholipids, hence lowering the synthesis of ARA-derived eicosanoids. By integrating n-3 fatty acids into membrane phospholipids, dietary n-3 fatty acids can affect any cell's membrane structure and function. The ARA content of platelet cell membranes is reduced due to N-3 LCPUFA consumption, resulting in lower n-6 eicosanoid synthesis. In addition to their anti-platelet effects, n-3 fatty acids have the ability to suppress the production of pro-inflammatory cytokines [137].

3.4 Fruit extract and platelet-vessel interactions

Several fruits extract, including tomato and kiwifruits, have been found in numerous studies to reduce platelet aggregation both *in vitro* and *ex vivo* [30,32,34,158]. Furthermore, anti-platelet components of tomato, strawberry, and kiwifruit inhibit the angiotensin-converting enzyme (ACE), as well as relax the endothelium, which protects the blood vessels [137,140]. Fruitflow® also reduced endothelial dysfunction-associated expression of adhesion molecules such as ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1) in endothelial cells, thereby enhancing blood flow[1].

Both Fruitflow® and aspirin modulate platelet membrane proteins, platelet secretion, fibrinogen beta chain 5, Ras-related proteins, redox system proteins, and HSP70s[158]. Fruitflow® and aspirin affected 11 of the 26 proteins with changed expression following intervention aspirin alone affected 14, and Fruitflow® alone affected one[158]. Consuming anti-platelets flavonoids present in fruits may lower blood pressure [32,140]. As the IC50 values of flavonoids were higher than those of the prescribed drugs for hypertension, flavonoids could be used as preventative nutraceuticals against hypertension rather than as a therapeutic drug.

3.5 Anti-platelet compounds and the role of platelets in cancer metastasis

Platelets play an essential part in almost every step of tumor growth and metastasis [173]. Several compounds from platelet are released due to direct interactions between platelets and cancer and stromal cells [174]. Several tumors can activate platelets, causing them to release various growth factors such as VEGF, PDGF, and fibroblast growth factors. These growth factors are associated with tumor progression, angiogenesis, metastasis, and poor prognosis[175].

Green tea contains an anti-platelet and anti-inflammatory factor, epigallocatechin gallate (EGCG), which strongly prevents cancers [176]. Furthermore, EGCG's impacts on suppressing colon tumor cells were enhanced by the

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ginseng compound, showing that green tea may function as a successful chemo-preventive agent when used along with an anticancer agent.

Anti-platelet curcumin inhibited the expression of PDGFR and increased the proliferation of human hepatic myofibroblasts [137,177]. Furthermore, curcumin inhibits the activity of ERK, JNK, and PI3/AKT and slows cell proliferation, and induces apoptosis in a dose-dependent manner[178]. Additionally, curcumin alleviates the inhibitory effect of PDGF signaling on cell growth via lowering the expression of PPARγ genes[179].

On the other hand, anti-platelet resveratrol inhibits smooth muscle cells' migration and monocytes' adhesion induced by TNF-α[137,180]. Finally, ellagic acid (EA), a platelet inhibitor, is an antimutagenic and anticarcinogenic compound. EA inhibits angiogenesis by repressing PDGF-R movement and phosphorylation of its substrate [181].

4. Anti-platelet bioactive compounds impacting atherosclerosis process

The anti-atherosclerotic effects of bioactive compounds have been demonstrated both *in vitro* and *in vivo* [182]. Consuming n-3 fatty acids modulate the cardiovascular system, including platelet function, fibrinolytic system, and coagulation cascade, thus reducing atherosclerosis's risk [16,183]. An increase in consumption of marine fish oil or fish products is associated with a lower incidence of CVD [132]. Polyphenolic substances also have antioxidant effects and increase eNOS activity. Expression of eNOS is a powerful biomarker for vascular tone and blood pressure regulation. Consumption of vegetables containing inorganic nitrates, which form nitrite intermediates, raises vascular NO levels. Nitrate is taken into the body via a mechanism that is not dependent on endothelium and depends on oral bacteria converting nitrate to nitrite and then forming NO in blood vessels. Strawberries lower blood pressure, increase HDL cholesterol, result in favorable changes in platelet function, and reduce CVD risks [184].

4.1 Diabetes mellitus, hypertension, and anti-platelet compounds

Diabetes mellitus (DM) is associated with accelerated atherogenesis and an increased risk of atherothrombotic complications[185]. DM patients have a prothrombotic state due to various mechanisms, including platelet hyperactivity, atherosclerosis, underscoring the importance of antiplatelet therapy for secondary prevention in these patients. After a CVD episode, patients undergoing percutaneous coronary interventions (PCI), dual antiplatelet therapy (DAPT) with aspirin, and the P2Y12 inhibitor clopidogrel has been the mainstay of

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treatment. Though DAPT reduces atherothrombotic recurrences in patients with DM, these rates remain high, highlighting the need for more effective treatments. In addition, platelet P2Y12 receptor inhibitors with enhanced potency, such as prasugrel and ticagrelor, and anti-platelet therapies such as vorapaxar inhibit the thrombin-mediated platelet signaling pathway be used to treat patients with DM and have been shown to reduce ischemic recurrences.

Quercetin enhances cell membrane fluidity and transmembrane potential while inhibiting inflammation in immunological and endothelial cells, notably useful in late-stage diabetes [186]. In diabetes, quercetin's antiplatelet action slows thrombus development and serves as an antioxidant by decreasing the synthesis of lipid hydroperoxides and enhancing glutathione peroxidase activity. Furthermore, it modulates NF-kB signaling and the mitochondrial pathway, avoiding cell death.

4.2 Obesity and human blood platelet activity

Obese people have increased platelet sensitivity to aggregation, increased sCD40L levels, and mean platelet volume [187]. Adipose tissue produces leptin, adiponectin, TNF-α, IL-6, and resistin, affecting platelet function, either directly or indirectly. Platelet leptin receptors increase platelet aggregation in response to agonists, implying a possible link between obesity and CVD. Platelets suffer functional changes due to obesity, which may compromise normal vascular function and perhaps poorly respond to anti-platelet medication. Obese people are resistant to anti-platelet medications. The poor response to the platelet P2Y12 antagonist such as clopidogrel increased comorbidities, diabetes, renal impairment, and obesity [188].

5. Human blood platelet functions and severity of COVID-19

Platelet hyperactivity plays a vital role in the pathology of COVID-19 from its onset, and platelets may play a vital role as COVID-19 progresses. In COVID-19, severe disseminated intravascular coagulation and platelet hyperactivity cases are associated with poor prognosis and a higher mortality rate due to hyperactivation of blood platelets and activation of the coagulation system [141].

Platelet hyperactivity is part of the general viral infection-mediated thrombosis process, but its effect on COVID-19 illness may be greater than expected. As blood platelets are found in abundance at sites near the cells that the SARS-CoV-2 virus initially targets, they could well be the first blood cells to interact in large numbers with the

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562 virus. Consequently, they may be able to internalize SARS-CoV-2 and play a significant role in initiating the first
563 wave of response [189].

564 Zinc has a potential association with CVD as it modulates platelet function. The role of zinc in platelet activation
565 and pathophysiological thrombus formation has received though little attention, despite being an essential and
566 physiologically relevant cofactor in hemostasis. Low zinc diets are associated with platelet-related bleeding
567 disorders in humans and rodents[104,190]. Zn^{2+} participates in blood clotting by modulating platelet aggregation,
568 coagulation, and fibrinolysis[191,192]. At the injury site, Zn^{2+} released from activated platelets accelerates
569 coagulation and attenuates fibrinolysis. The importance of Zn^{2+} in hemostasis was recognized in 1982, as Zn^{2+}-
570 deficient men had bleeding and clotting abnormalities[193].

571 The demand for nutritional supplements and nutraceuticals has increased during the pandemic due to their
572 perceived immune-boosting effects. It has been shown *in vitro* and *in vivo* studies that nutraceuticals containing
573 phycocyanobilin, N-acetylcysteine, glucosamine, selenium, or phase 2 inductive nutraceuticals (e.g., lipoic acid,
574 ferulic acid) can inhibit and modulate RNA virus infections through an increase in mitochondrial antiviral-
575 signaling protein activation and TLR7 activation[194].

576 **5.1 Effects of N-3 polyunsaturated fatty acids on platelets and COVID-19**

577 Anti-platelet compounds such as n-3 PUFAs have been studied for their ability to combat various viral infections
578 [195]. Blood samples from 100 patients with COVID-19 patients had higher omega-3 indexes, a measure of the
579 EPA and DHA content of red blood cells, had a lower risk of death [196]. Several studies have established a link
580 between N-3 PUFAs and clinical benefit in COVID-19 patients, as thrombotic complications, such as arterial and
581 venous thrombosis, are common in some COVID-19 patients [197].

582 **5.2 Anti-platelet polyphenols and COVID19**

583 The severity of COVID-19 illness may be lessened by consuming tomato extract, especially before or during the
584 early stages. It may be particularly beneficial for people at risk for endothelial dysfunction and platelet
585 dysfunction. Fruitflow® inhibits platelet granule secretion by suppressing the Src-PLCγ2- protein kinase C (PKC)
586 mediated granule secretory pathway[1,198]. Platelet granules secretion occurs when collagen and thrombin bind
587 to its receptor GPVI, and PARS causes activation of the downstream signaling pathway. In this pathway sarcoma,
588 a tyrosine-protein kinase (Src) family member (Lyn, Fyn, and Src), first activated an activated by phosphorylation,

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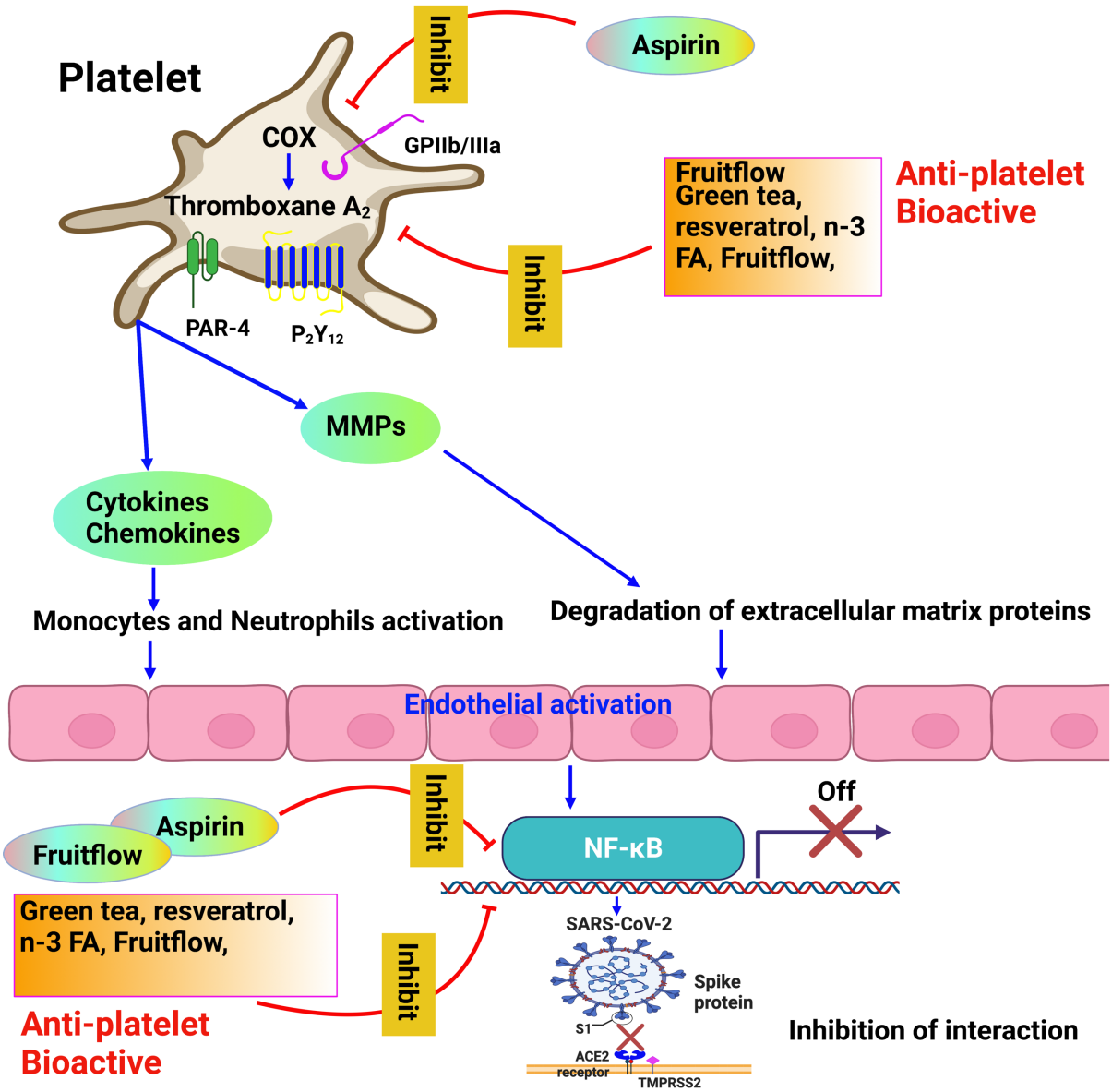
589 activated Syk then phosphorylate and activate LAT, which in turn causes phosphorylation of an adaptor protein
590 PLCγ2 in which PKC bind leading to the activation of downstream effector, which induces platelet granule
591 secretion[198]. Fruitflow® modulates the generation of different interleukins such as IL-1β, IL-6, IL-10, and IL-
592 12 and various chemokines such as CCL2/MCP-1, CCL3/MIP-1α, CCL5/RANTES, CXCL8/IL-8, CXCL10/IP-
593 10 in peripheral blood leukocytes [170]. **Figure-3** shows the effects of anti-platelet bioactive drugs on patients
594 with COVID-
595 19.



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597 **6. Conclusions**

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While the contributions of human blood platelets to hemostasis and thrombosis have been well established, it is increasingly evident that platelets have a more expansive repertoire of physiological roles. Platelets function like traditional immune cells such as macrophages and mast cells, binding to bacteria, secreting chemokines, and clearing invading organisms from the circulation. Platelets have emerged as critical biological factors of normal and pathologic vascular healing and other diseases such as cancers and inflammatory and immune disorders. They work not just by releasing a variety of lipid and protein mediators right away but also by triggering previously undiscovered time-dependent activities, including signal-dependent pre-mRNA splicing and constitutively expressed mRNA translation. New approaches are required to bridge the gap between the huge body of evidence supporting the role of platelets in the onset and course of experimental atherogenesis and the comparatively limited evidence for the role of platelets in human atherogenesis. Given the evidence of persistent platelet activation in obese women who are otherwise healthy and relatively young, fat people could provide a good group for feasibility studies, given the growing concern over the cardiovascular implications of obesity. Obesity research could also shed further light on the processes that link inflammatory mediators to platelet activation. The key to maintaining hemostasis and proper blood flow is regular platelet activity. Many of the fundamental mechanisms of platelet use in their immune response are similar to or extensions of hemostatic processes. The challenge for therapeutic intervention in these disorders will be to find drugs and bioactive compounds that preferentially block specific sites implicated in platelets' complicated contribution to

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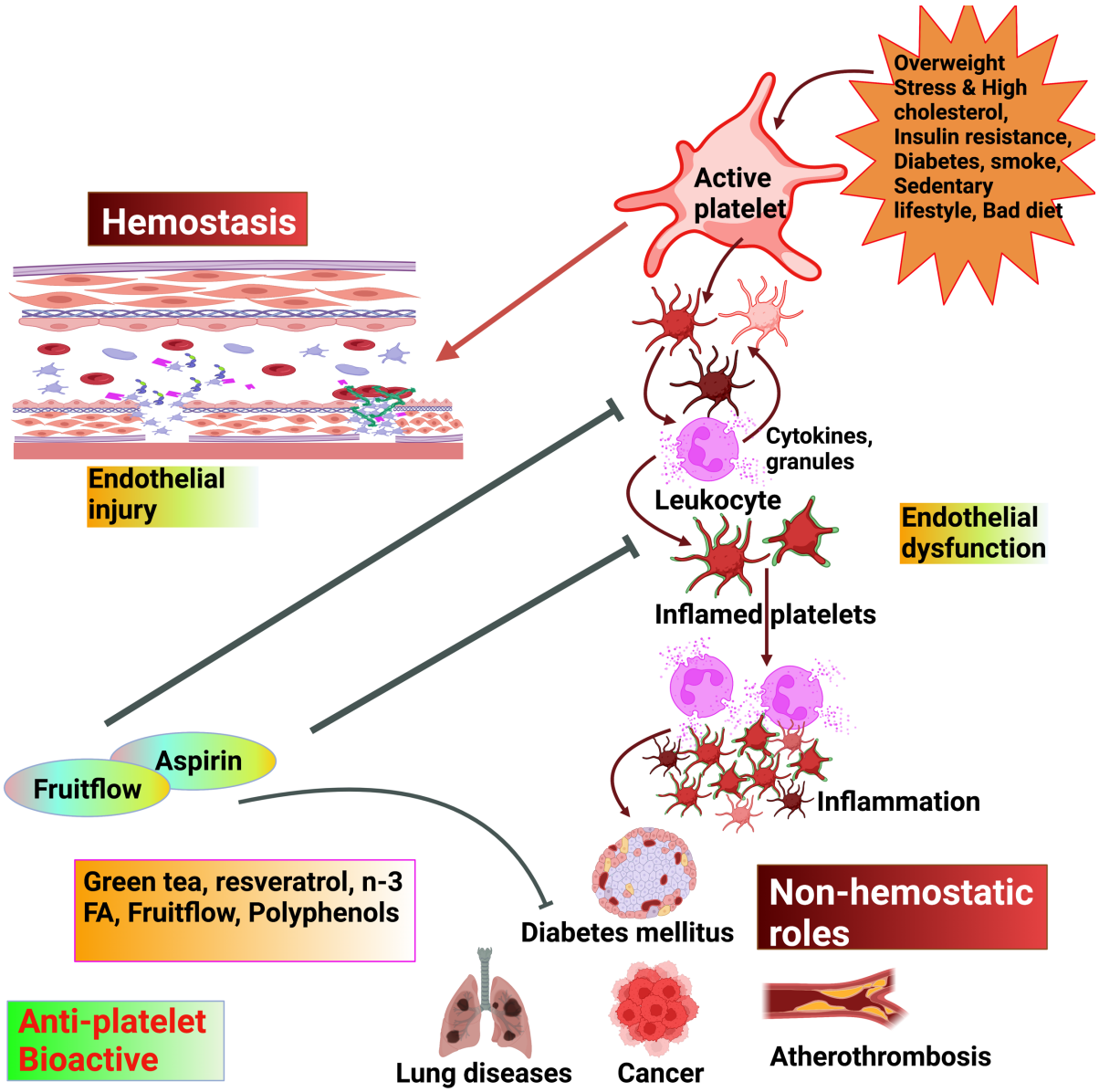
615 inflammation or tumor growth or other disorders while leaving at least some of their hemostatic function intact.



616

617 **Contributions:** DD and SA wrote the manuscript. AKDR had the idea for the article and critically revised the

618 manuscript. All other authors drafted the manuscript.

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620 **Conflict of interest:** The authors declare that they have no conflict of interest.

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Table-1: Anti-Platelet Bioactive Compounds from Plant and their mechanisms of action

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Bioactive anti-platelet compounds	**Actions**
Scopoletin	Inhibits platelet aggregation via Ca^{2+} mobilization[199]**.**
Doctrine	Inhibits TxA_2 formation and increasing the cyclic AMP level in rabbit platelets[200].
Rutaecarpine alkaloid	Inhibits collagen, and thrombin induced platelet aggregation via reduced TXA_2 levels and intracellular free Ca^{2+} [201].
Prenylflavonoids	Inhibit ARA, Collagen, and platelet-activating factor (PAF)- induced platelet aggregation[202].
Ruta graveolens	Inhibit platelet aggregation[203].
Isorhamnetin flavonol	Significantly inhibits collagen- induced platelet aggregation possibly via mitochondrial regulation[204].
Coffea arabica	Inhibits platelet aggregation induced by ADP, collagen, epinephrine, and ARA. Inhibitor of COXs [205].
Phenolic compounds	Inhibits human blood platelet activation and aggregation. In vitro anti-platelet effects require high, non-physiological concentrations[61].
Acid amides	Dose-dependently inhibits rabbit platelet aggregation induced by collagen, ARA, and PAF[206].
Piperlongumine	It inhibits collagen-induced aggregation in rabbit platelets acts via TXA_2 receptor antagonist[207].
Piperine	Inhibits platelet aggregation by reducing $cPLA_2$ and TXA_2 synthase[208].
Veratroylgermine alkaloid	Strongly inhibits platelet aggregation induced by ARA[209].
Spiramine C1 alkaloid	Diterpene alkaloids inhibit PAF-induced platelet aggregation[210].
Beta-carboline alkaloid	Inhibition of platelet aggregation is mediated by inhibiting PLCγ2 and suppressing Ca^{2+} mobilization and ARA release[211].
N-methoxycarbonyl aporphine alkaloid	Inhibits collagen, ARA, and PAF-induced platelet aggregation[212].
Leonurine pseudo-alkaloid	Inhibits platelet aggregation induced by thrombin, ARA, and collagen[213].
Ajmaline alkaloids	Inhibit PAF-induced platelet aggregation *in vitro* and *in vivo* studies**[214]**.

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Coumarin (polyphenolic compounds)	Inhibit platelet aggregation by inhibiting COX activity [215].
Mango extract	Inhibits ADP-induced platelet aggregation[216].
Pumpkin **seed** extract	Inhibits platelet aggregation induced by ADP, TRAP-6, and collagen. In addition, it inhibits P-selectin secretion and glycoprotein IIb/IIIa activation[217].
Asteraceae, Rutaceae, Fabaceae, Lamiaceae, Zygophyllaceae, Rhamnaceae, Liliaceae, and Zingiberaceae	Inhibits ADP-mediated platelet aggregation TXA_2 formation, reduction of intracellular Ca^{2+} mobilization, and phosphoinositide breakdown[54].
Olive oil	Reducing platelet sensitivity to aggregation reduces vWF and plasma levels of TX A_2 [218].
Onion	Reduces platelet aggregation and blood pressure[219].
Garlic	Inhibits platelet aggregation in vitro and ex vivo [220].
Pomegranate (Punica granatum) products,	Inhibits collagen and ARA-mediated platelet aggregation via Ca^{2+} mobilization and TXA_2 production [221].
Hawthorn leaf extract (terpenoid, flavones)	Inhibit ADP-induced platelet aggregation[222].
Leuzea carthamoides (Flavonoid)	Inhibits platelet aggregation induced by collagen and ADP[223].
Aristotelia chilensis (leaves and unripe fruits) *(phenolic and anthocyanin)*	Inhibits platelet aggregation and platelet granule secretion by reducing the platelet membrane exposure of P-selectin and CD63[224].
Citrus aurantifolia leave extract	Inhibits ADP and epinephrine-induced platelet aggregation [225].
Acanthopanax sessiliflorus (fruit extract)	Inhibits ADP- induced platelet aggregation[226].
Varthemia iphionoides	Inhibits ADP and collagen-induced platelet aggregation[227].
Extract of lemon balm (*Melissa officinalis)*	Inhibits ADP-induced platelet aggregation[228].
Dandelion root component (*Taraxacum officinale* L.)	Inhibits platelet action in an *in vitro* study[229].
Lavender extracts (*Lavandula hybrid)*	Inhibits platelet aggregation induced by ARA, U46619, collagen, and ADP[230].

1206

1207 **Figure Legends**

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Figure-1: Platelet function associated with various diseases.

A brief overview of altered platelet contributions to atherosclerosis, hemostasis, thrombosis, inflammation, immunity, COVID-19, vascular integrity, hypertension, and cancer.

Figure-2: Aspirin and anti-platelet bioactive that target platelet-vessel wall interactions may be interesting targets for future antithrombotic treatments.

The GPIb/IX/V complex or GPVI may promote early interference with thrombus development by limiting platelet adherence to the sub-endothelium. Furthermore, endothelial ADP metabolism, endothelial NO release, P-selectin-PSGL-1 interaction with immune cells, and PGI2-induced suppression of prothrombotic endothelium factors may be targeted**.**

Figure-3: Effect of anti-platelet drugs on patients with COVID-19.

An Infection with SARS-CoV-2 may be linked to the procoagulant components identified in severe COVID-19 patients. Anti-platelet bioactive demonstrates (1) Anti-viral effect: because SARS-CoV-2 entrance into epithelial cells is dependent on contact, binding of anti-platelet bioactive to viral spike proteins can block this interaction. (2) Anticoagulant effect: The anticoagulant function of anti-platelet bioactive can control a blood clot, which is mediated by interactions between anti-platelet bioactive and antithrombin-3 glycoprotein (AT3), potentiating the AT3 inactivation of thrombin, which is required for the formation of thrombi. (3) Anti-inflammatory action: (**3**) Anti-inflammatory effect: The anti-platelet bioactive has broad anti-inflammatory effects, primarily through blocking pro-inflammatory mediators such as TNF-, IL-6, and LTB4, resulting in reduced migration and activation of immune cells and avoiding systemic inflammatory response.