Nutrition Phytochemicals Affecting Platelet Signaling and Responsiveness: Implications for Thrombosis and Hemostasis

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Abstract

Cardiovascular disease, in particular due to arterial thrombosis, is a leading cause of mortality and morbidity, with crucial roles of platelets in thrombus formation. For multiple plant-derived phytochemicals found in common dietary components, claims have been made regarding cardiovascular health and antiplatelet activities. Here we present a systematic overview of the published effects of common phytochemicals, applied in vitro or in nutritional intervention studies, on agonist-induced platelet activation properties and platelet signaling pathways. Comparing the phytochemical effects per structural class, we included general phenols: curcuminoids (e.g., curcumin), lignans (honokiol, silybin), phenolic acids (caffeic and chlorogenic acid), derivatives of these (shikimic acid), and stilbenoids (isorhapontigenin, resveratrol). Furthermore, we evaluated the flavonoid polyphenols, including anthocyanidins (delphinidin, malvidin), flavan-3-ols (catechins), flavanones (hesperidin), flavones (apigenin, nobiletin), flavonols (kaempferol, myricetin, quercetin), and isoflavones (daidzein, genistein); and terpenoids including carotenes and limonene; and finally miscellaneous compounds like betalains, indoles, organosulfides (diallyl trisulfide), and phytosterols. We furthermore discuss the implications for selected phytochemicals to interfere in thrombosis and hemostasis, indicating their possible clinical relevance. Lastly, we provide guidance on which compounds are of interest for further platelet-related research.

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Introduction

With increasing prevalence around the world, cardiovascular diseases (CVDs) are leading causes of mortality and morbidity,[1] in which platelets play a crucial role.[2] In arterial thrombosis and thrombus formation, platelets become activated by several vascular and blood-borne agonists, but with major roles of subendothelial collagens, by secretion of autocoids such as thromboxane A_2 (TXA_2) and ADP, and by the coagulation product thrombin.[3,4] The conventional concept is that, after rupture of an atherosclerotic lesion, these agonists promote the formation of a platelet aggregate or thrombus, which is consolidated by fibrin clot formation and erythrocyte inclusion leading to vascular occlusion.[5] A similar set of platelet agonists induces in hemostasis the formation of a platelet plug after vascular injury.

Platelets in the circulation are prevented from activation by multiple inhibiting molecules such as prostacyclin, nitric oxide (NO), and antithrombin.[2] It is understood now that the continuous presence of inhibiting and activating factors establishes a certain balanced state, where platelets are more negatively or positively primed toward activation.[6] Antiplatelet therapies provide a strong inhibitory effect, and thereby reduce the risk of developing thrombotic complications, however at the expense of bleeding.[2,7] In the context of cardiovascular health, for long it has been cleared that many nutritional components and metabolites of these can influence the CVD risk.[8] This also holds for nutrients influencing platelet activation and hence the platelet priming state. In particular, edible plant-derived compounds or phytochemicals have been researched for effects on platelets, often by in vitro studies and less often in nutritional intervention studies. Effects of phytochemicals have been described not only on collagen, thrombin, ADP, or TXA_2 receptor-dependent activation processes, but also on specific signaling pathways in platelets. In this review we provide an overview of how the most commonly studied dietary phytochemicals can alter platelet activation properties and platelet signaling pathways.

Phytochemical Classes in Relation to Cardiovascular Health

Natural products and their synthetic analogues have been used for many decades as drugs for treatment of CVDs. For instance, a substantial part of the small molecules approved for cancer chemotherapy in Western medicine is structurally unmodified or modified natural products. Phytochemicals are plant-derived chemical compounds, produced for biological defense or growth regulation.[9] From a nutritional or subclinical perspective, the term phytochemical is mostly used for compounds from edible plant parts with a supposed effect on the human physiology, but also some poisons and herbs of traditional medicine can be considered as phytochemicals. In the present article, we focus on nutritional phytochemicals, such as those present in nontoxic plants.

For long, it has been considered that the regular intake of certain phytochemicals can ameliorate physiological processes by a presumed anti-oxidant, -inflammatory, -estrogenic, -immune, carcinogenic, or cardioprotective action, although for many compounds the evidence for this is still limited or mixed.[10] For instance, for carotenoids and polyphenols, authorities still discourage the use of specific health or disease claims.[11,12] In general terms, it can be stated that phytochemicals from common edible plants have relatively small effect sizes on health and disease, given their abundant presence in nutrition, which implies that high amounts may need to be ingested for improving health. At the other side of the spectrum, phytotoxins from nonedible plants often influence physiologic reactions already at low doses with high effect sizes.[9,13] From the perspective of cardiovascular health, plant-derived compounds that are not abundantly present in the diet with medium effect sizes are most interesting.

The common classification of nutritional phytochemicals is based on their chemical structure rather than on the reactive groups or the in-human metabolization. For the present purpose, four relevant classes are distinguished (►**Table 1**): general simple phenols (class I), flavonoid polyphenols (II), terpenoids (III), and a miscellaneous set of other compounds (IV).

General simple polyphenols (class I) include over 8,000 identified compounds, occurring in a wide variety of foods.[14] Structurally, these contain one or more phenol units, several hydroxyl groups, and sometimes a sugar residue (glycoside) attached to a hydroxyl group.[15] Class subdivision is according to the number and structure of the phenol rings, and to other structural elements.[16] For examples, see ►**Supplementary Fig. S1** (available in the online version). *Curcuminoids* include the yellow pigment curcumin found in turmeric and ginger species, with several claimed biological effects.[17] *Lignans* consist of two phenylpropane units, mostly present as glycosides, and are concentrated in flaxseed (matairesinol), rye (pinoresinol), magnolia bark (honokiol), and some seeds (silibinin). In vitro studies point to antioxidant and anticarcinogenic activities.[18,19] The *simple phenolic acids* contain a hydroxybenzoic or hydroxycinnamic acid group. The former set includes gallic acid that is relatively rare in grapes, teas, and legume seeds.[20] Compounds of the latter set are seen in many foods. Examples are caffeic and its ester chlorogenic acid, present in coffee beans and fruits, with health claims in the oncologic and cardiovascular areas.[21,22] Structurally, salicylic acid (aspirin) from nonedible willow leaves is also a phenolic acid. The phenolic acid derivative ellagic acid is a natural antioxidant found in numerous fruits and vegetables. *Stilbenoids* are derivatives of the bi-phenol stilbene. Best known is the stilbenoid resveratrol, found in grapes, peanuts, and red wine. Studies propose anticancer or antiatherogenic effects.[23,24]

Flavonoid polyphenols (class II) form the majority of phenolic compounds in vegetables, fruits, nuts, beverages, and medicinal herbs.[25] These water-soluble flavonoids contain two aromatic rings with one or more hydroxyl groups and 15 carbon atoms (►**Supplementary Fig. S1**, available in the online version), and are subclassified into six groups (►**Table 1**). A large database of the flavonoid content of foods

Table 1 Structural-based classification of phytochemicals linked to thrombosis and hemostasis, typical examples and presence in food components

Class phytochemical	Examples	Enriched in food components
I. General phenols (>8,000)		
a. Curcuminoids	Curcumin, demethoxycurcumin	Ginger, turmeric
b. Lignans	Honokiol, pinoresinol, silibinin, silybin	Bark, cereals, flax seed, thistle seed, rye
c. Phenolic acids	Caffeic, chlorogenic, coumaric, gallic, salicylic acids	Coffee bean, fruits, grains, vegetables
d. Phenolic acid derivatives	Ellagic, shikimic acids	Nuts, oak
e. Stilbenoids	Isorhapontigenin, resveratrol, piceatannol	Berries, grape, peanut, red wine
II. Flavonoid polyphenols (>5,000)		
a. Anthocyanidins	Anthocyanin, cyanidin, delphinidin, malvidin (glycosides)	Dark colored berries, fruits, vegetables
b. Flavan-3-ols	Catechin, epicatechin, gallocatechin, theaflavin	Cocoa, fruits, legume seeds, black teas
c. Flavanones	Eriodictyol, hesperetin, hesperidin, naringenin (glycosides)	Grapefruit, lemon, orange, tomato
d. Flavones	Apigenin, luteolin, morin, nobiletin	Carrot, celery, citrus, pepper, spices, spinach
e. Flavonols	Fisetin, galangin, kaempferol, myricetin, quercetin	Broccoli, berries, green teas, fruits, nuts, union
f. Isoflavones	Daidzein, equol, genistein, glistein	Legumes, soybean
III. Terpenoids (>4,000)		
a. Carotenoids (tetraterpenoids)	Carotenes, lutein, lycopene, zeaxanthin	Carrot, corn, tomato, paprika
b. Monoterpenes	Carvone, limonene, menthol, pinene, sabinene	Barks, citrus oil, mint, pepper
c. Sesquiterpenes (-penoids)	Abscisic acid, humulone, zingiberene	Hop, ginger
IV. Miscellaneous		
a. Betacyanins	Isobetanin, betanin, neobetanin	Beet, food dyes, fruits
b. Betaxanthins	Indicaxanthin, portulaxanthin	Beet, cactus
c. Indoles	Indole-3-carbinol	Broccoli, cabbage
d. Organosulfides	Allicin, diallyl disulfide, and trisulfide	Garlic, leek, union
e. Phytosterols	β-Sitosterol, campesterol, stigmastanol	Coconut, corn, olive, palm, sunflower oils

Note: Grouping is based on the plant component review of Frank et al.[126] For references, see the text.

was already established in 2003 by the United States Department of Agriculture, and by today contains over 5,000 molecules.

Anthocyanidins (flavonoid polyphenols) are abundantly present in the epidermal cells of berries, flowers, and fruits, and give these plant parts their pink to purple colors.[14] Partly accepted health claims are protection against obesity or diabetes, due to antioxidant, anti-inflammatory, or hypolipidemic actions.[26] Delphinidin (in violets) and malvidin (in primroses and grapes) are examples of anthocyanidins; the corresponding glycosides are called anthocyanins. *Flavan-3-ols* such as epicatechin are catalogued as derivatives with a phenyl chromenol skeleton (►**Supplementary Fig. S1**, available in the online version). They include catechin-like compounds and theaflavin, which are found in cacao, fruits, legume seeds, and teas. A health claim benefit of catechins in tea and wine has been disapproved, but a similar claim of (high-caloric) dark chocolate for ameliorating blood flow is still on the table.[27] *Flavanones* with a ketone group have a reactive structure (►**Supplementary Fig. S1**, available in the online version), and are sensitive to hydroxylation, glycosylation, and O-methylation. Orange-like fruits and tomato are some of the edible sources. Present as glycosides are eriodictyol in lemon, hesperidin in orange, and naringenin in grapefruit.[14] Such citrus flavanones have been studied for supposed antioxidant and lipid-lowering effects.[28] *Flavones* with a phenylchromenone backbone are also found as glycosides in spices and in yellow/orange fruits and vegetables.[14] Well-known flavones are apigenin, nobiletin, and luteolin, with antioxidant or anti-inflammatory activities.[29]

Flavonols with a hydroxy-phenylchromenone backbone form the most common flavonoid polyphenols of some foods.

Flavonols include the compounds fisetin, kaempferol, myricetin, and quercetin.[30] They are enriched in broccoli, berries, fruits, leek, and onion, cumulating as a daily intake of 20 to 50 mg.[14] A meta-analysis suggested that flavonols may help in decreasing CVD risk factors.[31] *Isoflavones* comprise flavonoids with a structural similarity to estrogens, although they are not steroids, and hence may have pseudo-hormonal properties. Isoflavones like daidzein, equol, and genistein are found in legumes and soybean, available with or without glycoside residues.[14] An earlier review discussed how isoflavones can act health-enhancing in obesity.[32]

The third class of *terpenoids (III)* represents a large family with over 4,000 primary and secondary plant metabolites (►**Table 1**). The terpenoids have an isoprene unit in common, and are subdivided according to the number of carbon atoms. *Carotenoids* (tetraterpenoids) are fat-soluble yellow-red pigments, of which 50 members are present in the common diet (α and β carotene, lycopene, zeaxanthin). Their antioxidant properties are often studied, as well as the role of carotenes as precursors of vitamin A biosynthesis.[33] The cyclic *monoterpene* limonene is a major component of citrus peel oil. It is also in use as a lipophilic solvent for cleaning purposes. *Sequiterpenes* with three isoprene units are found in essential oils and are infrequently studied with regard to health.

For the purpose of this review, remaining miscellaneous compounds are combined as class IV phytochemicals (►**Table 1**). *Betalains* like betanin and the related *β-xanthins* comprise yellow to red tyrosine-derived pigments, found in beets and cactuses, and are also popular as natural food dyes. *Indoles* (after the parent indole group, ►**Supplementary Fig. S1**, available in the online version), in particular indole-3-carbinol (in cabbage), have been studied for supposed anticancer properties.[34] *Organosulfides*, abundant in *Allium* plants such as garlic, onion, and leek, include the sulfur-containing allicin and diallyl sulfides.[35] A Cochrane review concluded insufficient evidence for health claims of garlic as having antithrombotic, hypoglycemic, or lipid-lowering activity.[36] *Phytosterols*, i.e., plant sterols and stanols, with a structural resemblance to cholesterol, are present in many vegetable oils, and have a discussable health claim for beneficial lipid-lowering effect. Some international societies still advise phytosterols as an additional dietary option in the management of hypercholesterolemia; however, other guidelines such as those from the National Institute of Health are more critical and draw attention to significant safety issues.[37] In general, in some parts of the world a high burden of proof is required for supplements or phytochemicals for health claims to be made, even meaning that clinical trials are required.

Platelet Signaling Pathways Targeted by Phytochemicals

Published studies to effects of certain classes of phytochemicals on platelets mostly describe altered responses such as TXA_2 release, platelet aggregation, or granule secretion, induced by agonists interacting with key platelet receptors. ►**Fig. 1** provides a simplified scheme, for relating these responses to specific signaling pathways, based on previous reports.[3–5] In brief, G-protein coupled receptors for ADP, TXA_2, and thrombin activate platelets via phospholipase Cβ and protein kinase C (PKC) isoforms, whereas especially the $P2Y_{12}$ ADP receptor triggers integrin $\alpha_{IIb}\beta_3$ activation via the route of phosphoinositide 3-kinases (PI3K), protein kinase B (PKB or Akt), and glycogen synthase kinase (GSK). Elevated cytosolic Ca^{2+} is required for the cyclooxygenase-dependent production of TXA_2, in a manner enforced by isoforms of mitogen-activated protein kinases (MAPKs) such as ERK and p38. Another route to platelet activation is provided by tyrosine-kinase-linked receptors, in particular the glycoprotein VI (GPVI) receptor for collagen. Here, via the kinases Src and Syk, platelet activation is achieved via PLCγ and PKC isoforms, both required for granule secretion. Under physiological conditions, platelet inhibition is accomplished by the cAMP- and cGMP-dependent protein kinases PKA and PKG, which become active via endothelial-derived prostaglandin I_2 (PGI_2, IP receptor) and NO, respectively. Isoforms of cAMP- and cGMP-dependent phosphodiesterases (PDEs) counteract this inhibition. In comparison to nucleated cells with proliferative, immune, and inflammatory actions, the roles of some signaling pathways in platelets are less well clarified. This concerns the signaling entities JAK (Janus kinase), mTOR (mechanistic target of rapamycin), or NFκB (nuclear factor kappa-enhancer of activated B cells).

Searching for Relations between Phytochemicals and Signaling Pathways

As a systematic approach to link common phytochemicals to signal transduction pathways relevant for platelets, we performed a set of PubMed searches (April 3, 2021). This search included papers in which phytochemicals were mentioned in combination with each of the 19 signaling modules mentioned above, regardless of the cell type. We then filtered for papers also mentioning "platelet." The complete datasets with phytochemicals arranged per class are given in **Supplementary Datafile 1** (available in the online version). A histogram of the total number of papers (integrating all signaling pathways) indicated that the most prominently investigated compounds are (≥1,500 counts, phytochemical class in brackets): carotenes (IIIa), genistein (IIf), curcumin (Ia), resveratrol (Ie), quercetin (IIb), catechin (IIb), gallic acid (Ic), and caffeic acid (Ic) (►**Fig. 2A**). To some extent, this also holds for the counts including platelets, with a notable exception that the most commonly mentioned phytochemical is genistein (215 counts), followed by quercetin (108 counts) (►**Fig. 2B**).

Examining the distribution profiles of these counts among the 19 selected signaling entities (PLC, PKC, PI3K, Akt, GSK, MAPK, ERK, p38, PDI, NO, cGMP, cAMP, PDE, Src, SHP, JAK, NFκB, mTOR, COX) revealed some interesting patterns. A condensed heatmap for all cell types is presented in ►**Fig. 3A**, and with filter for "platelet" in ►**Fig. 3B** (full data in **Supplementary Datafile 1**, available in the online version). In agreement with the considered broad influence of many phytochemicals on physiological and cellular processes, for

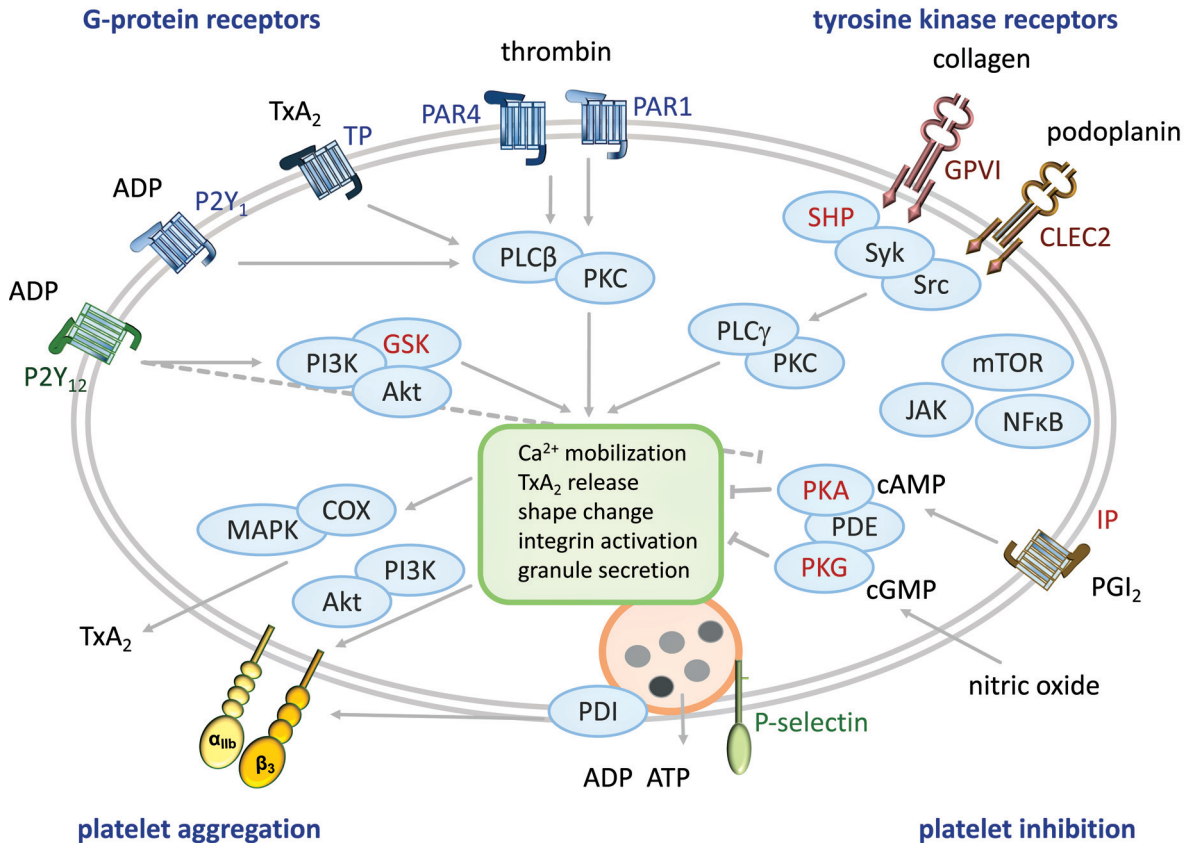

Fig. 1 General overview of signal transduction pathways underlying platelet activation and platelet inhibition. Triggering of G-protein-coupled receptors and tyrosine-kinase-linked receptors evokes a range of platelet responses, including Ca^{2+} mobilization, TXA_2 release, secretion of autocrine compounds from storage granules, integrin $\alpha_{IIb}\beta_3$ activation, and platelet aggregation. Note that signaling pathways indicated in *red* are negative regulators of platelet activation. For further explanation, see the text. COX, thromboxane synthase-cyclooxygenase; GPVI, glycoprotein VI; GSK, glycogen synthase kinase; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NFκB, nuclear factor kappa-enhancer of activated B cells; PAR, protease-activated receptor; PDE, cyclic nucleotide-dependent phosphodiesterase; PDI, protein disulfide isomerase; PGI_2, prostaglandin I_2; PI3K, phosphoinositide 3-kinase; PKA, cAMP-dependent protein kinase; PKB, protein kinase B or Akt; PKC, protein kinase C; PKG, cGMP-dependent protein kinase; PLC, phospholipase C; SHP, Src homology region 2 domain-containing phosphatase; Src, cellular tyrosine kinase c-Src.

the general analysis we obtained high counts for quite diverse pathways, i.e., NO (8k) > Akt, NFκB (5k) > MAPK, ERK, p38, COX (3k) > PKC, cAMP (2k) (**Supplementary Datafile 1**, available in the online version). After filtering for "platelet," the orders changed moderately, i.e., NO, PDE, Akt (>100) > MAPK, p38, cAMP, COX (>70) > PKC, PI3K, Src (>50). Examination of the unfiltered distribution profiles for all cell types indicated that especially curcumin (Ia), resveratrol (Ie), catechin (IIb), quercetin (IIe), genistein (IIf), and carotene (IIIa) showed an abundant and broad spectrum of links to general signaling pathways (►**Fig. 3A**). This distribution remained similar after filtering for "platelet" (►**Fig. 3B**). Markedly, for the phytochemicals of classes I–II, average hits (±standard deviation) as percentages were highest for NO (19 ± 7%), followed by NFκB (14 ± 4%) and COX (8 ± 2%). After filtering for "platelet," these percentages were for NO (14 ± 20%), NFκB (3 ± 5%), and COX (10 ± 19%). This is in agreement with the relatively poorly defined role of the NFκB pathway in platelets and the well-understood role of the aspirin-sensitive COX pathway in platelets.

In general, phytochemicals of classes III and IV are less frequently examined with regard to signaling pathways, most prominent being carotene (IIIa), lycopene (IIIa), sitosterol (IVe), indole-3-carbinol (IVc), diallyl trisulfide (IVd), and allicin (IVd). For platelets, with the exception of carotene and lycopene, there were only few hits.

Platelet Activation Affected by General Phenols (Class I)

When comparing the published effects of specific phytochemicals on platelets (►**Table 2**), it becomes apparent that mostly relatively high doses have been used in assays with washed platelets or platelet-rich plasma. A variety of platelet responses have been tested using aggregation measurements (by light transmission aggregometry, platelet function analyzer, or thrombus formation), commonly by focusing on specific platelet agonists, i.e., collagen acting via GPVI receptors, thrombin via PAR1,4 receptors, ADP via especially $P2Y_{12}$, and TXA_2 (including COX activity). Using flow cytometry or

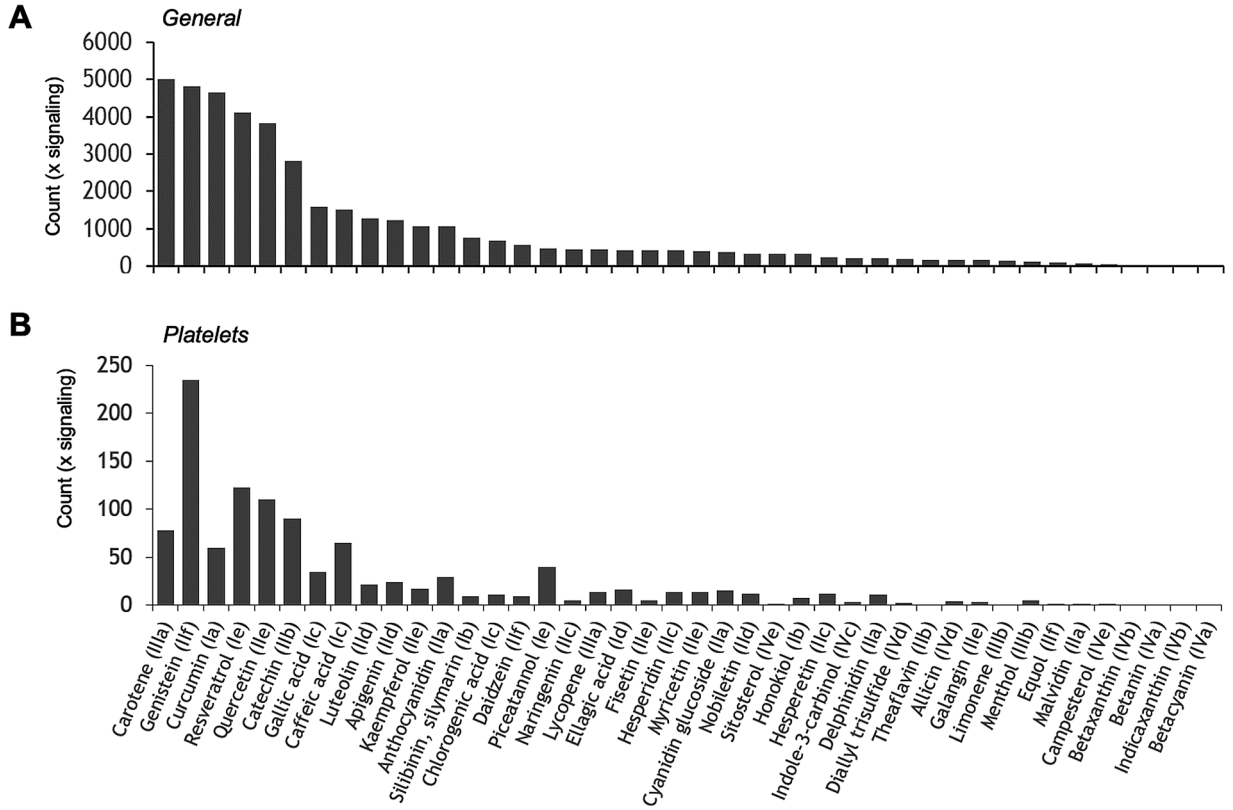

Fig. 2 Publication frequency of common phytochemicals reported in combination with signaling pathways. Summed counts of papers obtained from PubMed (search of April 3, 2021) of commonly studied phytochemicals in combination with 19 signaling entities: PLC, PKC, PI3K, Akt, GSK, MAPK, ERK, p38, PDI, NO, cGMP, cAMP, PDE, Src, SHP, JAK, NFκB, mTOR, and COX. Abbreviations as in ►**Fig. 1**. Shown are the unfiltered general counts (**A**) and the filtered counts for "platelet" (**B**). Searches included the title, abstract, and keyword fields. Also shown are the phytochemical classes (roman numbers). Full data are given in **Supplementary Datafile 1**.

Fig. 3 Distribution of papers reporting on phytochemicals in combination with specific signaling pathways. PubMed search as indicated for ►**Fig. 2**. Shown are the citation distribution of indicated phytochemicals in combination with the signaling entities: PLC, PKC, PI3K, Akt, GSK, MAPK, ERK, p38, PDI, NO, cGMP, cAMP, PDE, Src, SHP, JAK, NFκB, mTOR, and COX. (**A**) General publications, and (**B**) after filtering for "platelet." Note that paper inclusion was independent of effect of the phytochemical compounds. Full data are given in **Supplementary Datafile 1**.

luminescence, agonist-induced secretion (with roles of PLC and PKC) and integrin $\alpha_{IIb}\beta_3$ activation (with roles of PI3K and Akt) have been measured. In addition, triggered by the cAMP decrease upon $P2Y_{12}$ stimulation, some studies have examined phytochemical effects on (platelet-inhibiting) cAMP elevation or consequent PKA-dependent phosphorylation of the VASP proteins. In spite of the variation in assays, doses, and research approach, trends in phytochemical effects on platelet function can be observed. The total dataset per investigated phytochemical and study is given in **Supplementary Datafile 2** (available in the online version), while the summative results are provided in ►**Table 2**.

Curcumin as the main phenolic curcuminoid of turmeric shows positive results in many drug discovery assays, making it there to a false lead. This may be due to the color of curcumin, which can interfere in many assays. This agrees with our PubMed search, showing high counts with "general interest" pathways of PI3K, Akt, MAPK isoforms, NO, NFκB and mTOR, and COX. Curcumin effects on platelets have been studied up to submillimolar concentrations (►**Table 2**). Suppressive effects were seen of GPVI-induced aggregation and secretion responses, accompanied by a lower tyrosine phosphorylation of PLCγ2.[38] Suppression of $P2Y_{12}$-induced platelet aggregation and integrin activation has been observed as well. Dose studies indicated that also the pathway of (arachidonate-induced) COX activation was sensitive to curcumin,[39] and that anticoagulant effects exist.[17] Also in vivo studies revealed that curcumin can protect against collagen-epinephrine induced thromboembolism in mice and against $FeCl_3$-induced arterial thrombosis in rats.[40]

Honokiol, a phenolic lignan, has been proposed as a specific inhibitor binding to GPVI, but this was later extended to a broader inhibition of GPVI and other tyrosine kinase-dependent pathways.[41]

Silybin, along with silychristin and silydianin, all flavonolignans, has been evaluated mostly by one laboratory for ADP/$P2Y_{12}$-induced platelet activation, secretion, and integrin signaling (i.e., PI3K, Akt).[42,43] An effective dose of 10^{-5} M was reported, which is a physiologically reasonable concentration.[44]

Several authors have described effects of the polyphenolic *caffeic acid* (present in coffee beans, spices, red wine, chokeberry) at 10^{-5} M ranges, testing different aspects of platelet activation. The antioxidant activity of caffeic acid[45] may explain at least parts of its action. In vitro studies using human or mouse platelets claim especially a lowering of thrombin- (PAR1,4) and ADP-induced platelet signaling, including secretion, integrin activation, and aggregation, with possible contributions of the pathways of COX, Akt, and ERK.[46–48] A study with rat platelets points to stimulation of PKA-dependent processes, with collagen resulting in a decreased Ca^{2+} mobilization and TXA_2 formation.[49] An in vivo mouse study revealed that caffeic acid reduced thrombus formation, paralleling inhibition of ADP-induced platelet responses, with suggested roles of MAPK isoforms and PKA stimulation.[50]

Chlorogenic acid (polyphenolic ester of caffeic and quinic acid), also with antioxidant properties, has been studied in relation to various pathologies. One paper using platelets describes a range of GPVI-, PAR-, and ADP-dependent inhibitory effects (secretion, aggregation, and flow adhesion), with a possible role of adenosine receptor activation in the cAMP-PKA pathway.[51]

Gallic acid, a phenolic acid, esterifies with other phytochemicals like catechins to form gallates,[52] and is easily oxidized. By itself, gallic acid was found to have no more than modest effects on collagen and thrombin receptor-induced platelet responses, with even lower activities in the presence of plasma.[53,54]

The *polyphenolic acid derivative* shikimic acid at 10^{-3} M moderately affected $P2Y_{12}$-, but not GPVI-dependent platelet responses.[55]

Stilbenoids that are regularly studied are the analogs isorhapontigenin and resveratrol, both of which are pan-assay interference compounds, hence linking to a wide variety of signaling pathways. This also holds for platelet research. *Isorhapontigenin* (in Chinese herbs and grapes) in the 10^{-5} M range was found to inhibit ADP/$P2Y_{12}$-induced platelet aggregation, along with effects on PI3K-Akt (inhibitory) and cAMP-PKA (enhancing) signaling.[56] The analog *resveratrol* suppressed both collagen- and thrombin-induced platelet aggregation and secretion,[56,57] with a possible role of COX.[53] In washed platelets, but not in whole blood, resveratrol inhibited collagen-induced MAPK activation.[58]

Platelet Activation Affected by Flavonoid Polyphenols (Class II)

Anthocyanidin-flavonoid compounds commonly studied include mixed preparations, cyanidin-3- and delphinidin-3-glucoside (►**Table 2**). In washed platelets, anthocyanins at 10^{-6} M appeared to suppress PAR1-induced responses.[59] In whole blood, of the various anthocyanidins tested, only cyanidin-3-glucoside at 10^{-6} M was found to downregulate integrin activation with ADP.[60] The same compound at 10^{-5} M antagonized GPVI-induced signaling (Syk, Src), along with collagen-dependent thrombus formation under flow[61] and murine thrombus formation in vivo.[61] Such doses are close to the bioavailable concentration.[62] Delphinidin-3-glucoside was similarly effective on thrombus formation in mouse.[63]

Catechins comprise antioxidant flavan-3-ols present in cocoa, teas, fruits, and traditional herbs. In platelets, an antioxidant role has indeed been reported.[64] Reported inhibitory effects of catechins on collagen-induced platelet responses may not be directly downstream of GPVI, but by interfering with secondary mediators.[65] Yet, catechins derived from green tea showed inhibitory effects on aggregation via GPVI, PAR, and $P2Y_{12}$ aggregation and the connected PLC pathway.[66] The catechin derivative, epigallocatechin gallate, may inhibit (rat) platelet activation via MAPK (p38), TXA_2 production, and/or cAMP elevation.[52,67]

Apigenin, a yellow colored flavone, was proposed to inhibit platelets activated through PARs and other agonists by binding to the TXA_2 receptors (IC_{50} ~17 μM),[68] and/or by interfering with intracellular Ca^{2+} signaling.[69] Of other flavones, in one paper *morin* was found to dampen collagen-

Table 2 Nutritional phytochemicals affecting platelet signaling and responses in vitro

Phytochemical	Dose	GPVI (LTA)	GPVI (P-Tyr)	GPVI (thrombus)	PAR1, 4 (LTA)	Secretion (PLC/PKC)	COX, TXA2 (LTA)	P2Y12 (LTA)	Integrin act (PI3K)	P-Akt (Akt)	cAMP (PKA)	P-VASP (PKA)	cGMP (PKG)
Ia. Curcuminoids													
Curcumin or extract (Ia)	≤550 μM												
Ib. Lignans													
Honokiol (Ib)	≤25 μM												
Silybin or extract (Ib)	≤100 μM												
Ic. Phenolic acids													
Caffeic acid (Ic)	≤500 μM												
Chlorogenic acid (Ic)	≤1,000 μM												
Gallic acid (Ic)	≤1,000 μM												
Id. Polyphenolic acid derivatives													
Shikimic acid (Id)	≤2,000 μM												
Polyphenol extract (Id)	≤15 μg/mL												
Ie. Stilbenoids													
Isorhapontigenin (Ie)	≤100μμM												
Resveratrol (Ie)	≤200μμM												
IIa. Anthocyanidins													
Anthocyanidins (IIa)	≤1 μM												
Cyanidin-3-glucoside (IIa)	≤50 μM												
Delphinidin-3-glucoside (IIa)	≤50 μM												
IIb. Flavan-3-ols													
Catechins or extract (IIb)	≤100 μM												
Epigallocatechin (IIb)	≤100μμM												
IId. Flavones													
Apigenin (IId)	≤200 μM												
Flavone extract (IId)	≤10 mg/mL												
Morin (IId)	≤100μμM												
Nobiletin (IId)	≤30 μM												
IIe. Flavonols													
Fisetin (IIe)	≤400 μM												
Kaempferol (IIe)	≤400 μM												
Myricetin (IIe)	≤30 μM												

Table 2 (*Continued*)

Phytochemical	Dose	GPVI (LTA)	GPVI (P-Tyr)	GPVI (thrombus)	PAR1, 4 (LTA)	Secretion (PLC/PKC)	COX, TXA2 (LTA)	P2Y12 (LTA)	Integrin act (PI3K)	P-Akt (Akt)	cAMP (PKA)	P-VASP (PKA)	cGMP (PKG)
Quercetin (IIe)	≤400 µM												
IIf. Isoflavones													
Daidzein (IIf)	≤200 µM												
Genistein (IIf)	≤200 µM												
Isoflavone extract (IIf)	≤100 µg/mL												
IVd. Organosulfides													
Diallyl trisulfide (IVd)	≤100 µM												

Abbreviations: COX, thromboxane synthase-cyclooxygenase; GPVI, glycoprotein VI; LTA, light transmission aggregometry; PAR, protease-activated receptor; PKA, cAMP-dependent protein kinase; PKG, cGMP-dependent protein kinase.
Note: Shown are condensed literature data per phytochemical of receptor-induced signaling pathways changed in washed platelets or in platelet-rich plasma. Full data are in **Supplementary Datafile 2.**

and thrombin-induced platelet responses with suggested roles of the PLC, PI3K, Akt, MAPK (p38, ERK), and cAMP pathways.[70]

The flavonols *fisetin* and *kaempferol* (10^{-4} M) may have similar inhibiting profiles regarding collagen and thrombin stimulation. Kaempferol was shown to attenuate thrombin-induced phosphorylation of PI3K, Akt, ERK, and p38, and suppress murine thrombus formation.[71]

Myricetin exemplifies a flavonol with antioxidant properties, present in a range of vegetables, fruits, nuts, berries, and teas. It can partly reduce GPVI- and PAR-mediated responses, ranging from platelet aggregation, fibrinogen binding, granule secretion, and platelet adhesion under flow. Molecular docking studies pointed to an interaction with PDI, thus providing a mechanism for integrin inhibition and platelet aggregation.[72] A required dose in the 10^{-5} M range was reached in rats after oral intake of 100 mg/kg.[73] Relatively high effective doses are needed in the presence of plasma, when compared with washed platelets.[72] For myricetin also antiplatelet effects via COX have been described.[74]

Quercetin: the flavonol quercetin is a popular candidate antiplatelet phytochemical, acting at relatively low doses (10^{-5} M). In agreement with COX being one of the most frequent PubMed hits, quercetin may directly bind to COX.[53] Another report indicates a reduction of collagen and TXA_2 receptor- as well as COX-dependent platelet responses and of underlying signaling reactions.[68] Several studies point to an inhibitory effect of quercetin and its metabolites on collagen (GPVI)-induced platelet signaling (tyrosine phosphorylation) and aggregation.[65,69,75] However, quercetin can also suppress thrombin-induced platelet responses by interfering with the signaling (IC_{50} ~40 µM).[69] Early papers reported an effect of quercetin on (controversial) NO release from platelets,[76] or on inhibition of PDE to stimulate the cAMP-PKA pathway.[77,78] Synergistic inhibitory effects on collagen-induced platelet aggregation were obtained by quercetin in combination with catechin (both present in grape).[64,79]

Genistein (isoflavone from soy bean with antioxidant properties) has widely been studied for example to activate PPARs (peroxisome proliferator-activated receptors) or inhibit tyrosine kinases, providing it with a complex (anti) carcinogenic potential. *Daidzein* is a related isoflavone, which is considered to be inactive regarding tyrosine kinases. On platelets, both compounds at 10^{-5} M reduced the aggregation with collagen.[80,81] Confusingly, genistein was found to block Src phosphorylation, but enhance MAPK activity.[82] Several papers reported genistein effects on the (PAR-induced) PLC route,[68,69,83] and TXA_2-mediated platelet activation.[84] As a component of soy bean, genistein taken in vivo was thought to suppress collagen-induced platelet aggregation and thrombus formation.[81,85]

Platelet Activation Affected by Other Phytochemicals (Classes III–IV)

Diallyl trisulfide, an organosulfide present in crushed garlic, has been examined in few platelet papers. As indicated in ►**Table 2**, studies reported that diallyl trisulfide at 10^{-4} to 10^{-5} M decreased (human or animal) platelet aggregation

induced by collagen, thrombin, or ADP.[86,87] A suggested mechanism was reduced Ca^{2+} mobilization (IC_{50} ~28 µM for thrombin and C-reactive protein), but without affecting PLC.[88] Organosulfides derived from *Allium* can also modulate platelet sulfhydryl levels, suggesting a modulation of the cytosolic redox state.[89] Concerning carotenoids, the compound crocin was found to interfere with the formation of reactive oxygen species in platelets by an unknown mechanism.[90]

Nutritional Intervention Studies of Phytochemicals Targeting Platelet Activation

Multiple controlled intervention studies have been performed with phytochemical-enriched food components, aiming to find antithrombotic effects via platelets (**Supplementary Datafile 3**, available in the online version). However, the high inter-study heterogeneity in intervention type, duration, and outcome parameters excludes a formal meta-analysis. Across all studies, the overall effect sizes on platelet inhibition appear to be lower after dietary interventions (►**Table 3**) than after in vitro application (►**Table 2**). Explanations for this are the phytochemical complexity of the food interventions, the relatively low doses ingested, and the fast pharmacokinetics of the plant compounds (rapid metabolic modification and short half-lives in the body).[14,91] As the pharmacokinetics and active metabolites for most phytochemicals are not well established, a direct comparison of in vivo and in vitro studies is not straightforward and can be complex. Another complexity is that studies used different platelet function assays, and that numbers of (healthy) subjects per study usually were low. Yet, it should be noted that these dietary or supplementation intervention studies are major efforts, and that effect sizes are expected to be lower than the effects of approved pharmacological antiplatelet drugs (with a bleeding risk). A summative overview of controlled human intervention studies is given in ►**Table 3**, with study details in **Supplementary Datafile 3** (available in the online version).

General phenols (class I): red wine. Polyphenol-containing red wine consumption has proposed to be thrombo-protective versus white wine consumption. However, several intervention studies did not find evidence for altered platelet activation after moderate consumption of red wine other than an ethanol-related effect.[92,93] In contrast, in a large placebo-controlled study (72 healthy subjects), 2-week consumption of polyphenol-rich berries appeared to delay collagen/ADP-induced platelet aggregation under shear.[94]

Flavonoid polyphenols (class II): grape seed or kiwi. In a controlled, 8-week study, where flavonoid-containing grape seed extract was given to hypertensive subjects, no evidence for antiplatelet effects was seen.[95] Regular consumption of kiwi, also containing polyphenols, though led to a reduced collagen/ADP-induced platelet aggregation.[96]

Anthocyanidins (IIa): dark grape juice or anthocyanin supplement. Surprisingly strong antiplatelet effects were reported after regular intake of anthocyanin-rich food additives, in 11 small- to medium-sized controlled studies. Drinking purple grape juice (but not orange juice) for 1 week reduced collagen-induced platelet aggregation.[97] In obese subjects, intake of anthocyanin capsules during 4 weeks reduced ADP- and collagen-induced platelet activation parameters.[98,99] In a large study with 150 hypercholesterolemic individuals, anthocyanin supplementation decreased the plasma levels of platelet secretion products.[100] In several trials, dark (anthocyanin-rich) plum or orange juice was given to healthy subjects for 1 to 4 weeks (**Supplementary Datafile 3**, available in the online version). Jointly, these trials identified after intervention a lowering of GPVI- and ADP/$P2Y_{12}$-dependent platelet responses, but not of PAR-dependent responses.

Flavan-3-ols (IIb): dark chocolate or cocoa drink. Supplementation with dark chocolate or cocoa drink, rich in flavan-3-ols, mostly by single intake, has also been popular to check for antithrombotic effects (see **Supplementary Datafile 3**, available in the online version). Overall, the study outcomes indicated a moderate suppression of collagen/GPVI-, thrombin/PAR-, and ADP/$P2Y_{12}$-induced platelet responses (►**Table 3**). An unexplained gender difference after dark chocolate intake was noted here.[101] In a large study with 1,535 healthy subjects, again an effect was seen of casual chocolate consumption on collagen- and flow-dependent platelet activation, along with lower TXA_2 levels.[102] Similarly, flavan-3-ol-rich extracts from grapeseed were shown to have a platelet-inhibiting effect under flow in response to collagen/ADP.[103]

Flavonols quercetin and catechin: black tea. Four controlled approximately 4 weeks intervention studies have appeared, where effects were examined of black tea (rich in quercetin and catechins), but no consistent effects on platelet function could be measured (►**Table 3**). One intervention study with 12 subjects reported a strongly decreased collagen/GPVI-induced platelet activation after single intake of quercetin.[75] However, such quercetin effects were not reproduced in longer time intervention studies.[104,105]

Isoflavones (IIf) genistein and daidzein: soy preparations. An early study examining soy protein (rich in genistein and daidzein) intake during 4 weeks did not find alterations in collagen- or TXA_2-induced platelet aggregation.[106]

Organosulfide (IVa) diallyl trisulfide: garlic preparations. Dissimilar from the large effect sizes of diallyl trisulfide on platelet properties in vitro, preparations of this phytochemical in garlic in vivo (given for up to 16 weeks) were no more than weakly active. In small-size studies, reduced effects of intake of garlic preparation on ADP-induced aggregation were reported (but less strong than a pharmacological $P2Y_{12}$ inhibitor).[107–109] However, this was not seen in other studies.[110,111] In a 4-week intervention study with hyperlipidemic subjects, no antiplatelet effects of dried garlic were seen.[112]

Platelet Receptor and Signaling Pathways Affected by Phytochemicals In Vitro or In Vivo

The current literature on phytochemicals and platelets is quite diverse with most papers using different doses, types of

Table 3 Nutritional phytochemicals affecting platelet signaling and responses in vivo

Class	Phytochemical	Type and duration of intervention	Total sample size	GPVI (LTA)	GPVI (PFA-100)	GPVI (P-Tyr)	PAR1,4 (LTA)	Secretion (PLC/PKC)	COX, TXA2 (LTA)	P2Y12 (LTA)	Integrin act (PI3K)
I. General phenols											
	unspecified	red wine (1–24 weeks)	48								
	unspecified	berries (2 weeks)	72								
II. Flavonoid polyphenols											
	polyphenols	grape or seed (2–8 weeks)	105								
	polyphenols	kiwi (4 weeks)	30								
IIa. Anthocyanidins											
	anthocyanins (glycosides)	anthocyanins various sources (1–4 weeks)	194								
	anthocyanins (glycosides)	anthocyanin supplement (24 weeks)	150*								
	anthocyanins (glycosides)	anthocyanins from elderberry (12 weeks)	52[b]								
IIb. Flavan-3-ols											
	flavan-3-ols	dark chocolate, cocoa (2–6 hours 4 weeks)	218								
	flavan-3-ols	dark chocolate (2 days)	1535								
	flavan-3-ols	grapeseed (6 hours, 8 weeks)	40								
IIe. Flavonols (mixed flavonoids)											
	quercetin, catechins	black tea (4–6 weeks)	178								
	quercetin	quercetin supplement (1 day)	12								
	quercetin	quercetin supplement (1–8 weeks)	51								
IIf. Isoflavones											
	daidzein, genistein	soy (4 weeks)	20								
IVd. Organosulfides											
	diallyl trisulfide	garlic (1–16 weeks)	131								
	diallyl trisulfide	garlic (4 weeks)	20[b]								

Abbreviations: COX, thromboxane synthase-cyclooxygenase; GPVI, glycoprotein VI; LTA, light transmission aggregometry; PAR, protease-activated receptor; PKC, protein kinase C; PLC, phospholipase C.
Note: Shown are condensed literature data per phytochemical of receptor-induced signaling pathways changed in platelets, as observed in controlled intervention studies.
[a]Hypercholesteremic subjects.
[b]Postmenopausal women. Full data are in **Supplementary Datafile 3.**

phytochemical preparations tested, intervention schemes, types of functional assays with or without plasma, and receptor and signaling pathways examined. Nevertheless, in agreement with the hit list of ►**Fig. 3B**, several "hot-spot" receptor signaling entities can be identified that are most strongly influenced by the investigated phytochemicals. From in vitro studies (see ►**Table 2**) it appears that the following pathways are preferably affected, although the precise molecular targets are unknown. Note that these listed pathways may partly overlap.

- *GPVI collagen receptor signaling via PLCγ2, tyrosine kinases Src and Syk.* Compounds (phytochemical class) that are interfering include: curcumin (Ia), honokiol (Ib), chlorogenic acid (Ic), resveratrol (Ie), anthocyanidins like delphinidin-3-glucoside (IIa), catechins (IIb), morin (IId), kaempferol and quercetin (IIe), genistein (IIf), and diallyl trisulfide (IVd).
- *PAR thrombin receptor activation along with PLC route of Ca^{2+} mobilization* may be less frequently influenced, with most strongly reported effects of caffeic acid (Ic), catechins (IIb), apigenin and morin (IId), kaempferol and quercetin (IIe), and diallyl trisulfide (IVd).
- *TXA_2 receptor and formation via COX.* Best reported effects of the COX enforcement pathway are by: curcumin (Ia), caffeic acid (Ic), resveratrol (Ie), apigenin (IId), myricetin and quercetin (IIe), genistein (IIf).
- *$P2Y_{12}$ receptor and signaling to integrin activation via PI3K and Akt.* The main route of autocrine platelet aggregation is mostly suppressed by: curcumin (Ia), silybin (Ib), caffeic and chlorogenic acid (Ic), isorhapontigenin and resveratrol (Ie), delphinidin 3-glucoside (IIa), catechins (IIb), apigenin (IId), kaempferol and quercetin (IIe), and diallyl trisulfide (IVd).
- *MAPK isoforms including ERK and p38.* Inhibitory compounds include caffeic acid (Ic), resveratrol (Ie), epigallocatechin (IIb), morin (IId), kaempferol (IIe), genistein (IIf).
- *Integrin $\alpha_{IIb}\beta_3$ activation via PDI.* The compound myricetin (IIe).
- *Enforced platelet inhibition via cAMP, PKA, cGMP, PDE.* Compounds reported are: silybin (Ia), caffeic and chlorogenic acid (Ic), isorhapontigenin (Ie), epigallocatechin (IIb), morin and nobiletin (IId), and quercetin (IIe).

Comparing this to the overall results of in vivo interventions (►**Table 3**), it appears that only the effects of anthocyanidins (IIa), flavan-3-ols (IIb, cocoa), and the flavonol quercetin (IIe) are recapitulated in terms of these antiplatelet effects, although with lower strength, while organosulfides (IVd, garlic) has a low residual effect as well. Promising, furthermore, is that in vivo in mouse models arterial thrombosis tendency was found to be reduced by anthocyanidins[71] and by the flavonol kaempferol,[63] whereas intake of organosulfides attenuated murine atherosclerosis.[113]

Implications for Thrombosis and Hemostasis

The majority of the reviewed phytochemicals required relatively high doses (10^{-4}–10^{-5} M) to be active on platelets in vitro, and these doses may further increase when plasma is present, for instance in case of resveratrol.[58] This in general explains the relatively small effect sizes on platelets observed in the nutritional intervention studies, in which relatively low doses are ingested. Since nutritional intervention in general appears to be of limited platelet-modulating consequences, specific dietary interventions are not expected to strongly impact the thrombosis risk purely by affecting platelet function. However, direct phytochemical supplementation can have a stronger effect, especially when some of the most active phytochemical types are further improved. The current high dosing is only one drawback for the testing of such compounds for possible therapeutical intervention. Other limitations are the often unclear metabolic absorption of the phytochemicals and their metabolites,[114] the pharmacokinetic profile in blood and nonplatelet effects, which for the cardiovascular system may be positive or negative. However, as already postulated by others, the acquired knowledge on effects of certain phytochemicals, as platelet-inhibiting compounds, can be employed for the further selection and chemical modification of these in the design of effective antiplatelet drugs.[115] In other words, those phytochemical compounds with a proven effect on platelets and thrombus formation can trigger new ways for drug discovery. This could develop into new antiplatelet drugs, and also to potentiate the action of current antiplatelet drugs, as several of the phytochemicals seem to have priming effects on platelets. Interestingly, combinations of phytochemicals can have synergistic effects on platelets,[64,79] which will further enhance the priming.

Of the examined phytochemicals, several appeared to stand out as interesting targets for possible clinical use. Quercetin (class IIe) is interesting, as its supplementation showed promising effects in vivo with a clinically relevant reduction in GPVI-induced platelet aggregation.[75,116] Moreover, multiple in vitro studies showed antiplatelet effects regarding several signaling pathways.[53,64,65,69,105,117,118] Also, flavan-3-ols (class IIb) are of interest, as these showed a reduced platelet activation in response to ADP, thrombin, and collagen in vitro.[66,119,120] In vivo, flavan-3-ols have only been studied in food intervention trials, leaving the possibility that supplementation in purified form has an even stronger effect. Lastly, anthocyanidins are of interest, as they inhibited GPVI, PAR, and P2Y-mediated platelet activation in vitro[59,60] as well as platelet activation in vivo.[98,99]

Regarding quantitative or qualitative platelet changes and hemostasis (bleeding risk), only few information is available, limited to animal studies. Indications on an increased tail bleeding time were made for animals treated with diallyl trisulfides,[121] curcumin,[40,122] epigallocatechin,[123] nobiletin,[124] or chlorogenic acid.[51] Few other papers indicated that phytochemicals can inhibit thrombus formation and platelet function without increased tail bleeding times, i.e., for quercetin,[125] myricetin,[72] and delphinidin glucoside.[63]

In conclusion, this overview indicates that many phytochemicals to a smaller or larger extent can influence platelet function, albeit only a few can do so at an affordable and clinically relevant dose. However, only for some

phytochemicals it is clear how they interfere with platelet signaling pathways or receptors, which makes these interesting candidate pharmaceuticals. Future research will need to focus on: (1) chemical modification of these compounds to obtain better or more specific antiplatelet agents, and (2) optimization of the isolation or synthesis of selected phytochemicals for concentrated supplementation, before use as antiplatelet drugs.

Author Contributions

F.T., B.M.E.T., M.J.E.K., T.A.M.C., and J.W.M.H. performed research, analyzed data, drafted, and wrote the manuscript.

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Conflict of interest

None declared.

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