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AN OVERVIEW OF NATURAL PHENOLIC COMPOUNDS AS ANTIPLATELET AND ANTI-INFLAMMATORY AGENTS IN MEDICINE

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ABSTRACT
Cardiovascular diseases are a major cause of mortality and morbidity in the world, having to do with alterations in blood platelet activation. Phenolic acids and flavonoids (two main classes of polyphenols) demonstrate beneficial pro-health effect on the human body, including anti-inflammatory, cardioprotective, antilipidemic, antiviral, antibacterial and anticancer. We reviewing here, the latest data in the literature, regarding the antiplatelet and cardioprotective effects of these polyphenols, obtained by *in vitro*, clinical and *in vivo* studies. Bioavailability and their role on preventing cardiovascular health problems are commented. The potential benefits of these polyphenols to circulatory system and metabolic alterations from human intervention studies are also discussed. Despite the huge information about their efficacy and potency, controversial results has been obtained in some cases questioning their applicability. The need for well-designed and uniform methods to assess their therapeutic potential to humans is highlighted. The review has evaluated outcomes available from a number of fields and has attempted to channel it into an understanding of the effect and applicability of natural phenolics as antiplatelet and anti-inflammatory drugs.

KEYWORDS: Platelets, phenolic compounds, hemostasis, inflammation, bioavailability, cardiovascular diseases.

INTRODUCTION
Platelets play a central role in clot formation resulting in hemostasis after endothelium injury. Platelet activation and aggregation are common factors in atherothrombotic events and process.[1-5] Platelets activate by several agonists, including collagen, adenosine diphosphate (ADP), epinephrine, serotonin, thromboxane A_2, ristocetin, adrenaline and protease-activated receptor 1(PAR -1-activating peptide).[6] The above panel of agonists is expanding to gamma thrombin or alpha thrombin, TRAP-4, thromboxane mimetic U46619 (stable analogue of the endoperoxide prostaglandin H2), calcium ionophore A23187, polymerized immunoglobulins, collagen-related peptide, misfolded proteins like AGE-proteins, alpha defensins, proteins from microorganisms and snake venoms.[7,12] Activated platelets release several pro-inflammatory molecules such as P-selectin and CD4 ligand and convert glycoprotein GPIb/IIIa complex (a central platelet receptor mediating platelet aggregation) into an active form, thus giving rise to platelet aggregation.[10]

Natural polyphenols are secondary metabolites of plants, fruits and vegetables, with pro-health or preventive effect on human diseases. Polyphenols are added value products and are first known for their antioxidant activity. Based on their chemical structure polyphenols are classified into phenolic acids, flavonoids, stilbenes, lignanes and tannins (Scheme 1). Phenolic acids having one benzene ring and at least one carboxyl group are characterized as benzoic acid derivatives and hydroxycinnamic derivatives (Scheme 2).

Flavonoids constitute the largest group of low-molecular-weight phenolic compounds characterized by a phenyl-benzopyran chemical structure consisting of two aromatic rings (A and B) and a heterocyclic benzopyran ring (C) with oxygen atom (Scheme 3). Flavonoids and phenolic acids represent the two major classes of plant-based phenolic compounds.[13,14]

Ingestion of flavonoids reduces the risk of cardiovascular diseases, metabolic disorders, and other related diseases by reducing oxidative stress, inhibiting platelet aggregation and acting as vasodilators in blood vessels.[15,16] The function of the cardiac system is to pump oxygen rich blood to the organs, tissues, and cells. Hemostasis is an important physiological process,

wherein activated platelets adhere to the injured vessel wall, form aggregates to stop bleeding and create a barrier for infections.

Reviewing recent literature, regarding the multi functionality of polyphenols to human health, we tried to focus on the current state of the art and draw some conclusions about applicability of flavonoids and phenolic acids, in the treatment of various coagulation disorders, and cardiovascular diseases. Questions having to do with their interrelationship and transformation to drugs, complementing or substituting synthetic ones in the field have been answered.

Chemistry and biology of flavonoids

Flavonoids are classified into various types depending on their chemical structure, degree of unsaturation, and oxidation of carbon ring, including flavones, flavanones, isoflavones, flavonols, flavanols, and anthocyanins (Scheme 4). Each one of these flavonoids is widely distributed in nature.[13,16]

There have been several reports on antiplatelet activity of plant extracts containing flavonoids.[17,21] Flavonoids are known for their venotonic activity, but their mechanism of action has not yet been elucidated. Supposedly, their activity is mediated by the regulation of prostaglandin metabolism. Specific phytochemicals may interfere with the arachidonic acid cascade reactions and its metabolites, which are directly related to platelet aggregation regulation.[22,23]

Flavonols are a class of flavonoids that have the 3-hydroxyflavone backbone in their structure (Scheme 4). Their diversity stems from the different positions of -OH groups. Quercetin, galangin, kaempferol, and myricetin are common flavonols (Scheme 5) distributed in vegetables and fruits, such as asparagus, onions, lettuce, broccoli, tomato, and apples. They exhibit interesting biological activities *in vitro*, including antioxidant, anti-inflammatory, antibacterial, cardioprotective, anticancer, and antiviral activities.[24,30]

Quercetin influences some carcinogenesis markers and has small effects on plasma antioxidant biomarkers in vivo, although some studies failed to find this effect.[26] Fractions of isolated phenolics from extracts, containing quercetin, kaempferol showed antiplatelet activity *in vitro* and anti-inflammatory activity by measuring the inhibition of cyclooxygenases 1 and 2 (COX1 and COX2).[27,28] Quercetin reported to block nuclear factor kB (NFkB), signaling and expression, down regulate tumor necrosis factors (TNFa, 1b), the synthesis of interleukin-6 (IL-6) and reduce the expression of MCP-1and MIP-1a.[26,31,33] Kaempferol is a more potent inhibitor than quercetin, as previously reported.[27,28] Myricetin, present in edible plants, presents anticarcinogenic, antimutagenic and antiplatelet activity.[29,34,35] It displays moderate membrane permeability and degrades rapidly at elevated pH. As reported above, myricetin comprises two benzene rings A and B (Scheme 3) and in that case ring B intercalates with nucleotide staking and inhibits bacterial DNA synthesis.[35] It was shown that myricetin protects against oxidative stress generated by tert-butyl hydroperoxide in diabetic rats, improves the activity of glutathione peroxidase and xanthine oxidase enzymes and reduces the glycosylation of low-density lipoprotein. Moreover, myricetin has been presented as a functional agent towards preventing atherosclerosis through inhibition of CD36 cell surface protein and mRNA expression in a significant manner.[36] Previous studies have demonstrated that myricetin also has positive effects on the human vascular system. Specifically, in human umbilical vein endothelial cells, myricetin, at 100μM concentration, showed vasculoprotective effects through changes at the transcriptional level.[33,36] Isorhamnetin, another flavonol, isolated from sea buckthorn berries showed strong antiplatelet and anticoagulant activity in whole blood *in vitro*.[37]

The main reported mechanisms of action for phenolic compounds, other than the antioxidant effects, include the suppression of cytoplasmic Ca^{2+} increase and inhibition of thromboxane formation and arachidonic acid (AA) pathway.[35] Quercetin, at 200μM concentration, found to completely inhibit AA and thrombin-induced platelet aggregation, by impairing Ca^{2+} mobilization and serotonin secretion.[35,36] Resveratrol, a non-flavonoid polyphenol (stilbene), present in grapes and other fruits, could also inhibit the arachidonate-dependent synthesis of inflammatory agents, such as TXB2, hydroxyheptadecatrienoate, and 12-hydroxyeicosatetraenoate.[38]

Flavones, another large class of flavonoids, present mostly as glycosylated products, which are found in celery, parsley, red pepper, chamomile, mint, and ginkgo biloba show antiplatelet activities.[39,40] Apigenin and luteolin are two common flavones in nature. Apigenin is usually found in a glycosylated form, with a sugar moiety attached to the tricyclic core structure via hydroxyl groups (*O*-glycosides) or directly to carbon (*C*-glycosides).[40] Apigenin can scavenge free radicals and regulate antioxidant enzyme activity in pancreatic cells, and can decrease inflammation in cancer, neuro-inflammation, and cardiovascular diseases.[40]

Apigenin from soy extracts reported to prevent cardiovascular diseases by inhibiting endothelial cell dysfunction.[41,42] Abshirini and coworkers revised the literature to find randomized controlled trials that evaluated the impact of soy protein supplementation. They found that isoflavone intake, ranging from 49.3 to 118 mg/day) affected endothelial function parameters in postmenopausal women (n = 802).[43] As it was proposed, soy isoflavones modified adhesion molecules by binding to vascular endothelium and mimicking the effect of a modulator of estrogen receptors.[43] A systematic review and meta-analysis reported by Man

and his coworkers revealed that supplementation of soy isoflavones had a positive effect in reducing arterial stiffness.[44] The physical stiffening of arteries has major health implications for its connection to various cardiovascular diseases, such as coronary heart disease, stroke, hypertension or heart failure.[45] However, the authors acknowledged several limitations to their study, as the small sample size in the meta-analysis (middle-aged 276 women and 209 men), and recognized that a large number of subjects as well as a longer intervention time are needed to investigate whether supplementation of soy isoflavones actually improves these outcomes.[44] Chrysin **(**5,7-dihydroxy-flavone) occurs in many plants, as honey, and propolis.[46,47] It exerts an antioxidant effect by enhancing the antioxidant system, suppressing pro-oxidant enzymes, scavenging free radicals and chelating redox active transition metal ions. Chrysin modulates vascular function by increasing the bioavailability of endothelial nitric oxide, inhibits the development of atherosclerosis by decreasing vascular inflammation. The anti-inflammatory effects of chrysin may relate to its inhibitory effect on the NF-kB signaling pathway. It also prevents vascular smooth muscle cells proliferation and thrombogenesis. In general, chrysin could be effective as a natural agent for the prevention and treatment of cardiovascular diseases.[47]

Curcumin is a biphenolic compound (stilbene type), existing in two keto-enol tautomers. It has been reported to exert numerous pharmacological effects by modulating multiple molecular targets including those involved in the pathogenesis of cancer.[48,50] It promotes anti-angiogenesis, meaning it helps prevent the development of additional blood supply necessary for cancer cell growth. It inhibits the proliferation of tumor cells, the transformation of normal to human cells and decreases inflammation. In addition, the active component of *Curcuma longa L*. ar termerone found to inhibit platelet aggregation induced by collagen and AA.[20] Available pre-clinical data suggest the ameliorating effect of curcumin in pain and inflammation. It inhibits a number of pro-inflammatory mediators such as oxidative stress and COX-2, down-regulates Ca2+/calmodulin-depended protein kinase II.[49]

Flavanols, known also as catechins or flavan-3-ols, have a hydroxyl group at position 3 in the C-ring of their structure (Scheme 4). Flavanols lack a double bond between positions 2 and 3 in the C-ring.[51] Flavanols, including catechin, gallocatechin 3-gallate, gallocatechin, epicatechin, epicatechin 3-gallate, catechin 3-gallate, and epicatechin 3-gallate, are widely distributed in fruits (apples, bananas, pears, and blueberries).[52,54] Flavanols can protect blood vessels against tobacco by increasing the content of nitric oxide in blood vessels. As reported, flavanol-rich diet facilitates the permanent improvement of endothelial function and prevents the development of cardiovascular diseases.[55]

Phenolic acids, another class of the phenolic compounds, are distributed in several fruits and vegetables as well and exert antiplatelet and antithrombotic activities.[56] Olive products contain a number of hydroxybenzoic acids, which have antioxidant, anti-inflammatory, and cardioprotective effects.[57] Hydroxycinnamic acid derivatives include caffeic acid, ferulic acid, coumaric acid, sinapinic acid, cinnamic acid.[14,58] In a previous study we had examined the antiplatelet activity of kaempferol, quercetin, myricetin catechin and epicatechin, and of three phenolic acids caffeic, ferulic and coumaric acid. All compounds were found to inhibit platelet activation induced by collagen to a wide range. Epicatechin, with IC_{50} value 0.08mM, was the most potent one followed by myricetin, coumaric acid and ferulic acid.[54]

Anthocyanins are flavonoids (pigments) primarily responsible for the color (red, pink, purple) in fruit and vegetables.[59,60] The cardioprotective role of anthocyanins has been also emphasized. They reduce the risk of myocardial infarction in humans, improve systolic blood pressure, and reduce the content of triglycerides, total cholesterol, and low-density lipoprotein cholesterol. Regarding mechanism of action in atherosclerosis, it is believed that anthocyanins proceed via activation of Nrf2-ARE as an indicator and modulator of redox balance.[61]

Anti-inflammatory activity

Phenolic compounds are essential compounds among phytochemicals for the suppression of inflammation, and the recent literature has revealed their potent anti-inflammatory capacity.[62,63] Production of pro inflammatory mediators during inflammation is common in some cells, mainly in macrophages, with interleukins, tumor necrosis factor, reactive oxygen species (ROS), nitric oxide (NO), and prostaglandins being the most commonly produced inflammation mediators.[64] Inhibition of COX-1 and COX-2 enzymes and production of cytokine/chemokine by flavonoids, in human whole blood has been reported.[65,30] In this case, the assay for COX-1 and COX-2 enzymes activities is based on the amount of prostaglandins generated in the reaction tube, which are detected using immunoassay kit. In other studies, association of the phenol chemical structure with its anti inflammatory activity was attempted.[65] This information is valuable and may lead to specific phenol structure responsible for the activity. Phenols are able to modulate transcriptional factors, like down regulating NF-κB or up regulating Nrf-2.[66] NF-κB regulates the expression of several pro inflammatory cytokines, such as IL-1β, TNF-α, and enzymes, like inducible nitric oxide synthase (iNOS). Catechin and quercetin, for example, have the potential to down-regulate the initial signaling molecule NF-κB, which may further inhibit the downstream cascade including TNF-α and NO.[67,68]

Nrf-2 regulates the expression of anti-inflammatory enzymes by possessing an antioxidant responsive element, able to activate several antioxidant enzymes needed for redox balance. Thus, they inhibit the gene expression and the activity of pro inflammatory mediators at the same time that they activate the expression and activity of anti-inflammatory mediators that are targets of transcription factors. The inhibition of inflammatory mediators, ROS, NO, and PGE2, and pro inflammatory mediators, like cytokines, TNF-*α*, and COX-2, is one of the major targets for the treatment of cardiovascular diseases. The overexpression of TNF-*α* and IL is linked to NF-*κ*B activation. Additionally, phosphorylation of p38 mitogen-activated protein kinases plays an important role in chronic inflammation by activating NF-κB as well as regulating the NO and pro inflammatory gene production from macrophages.[69]

As stated, NF-*κ*B is associated with the Nrf-2 regulation that regulates the expression of anti-inflammatory enzymes. Considering such mechanisms and their ability to inhibit ROS, the cardioprotective effects of these molecules are due to their ability to improve endothelial dysfunction in CHD, since it also increases the bioactivity of endothelial NO.[69] Moreover, flavonoids may reverse endothelial dysfunction in addition to lowering blood pressure.[71] Phenolic acids, the other class examined here, are also known for their bioactivities *in vitro* and *in vivo*.[70] Pragasam and coworkers studied the anti-inflammatory effects of *p*-coumaric acid by monitoring the expression of TNF-α in synovial tissue of adjuvant-induced arthritic rats. The anti-inflammatory activity of *p*-coumaric acid was determined by lowering the expression of inflammatory mediator TNF-α.[71] Anti-inflammatory activity of caffeic acid and ellagic acid has been also determined in other studies.[72,73] In this case, caffeic and ellagic acids were supplied to mice by mixing them at a ratio of 2.5 and 5.0% respectively. The assays showed that the two acids decreased the expression of inflammatory mediators IL-6, IL-1-β, TNF-α.[73] The anti-inflammatory capacities of caffeic acid and its derivatives, was also reported by da Cuhna and coworkers, who measured the inhibition of lipopolysaccharide- induced iNOS expression in RAW 264.7 macrophage.[72] Furthermore, from *in vitro* experiments is indicated that polyphenols reduce platelet NADPH oxidase activation, ROS formation, thromboxane formation, AA pathway and platelet stimulation through PI3K/AKT.[28,73] The positive role of platelet biomarkers as well as of natural polyphenols on inflammation has been reported.[73,74] The *in vitro* experiments for selective antiplatelet and anti-inflammatory activities of phenolic acids and flavonoids are numerous. On the contrary to these, there is limited *in vivo* evidence showing that polyphenols can inhibit ADP-induced platelet activity and reduce AA- induced platelet activation.[75,76] It is evident that the *in vitro* data cannot be fully translated into the *in vivo* condition, because the molecules undergo biotransformation reactions that alter their bioavailability. As a consequence, this could lead to discrete and contradictory biological effects and question their applicability.

Bioavailability

Bioavailability is significant to know and understand, since only the bioavailable phenolic compounds in our diet will have best effects on the human body. There have been many reports and reviews regarding biovailability of phenolic compounds to humans. Bioavailability has to do with the fraction of an ingested nutrient or compound that reaches the systemic circulation and the target tissue. The bioavailability of polyphenols has been investigated through several intervention and clinical studies.[77,82]

Bioavailability differs among various flavonoids. Phenolics liberated from the food matrix are absorbed in the small intestine; pass through the epithelial cells, conjugate with other molecules such as glucuronic acid and sulfonate, followed by introduction in the plasma.[80] However, the small intestine absorbs only a small portion of free phenolics in the food matrices and only 5–10% of them are incorporated into the plasma; the remaining 90-95% are directly transferred to the colon.[16] For example, quercetin after a meal containing onions, catechins after red wine consumption, and isoflavones after soy consumption, reach micromolar concentrations in the blood.[83,84] These findings demonstrate that polyphenols cross the intestinal barrier and reach concentrations in the bloodstream. Although, most polyphenols are absorbed, this is very dependent on the type of polyphenol. Despite the lack of convincing evidence for consistent effects of quercetin in humans, there are numerous studies on the properties of quercetin *in vitro*. Generally, quercetin was not found in the plasma as the free form or as the parent glucoside. At the doses used in intervention studies (21-1000 mg), it was found exclusively as methyl, sulfate, or glucuronic acid conjugates when added together.[80] Lower doses of quercetin are more methylated than higher doses in humans. Quercetin has a relatively long plasma half-life of 11-28 h, and a 50-mg dose would lead to concentrations of up to 1.5 μmol/L in plasma. Conjugates *in vitro* have quantitatively different properties and are generally less biologically active, compared with the aglycones.[80,83] As it is reported, the bioavailability issues may partially account for the lack of biological activity *in vivo*. Though, the lack of activity may reflect the short-term studies of quercetin and the selection of inappropriate biomarkers, in the study.[80]

In human intervention studies, catechins increased plasma antioxidant activity, as assessed with a variety of assays, decreased plasma lipid peroxide, increased plasma ascorbate concentrations, decreased non heme iron absorption, and increased the resistance of LDL to oxidation. In addition, the green tea catechins, including the galloylated catechins, increased fat oxidation and energy expenditure and decreased

the respiratory quotient and body weight. There were also recorded effects on vascular dilation.[84] It is worth noting that the amounts of catechins administered in various intervention studies varied among individuals and among different studies based on the dose and the duration.[84]

There have been major advances in the past few years in our knowledge regarding polyphenol absorption and metabolism, and it is apparent that most classes of polyphenols are sufficiently absorbed.[85,86] There are now intervention studies in the literature demonstrating significant biological effects of polyphenol consumption among humans, with the use of many different biomarkers.[87] Metabolites of flavanols in plasma were found at various concentrations and the time of urinary excretion was rather high due to the wide variability of flavanols.[58,80] As far as phenolic acids concern, their availability and absorption has been also investigated.[88,89] Chlorogenic acid and caffeic acid have been reported to prevent CVDs in several experimental studies on animal models.[90,91] The major representative of hydroxycinnamic acids in food is caffeic acid. It occurs largely conjugated with quinic acid. The biological properties of hydroxycinnamic acids depend on their absorption in the gut and on their metabolism. Hydroxycinnamic acids concentration found higher than that of hydroxybenzoic acids. The absorption of caffeic acid in the small intestine has been well characterized in both experimental animals and in humans.[90,91]

Concerning their consumption, hydroxycinnamic acids p rovide larger contributions to the total polyphenol intake than benzoic acid derivatives or flavonoids.[88] Coffee, one of the most widely consumed beverages in the world, is the major dietary source of chlorogenic acid. In some studies, chlorogenic acid has been detected in urine with a recovery varying from 0·3 to 2.3 %, suggesting absorption without structural modification.[91] Other authors have failed to detect chlorogenic acid in the plasma of both rats and humans after ingestion as a pure compound or in coffee.[92] Caffeic acid and its O-methylated metabolites are found in plasma and urine after ingestion of chlorogenic acid in rats and man, showing that chlorogenic acid is hydrolysed in the body.[90,91] The estimation is that bioavailability of chlorogenic acid is rather controversial. The bioavailability of ferulic acid is governed primarily by the food matrix than its metabolism in intestine and liver in rats.[92,93] Ingested caffeic acid was absorbed from the alimentary tract and was present in the rat blood circulation in the form of various metabolites. On the other hand, only traces of metabolites, supposedly caffeic and ferulic acids conjugates were detected in rat plasma for 6 h after chlorogenic acid administration. Chlorogenic acid and small amounts of caffeic acid were found in the small intestine for 6 h after chlorogenic acid administration. These results suggest that chlorogenic acid is not well absorbed from the digestive tract, unlike caffeic acid, and it is not metabolized to the easily absorbed forms.[90]

Platelet activation and cardiovascular diseases

Blood platelets play a crucial role in hemostasis, a process responsible for keeping the blood flowing in the circulatory system. Platelets are generated from megakaryocytes in bone narrow, with daily production providing 150-400 x 10^9 platelets per liter of blood.[94] The cells display a range of surface receptors and adhesion molecules, and contain numerous granules; these are used to initiate coagulation cascades in primary hemostasis, where blood platelets adhere to the extracellular matrix.[95] There are several articles and reviews highlighting the importance of dietary polyphenols in preventing cardiovascular diseases.[96,98]

Platelet activation can lead to the development of atherothrombotic diseases caused by aggregation and thrombus formation at the site of an atherosclerotic plaque rupture. The rupture of an atherosclerotic plaque results in the formation of a pathological arterial thrombus, leading to the exposure of highly reactive sub endothelial matrix proteins, such as collagen and vWF.[96] The above interaction is required for the initial adhesion of platelets to sub-endothelium. In arterial thrombosis, increased platelet activation can be measured indirectly, through quantification of activation markers on their cell surface. These platelet biomarkers are of great importance, as they may predict thrombotic situations. Among these, P-selectin (also known as CD62p), CD63, CD40L (also known as CD154), GPIIb/IIIA complex are well studied and extensively used.[4,99] P-selectin is an integrin belonging to heterodimeric trans membrane receptors, formed by noncovalent association of α and β chains and its main role is to meditate interactions with adhesion molecules on other cells and extracellular matrix molecules.[4,100] CD62P is found in the α-granules of platelets. CD63, moves from granules and lysosomes to the plasma membrane after platelet activation. CD40L also migrates to the platelet surface from a-granules, a similar manner to P-selectin. Platelet reactivity can be easily evaluated, recording CD62P levels on platelets stimulated by using classic agonists such as collagen and ADP. Estimation of surface-bound CD62P alone or/in combination with CD63 or CD40L, by flow cytometry analysis is also widely used for diagnosis of platelet activation state in ex vivo patient-derived samples.[100] Elevated levels of CD62-P were detected in several diseases such as peripheral artery and ischemic stroke.[101]

The protective effect through the inhibition of endothelium dysfunction has been also reported. [99,100] Arterial thrombosis is responsible for myocardial infraction and ischemic stroke, which are often treated pharmacologically with antiplatelet drugs.[103]

Cardiovascular diseases are related to alterations in metabolism.[103] Recent data have shown that

polyphenols interact directly with the activator site of both estrogen receptor- (ER-) α and ER-β, leading to eNOS activation and stimulation of NO production and endothelium-dependent vasorelaxation.[75] As polyphenols are known for their antioxidant, immunomodulatory and vasodilatory properties, an increased intake of such dietary antioxidants found to contribute to cardiovascular risk reduction, inhibit oxidation of human LDL, ultimately preventing atherosclerotic plaque formation. The mechanisms involved in the cardioprotective effects of phenolic compounds have been studied and reported in preclinical (*in vitro* and *in vivo*) and clinical studies. In this case, polyphenols are acting via inhibition of ROS production, mitochondrial dysfunction, apoptosis, NF-κB, p53, and DNA damage. As stated above, phenolic compounds are able to modulate some transcriptional factors (e.g. NF-κB) to regulate the expression of some pro inflammatory cytokines (IL-1β and TNF-α) and even enzymes iNOS and COX-2 that are present in inflammatory processes.[75]

Considering such mechanisms and their ability to inhibit ROS, the cardioprotective effects of phenolic compounds are due to their ability to improve endothelial dysfunction in CHD since it also increases the bioactivity of endothelial NO. Moreover, as it has been reported, flavonoids may reverse endothelial dysfunction in addition to lowering blood pressure. [102] From *in vitro* experiments is indicated that polyphenols reduce platelet NADPH oxidase activation, ROS formation, thromboxane formation, AA pathway, and platelet stimulation through PI3K/AKT.[104]

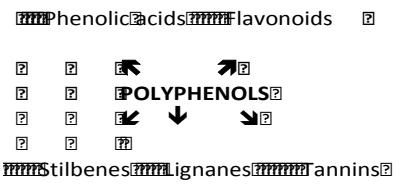
Flavonoids can regulate oxidative stress and inflammation, commonly cause vasodilation, and regulate endothelial cell apoptosis.[105] Recent studies have revealed that dietary flavonoid intake can effectively reduce the risk of cardiovascular death in adult Americans.[106] *In vitro* and in animal models, some flavonoids have vasodilatory effects, improve endothelial dysfunction and insulin resistance and exert antiplatelet aggregation and atherosclerotic protective effects, in addition to lowering blood pressure.[107] Isoflavones seem to protect against inflammatory vascular diseases by inhibiting monocyte-endothelial cell adhesion.[42,43] Quercetin exerts atheroprotective activity and cardioprotective effects against ischemia-reperfusion injury in the heart.[120] Chrysin has been reported to possess antiplatelet activity.[47] Anthocyanins reduce the risk of myocardial infarction in humans, improve systolic blood pressure, and reduce the content of triglycerides, total cholesterol, and low-density lipoprotein cholesterol. Anthocyanins prevent atherosclerosis by activating Nrf2-ARE, an indicator and modulator of redox.[107] Dasgupta and Milbrandt found that resveratrol targets and activates AMP-activated protein kinase, resulting in reduction of fat accumulation, and inflammatory cytokines.[108] AMPK plays a crucial role in controlling oxidative stress in ischemia-reperfusion, cardiac hypertrophy or atherosclerosis. Resveratrol could also stimulate SIRT1 enzyme at about 10-fold that plays a vital role in energy metabolism.[106] SIRT1 enzyme regulates a variety of cell functions, mainly mitochondrial function, by activating the transcriptional activity of peroxisome proliferator-activated receptor-gamma co activator- 1α and triggering the activation of AMPK.[107]

Stimulation of SIRT1 and AMPK boosts the eNOS activity in human coronary arterial endothelial cells and increases NO production and mitochondrial biogenesis. Subsequently, these trigger vasodilation and decrease atherosclerosis.[107] The role of dietary strawberry powder on vascular health in adolescent males has been also indicated.[108] Flavonoids from *Myrica rubra* exert cardioprotective effects by modulating the PI3K/Akt/GSK3β pathway to attenuate oxidative damage and cardiomyocyte apoptosis.[109] SIRT1 plays a key role in the regulation of many physiological functions, and its reduced expression often causes aging-related diseases such as myocardial hypertrophy, myocardial infarction, and endothelial dysfunction. Testai and coworkers found that the long-term administration of the citrus flavonoid naringenin at a dose of 100 mg/kg/day in mice resulted in enhanced expression of SIRT1 enzyme, reduced ROS production in myocardial tissue with significantly lower levels of the inflammatory markers TNF-α and IL6. This proposes that nutritional therapy with naringenin may help improve myocardial aging and protect cardiac function.[110] Flavonoid extracts from *Oxytropis falcata* protect against myocardial ischemia-reperfusion injury by down-regulating the ROS-mediated JNK/p38MAPK/NFκB pathway to regulate inflammatory responses, oxidative stress, and apoptosis.[111] The therapeutic potential of polyphenols in cardiovascular diseases by regulation of mTOR signaling pathway has been also reported.[112] mTOR is a serine/threonine-specific protein kinase which plays a central role in many physiological processes including cardiovascular diseases.

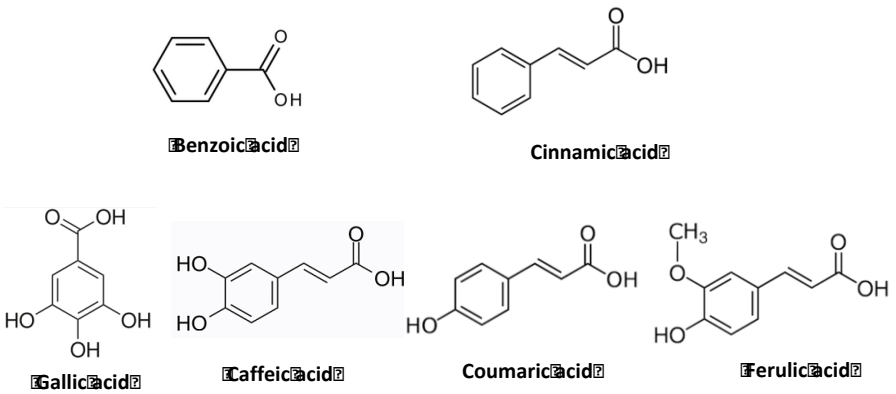
It was shown that different actions of flavonols on platelet activation depend on their binding ability to various receptors on blood platelets. However, the mechanism of their anti-platelet potential requires further additional studies, including in vitro and in vivo experiments.[37] *In vitro*, high doses of herbal compounds with antiplatelet activity would suppress platelet aggregation. On the contrary, low dose concentrations *in vivo* would have a minor effect. It was shown that phenolic compounds demonstrate a range of pro-health effects on the human body, including anti-inflammatory, antilipidemic, antiviral and antibacterial, hepatoprotective and cardioprotective properties. These properties allow them to be used as active ingredients in various nutraceutical, cosmetic and pharmaceutical preparations.[37] For example, they may inhibit P-selectin exposition, which has a crucial role in the connection of inflammation and hemostasis.[101] Experimental data related to the antiplatelet aggregation activity of dietary

polyphenols *in vivo* are scarce, and results are often conflicting. For example, Ostertag and his coworkers demonstrated in an *ex vivo* study, that phenolic compounds affect the collagen-induced platelet aggregation and thrombin receptor-activating peptide-induced P-selectin expression but only at very high non-physiologically attainable concentrations.[82] In streptozotocin-induced diabetic rats, Schmatz and coworkers also proved in an *ex vivo* study that moderate consumption of grape juice and red wine modulates the hydrolysis of the adenine nucleotides and decreases platelet aggregation.[104] The *in vitro* experiments for selective antiplatelet and anti-inflammatory activities of phenolic acids and flavonoids are numerous. On the contrary, there is limited *in vivo* evidence showing that polyphenols can inhibit platelet aggregation induced by common agonists.[74] There is no doubt that the *in vitro* data can be easily translated into the *in vivo* condition. Another issue that matters is the cytotoxicity effect that may have certain biologically active phenolics. It was recently reported that several extracts, as Goji berry, sea buckthorn berries and individual phenolic compounds were not toxic to mice fibroblast cells L929 only at low concentrations.[113] It is interesting, that a high percentage up to 50% of currently marketed drugs use natural products to alleviate or to cure diseases.[7,114] According to Liu, the beneficial effect of fruits and vegetables to human health is additive and synergistic of several phytochemicals.[115] This, further arises the question whether plant extracts or individual components should be used for the treatment of vasculatory or other related diseases?

Platelets have emerged as important markers for various types of diseases. They are multifunctional blood particles and now regarded to be very important clinical targets for many pathophysiology diseases. In addition to playing a central role in normal hemostasis and thrombosis, platelets can make important contributions to host inflammatory and immune responses to infection or injury. Platelets have profound roles not only in atherosclerosis cardiovascular diseases and inflammation but also in a number of other pathogenic processes. Neuro-degeneretavive diseases including Alzheimer's and Parkinson's diseases and tumor metastasis complete the above list.[116,117] Platelets also contribute to the immune response by modulating their surface protein profile and releasing pro- and anti-inflammatory mediators.[116] In Alzheimer's disease, increased levels of platelet amyloid precursor protein raise the production of amyloid-beta peptides promoting platelet activation, triggering at the same time amyloid-beta fibrillation. In Parkinson's disease, increased platelet α-synuclein is associated with elevated ROS production and mitochondrial dysfunction.[118,119]



Scheme 1: Classification of polyphenols.



Scheme 2: Chemical structure of common phenolic acids.

Flavonols Flavonones Isoflavones

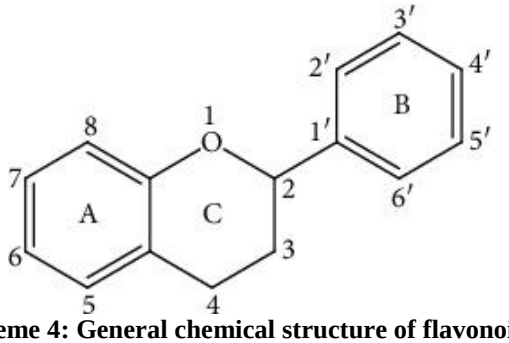
↖ ↑ ↗

Flavonoids

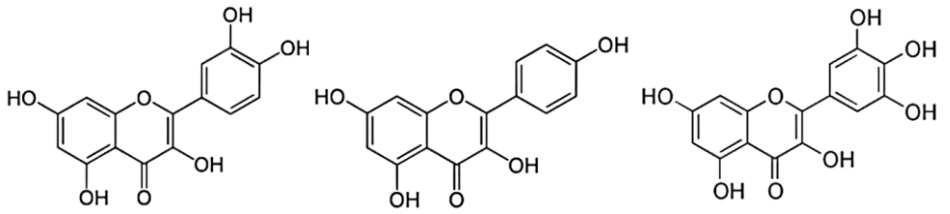
↙ ↓ ↘

Flavones Flavanols Anthocyanins

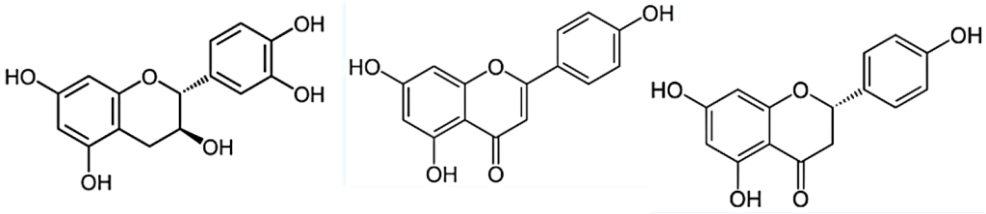
Scheme 3: Classification of flavonoids.



Scheme 4: General chemical structure of flavonoids.



Quercetin **Kaempferol** **Myricetin**



Catechin **Apigenin** **Naringenin**

Scheme 5: Chemical structure of common flavonoids.

CONCLUSION

Currently antithrombotic drugs used to protect affected individuals against ischemic stroke demonstrate significant limitations. Platelet inhibitors possess only moderate efficacy, while thrombolytics and anticoagulants significantly increase hemorrhage. In this sense, new approaches are currently under consideration to develop next-generation antithrombotics with improved efficacy and more personalized and targeted application. For decades, plant polyphenols, especially flavonoids, were known for their vital role in preventing various diseases. Mitigating excessive oxidative stress caused by reactive oxygen species with anti-oxidant-rich flavonoids may reduce the risk of hyper-activation of platelets, cardiovascular diseases, pain, and thrombosis. Furthermore, flavonoids mitigate endothelial dysfunction, which generally correlates to the development of coronary artery and vascular diseases. Flavonoids also reduce the risk of atherosclerosis and atherothrombotic disease by inhibiting excessive tissue factor availability in the endothelium.

Although the role of flavonoids in cardiovascular diseases is profound, to the best of our knowledge, their role as anti-thrombotic agents has not been sufficiently documented. Despite the numerous molecules from natural resources with potential bioactivity that introduced every day only a few have been adequately evaluated for their suitability for use as drugs. Reviewing mostly recent published research articles and reviews we may come to some interesting conclusions

1. Polyphenols are the major natural compounds involved in the inhibition of platelet aggregation and inflammation.

2. Their positive effect though depends on many factors as dosage, duration time, and route of administration.
3. Dosage is very important since phenolic compounds may be toxic at the concentrations where they exert the specific biological effect.
4. The knowledge about their efficacy and bioavailability is based on a small number of flavonoids examined either in extracts or as individual components.
5. Most flavonoids are sufficiently absorbed to have the potential to exert biological effects and this is very depended of the type of polyphenol.
6. Moving from *in vitro* to *in vivo* experiments due to different environment and possible interactions with other anticoagulants and antiplatelet drugs, adverse effects may be recorded.
7. Different actions of flavonoids on platelet activation may also depend on their binding ability to various receptors on blood platelets. Such interactions, including mechanism of inhibition of the synthesis of thromboxane or COX activity, may increase the risk of bleeding in such patients.
8. Certain phenolic extracts rather than isolated compounds may replace synthetic antiplatelet and anticoagulant drugs. Since many plant products interact with antithrombotic drugs in a synergistic manner their role may be complementary.
9. More animal studies, long-lasting intervention studies in humans, pre-clinical and toxicological studies with certain biologically active phenols should be designed and performed to ensure their applicability and efficacy as antiplatelet drugs.

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