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NEW APPROACHES OF ANTIPLATELET THERAPY IN THE PREVENTION OF CARDIOVASCULAR DISEASES

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ABSTRACT

Cardiovascular diseases are considered to be the leading cause of mortality in the world. Modifiable and non modifiable risk factors with different mechanisms affect the endothelial cells and lead to development of endothelial dysfunction. Endothelial dysfunction as a cornerstone of cardiovascular diseases' pathophysiological mechanisms, causes overactivation and over aggregation of platelets resulting in the development of ischemic complications.Though we have huge arsenal of antiplatelet and anticoagulant drugs used for prevention and treatment of ischemic consequences, there is an increase of annual cases of side effects associated with pharmacotherapy.The "gold standard" of antiplatelet therapy - Aspirin gradually loses its role and importance in the primary and secondary prevention, as well as at the treatment of cardiovascular diseases due to the haemorrhage mostly on those patients who are under 70, have diabetes or are in the low and mild risk group of cardiovascular disease.That is why the development of newer and safer substances with possible less hemorrhagic complications has become an important task of modern medicine.In this point of view the plant based agents, containing rich composition of polyphenolic substances, particularly anthocyanins and flavonoids, could serve as potent and promising sources due to their antiplatelet effects, which is conditioned with several action mechanisms.Each action mechanism of polyphenolic substances is directed to the different phases of platelet aggregation. In this paper we have discussed the mechanisms and side effects of antiplatelet drugs with proven activity, the plants as a source for developing new and safe antiplatelet dosage forms and the technological ways to develop optimal drug dosage forms.

KEYWORDS: *cardiovascular diseases, antiplatelet therapy, anthocyanins, flavonoids*

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of global mortality and morbidity and 85% of deaths are due to ischemic heart diseases and cerebrovascular diseases [*Kim H C, 2021*].Though the antiplatelet and anticoagulant drugs show high effectiveness for prevention and treatment of CVDs, the fast increase of pharmacotherapy associated with complications especially haemorrhage in case of chronic usage, continues to be a problem and promotes the development of new and safer drugs [*Jourdi G et al., 2021*].

The importance of antiplatelet and anticoagulant drugs in the treatment of CVDs is dictated by activation of platelets during CVDs after endothelial dysfunction, which is the cornerstone of ischemic disorders [*Sun H J et al., 2020; Xu S et al., 2021*].

Antiplatelet drugs inhibiting platelet aggregation, mostly affect the process of primary hemostasis, whereas the group of anticoagulant drugs has a purpose to inhibit coagulation factors [*Jhansi K Vanita P et al., 2014*].

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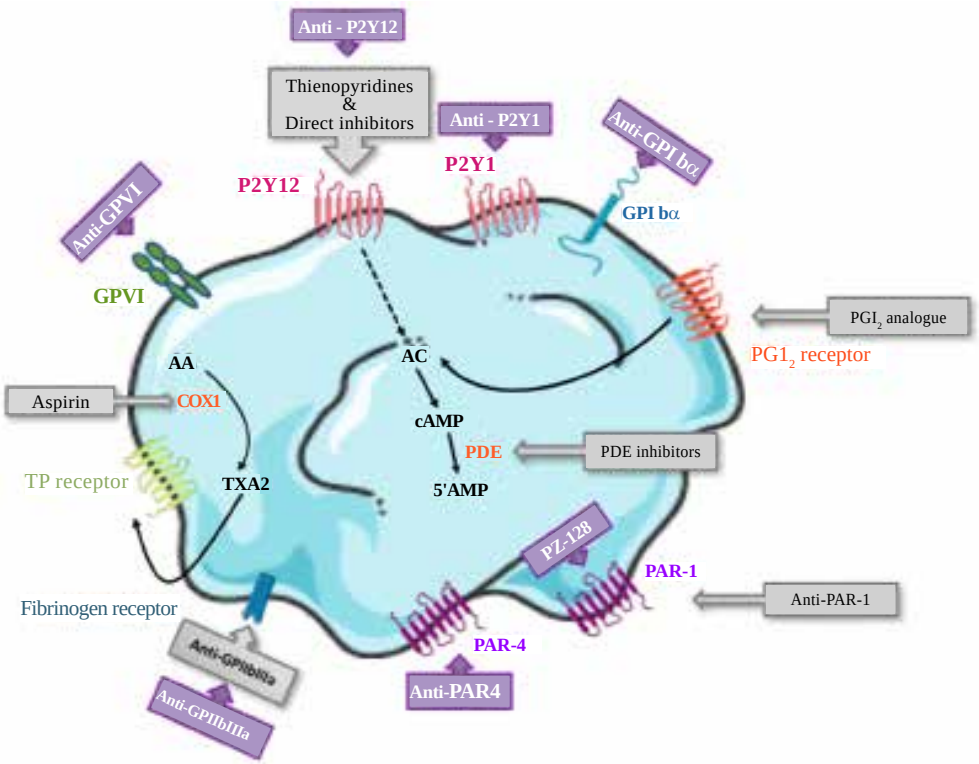

FIGURE 1. *Pharmacological targets of current and emerging antiplatelet therapies [Jourdi G et al., 2021]*

Antiplatelet drugs include COX-1 inhibitors, Phosphodiesterase (PDE) inhibitors, adenosine diphosphate (ADP) receptors blockers, GPIIb/IIIa receptors blockers, TxA_2 inhibitors, PgI_2 analogues, PAR-1 receptors blockers of thrombin.Drugs include COX-1 inhibitor (Aspirin), ADP P_2Y_{12}-receptors blockers (Clopidogrel, Prasugrel, Ticagrelor, Cangrelor), GPIIb/IIIa receptors blockers (Abciximab, Eptifibatide, Tirofibane) and the newest drug PAR-1 antagonist (Vorapaxar) [*Smith J et al.,2018*]. Figure 1. displays possible ways of pharmacological intervention of antiplatelet therapy.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Low doses of Aspirin are the "gold standard" of antiplatelet therapy.Irreversibly inhibiting the COX-1 enzyme, Aspirin inhibits the formation of endoperoxides and TxA_2 production.As it is known TxA_2 has pivotal role in aggregation processes, that is why Aspirin impairs the process of primary hemostasis [*Hybiak J et al., 2020*]. But the side effects limit the usage of this agent. It is estimated that 2–57% of Aspirin users exhibit a suboptimal response to this compound. Consequently, a proportion of individuals do not respond to the action of this drug and may suffer recurrent thromboembolic vascular events [*Ferreira M et al., 2020; Paven E et al., 2020]*. Vice versa, it can cause bleeding from the GIT, due to inhibiting the synthesis of protecting prostaglandins, and also intracranial or subarachnoid haemorrhages [*De Berardis G et al., 2012; García Rodríguez L et al., 2016*].

ADP receptor blockers (Clopidogrel, Prasugrel, Cangrelor) irreversibly or reversibly (Ticagrelor) block the $P2Y_{12}$ receptors of ADP [*De Luca L et al., 2021; Avecilla, S T, 2019*].The action mechanism of these drugs is to impair the mobilisation of Ca^{2+} and the activation of IIb/IIIa receptors.By the way, Ticagrelor compared to Prasugrel has more effects.This is conditioned with the fact that Ticagrelor is not a prodrug, that is why the effect development time is shorter and does not depend on the biotransformation processes.Ticagrelor and prasugrel have proven superior to clopidogrel in reducing the risk of major adverse cardiac events, but at the expense of a higher bleeding rate [*Venet-*

sanos D et al., 2021] Additionally, Ticagrelor inhibits adenosine reuptake via the ENT-1 transporter in erythrocytes and platelets, which may improve its antiplatelet effect [*Franchi F et al., 2015*].The mentioned compounds also are not deprived of side effects, especially bleeding.

Abciximab, Eptifibatide and Tirofiban are ligand-mimic molecules.They block IIb/IIIa receptors and inhibit platelet aggregation associated with fibrinogen.Abciximab is a monoclonal chimeric antibody, has short $T_{1/2}$.Eptifibatide is a cyclic heptapeptide, but Tirofiban is not a peptide.These drugs are mostly used i/v, but their usage is limited due to hemorrhagic events [*Wilson R E, Ziada K M, 2019*].

PDE inhibitors increase intracellular levels of cAMP, which induces the production of prostacyclin. Besides inhibiting PDE, Dipyridamole also inhibits the uptake of adenosine, thus potentiates its action.As we know, adenosine is a vasodilator, that is why patients, who have atherosclerotically changed coronary arteries, are in the risk of having "steal phenomenon''. Also it is important to mention, that monotherapy with Dipyridamole shows less effectiveness compared to Aspirin monotherapy, that is why nowadays Dipyridamole is mostly combined with Aspirin or with Clopidogrel [*Bieber M et al., 2019*].Cilostazol, like Dypiridamole, also possesses a vasodilatory effect, but it induces vascular smooth muscle cell relaxation via PKA-mediated inhibition of myosin light-chain kinase and activation of calcium-activated potassium channels, thus improves endothelial function by decreasing the endothelial oxidative stress via the suppression of nicotinamide adenine dinucleotide phosphate oxidase (NoX)-2 expression [*Jourdi G et al., 2021*].

The use of TxA_2-receptor blockers and PGI_2-analogues is limited in clinical practice due to their side effects obtained in preclinical trials [*Rogula S P et al., 2021*] .

Vorapaxar is an oral PAR-1 reversible antagonist.This drug has been obtained from a natural product, himbacine.In 2014 the Food and Drug Administration approved this antiplatelet drug and it is the last antiplatelet drug discovered recently. This drug is mostly used for the reduction of thrombotic cardiovascular events in patients with a history of heart attack or with peripheral artery disease (PAD). Unfortunately Vorapaxar has not gained the European Medicines Agency approval yet[*Gryka R J et al., 2017; Magnani G et al., 2015*].

The group of anticoagulant drugs includes low and high weight heparins, direct and indirect inhibitors of Xa factor, direct inhibitors of thrombin, and indirect anticoagulant epoxide reductase enzyme inhibitor-Warfarin [*Vene N, Mavri A, 2018; Chen A et al., 2020*].

Thus, it is obvious that during the last decades a wide range of antiplatelet and anticoagulant drugs was discovered and developed, but because of the side effects including resistance development, genetic enzymopathies reducing the effectiveness of antiplatelet drugs [*Mărginean A et al., 2016; Zhang L et al., 2022*] outweigh their benefits, they need very accurate prescriptions that is why the necessity to look for a new approach in antiplatelet therapy remains the pending task of European Society of Cardiologists (ESC).So in order to prevent and treat ischemic diseases ESC does not recommend to prescribe Aspirin to low and mild rate risk patients, diabetic patients, those who are over 70, as well as to those who don't have any clinical sign of CVD, because bleeding disorders caused by Aspirin lead to the development of hemorrhagic stroke which is as much serious as ischemic diseases [*Timmis A et al., 2022*].

In a search for safe and effective agents the attention of investigators was directed to the plant based substances showing a great interest for a wide range of pharmacological activities [*Mathur S, Hoskins C, 2017; Albadawi DA et al., 2022*]. Especially high antiplatelet activity was more manifested for polyphenolic substances [*Ed Nignpense B et al., 2019; Sharifi-Rad J et al., 2021*].

Polyphenolic substances have an important role in the growth, pollination and adaptation processes of plants [*Santhakumar A B et al., 2013*]. From the pharmacological point of view, flavonoids and anthocyanins are the most common polyphenolic substances and their biological activity depends on their chemical structure, which greatly varies from substance to substance, that is why the expressiveness of effects differ [*Hanuka Katz I et al., 2020*].

Anthocyanins are one of the water-soluble flavonoids classes widely present in fruits and vegetables. Dietary sources of anthocyanins include red and purple berries, grapes, apples, plums, cabbage,

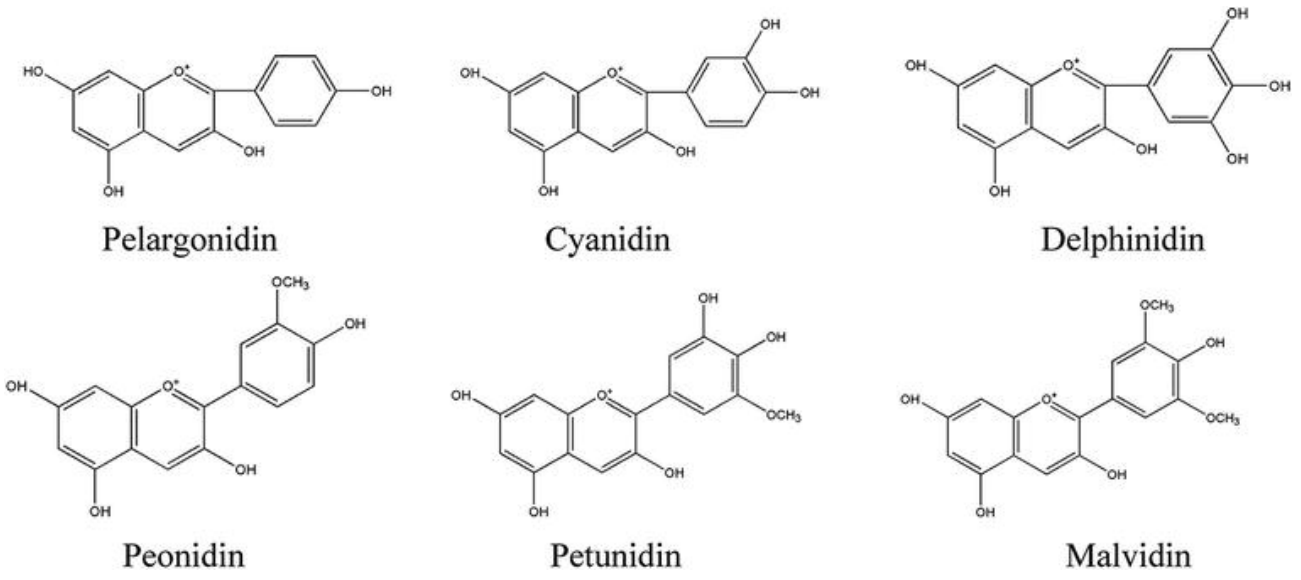

FIGURE 2. *Chemical structure of main anthocyanins [Martín J et al., 2017]*

or foods containing high levels of natural colourants [*Mattioli R et al., 2020*]. Anthocyanins are glucosides of anthocyanidins, flavonoid derivatives, produced via the phenylpropanoid pathway. They are present in all tissues of higher plants, including leaves, stems, roots, flowers and fruits and provide a specific colour of the plant. The six predominant anthocyanidins found in foods are: cyanidin, delphinidin, pelargonidin, peonidin, petunidin, and malvidin (Fig. 2) [*Salehi B et al., 2020]*.

Flavonoids are a group of natural compounds with variable phenolic structures, first substances which were isolated from oranges. Firstly it was believed that flavonoids were a new group of vitamins, and was given the name vitamin P, but lately it became clear that these substances were the group of flavonoids (rutin), and till now about 4000 and more flavonoids have been identified [*Kaurinovic B, Vastag D, 2019*].

Chemically flavonoids are based upon a fifteen-carbon skeleton consisting of two benzene rings (A and B) as shown in Fig. 3. [*Kumar S, Pandey A K, 2013*] linked via a heterocyclic pyran ring (C). They can be divided into a variety of classes such as flavones (e.g., flavone, apigenin, and luteolin), flavonols (e.g., quercetin, kaempferol, myricetin, and fisetin), flavanones (e.g., flavanone, hesperetin, and naringenin), and others. These classes of flavonoids differ in the level of oxidation and pattern of substitution of the C ring, while individual compounds within a class differ in the pattern of substitution of the A and B rings. Flavonoids occur as aglycones, glycosides, and methylated derivatives. The basic flavonoid structure is aglycone (Figure 3**)**. Six-member ring condensed with the benzene ring is either a α-pyrone (flavanones) or its dihydro derivative (flavonols). The position of the benzenoid substituent divides the flavonoid class into flavonoids (2-position) and isoflavonoids (3-position). Flavonols differ from flavanones by hydroxyl group at the 3rd position and a C2–C3 double bond. Flavonoids are often hydroxylated in positions 3, 5, 7, 2, 3' , 4', and 5'. Methyl ethers and acetyl esters of the alcohol group are known to occur in nature [*Kumar S, Pandey A K, 2013*]. The most common glycosylation site is position 3 where glucose is usually found as single sugar, especially for cyanidin. In some cases, an additional glucose may be attached in position 5, more often seen for peonidin, pelargonidin and delphinidin. Other sugars bound in position 3 were described in some studies, such as galactose and arabinose, as well as complex oligosaccharides such as rutinose, sophorose and sambubi-

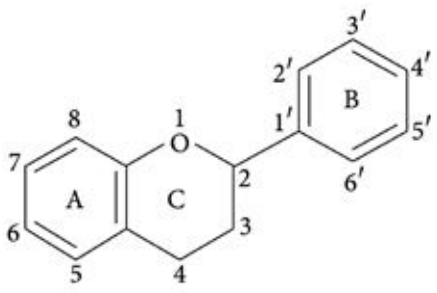

FIGURE 3. *Flavonoids' basic structure* [*Kumar S, Pandey A K, 2013*]

ose. They are commonly found in berries, especially strawberries and blueberries, red grapes, apples and pears, plums, sweet and sour cherries, nectarines, peaches, pomegranate, avocados, bananas, nuts (almonds, hazelnuts, pistachio, pecan nuts), black rice, purple corn, beans, cabbage, beets and onions, red and black carrots, purple sweet potato, beans, pepper, black olives, and fruit-derived products like red wine, juices, jam, and marmalade. During berry ripening, anthocyanin content rises [*Mozos I et al 2021*].Some investigations indicate sour cherry which according to some authors' observations could be a very promising substance for developing new drugs with various pharmacological activity [*Kelley D et al., 2018*].

According to the structures presented above, flavonoids were investigated for their anti-inflammatory, analgesic and cerebrovascular activity. It has been demonstrated that flavonoids decrease the level of reactive oxygen species (ROS) preventing endothelial dysfunction and changing the molecular pathways underpin the pathogenesis of CVDs [*Kattoor A J, 2017; Alotaibi B et al., 2021*]. Also the role of flavonoids is very important in preventing the consequences of sedentary lifestyle, smoking, obesity, poor diet and other modifiable risk factors of cardiovascular diseases as they lead to development of proinflammatory state. In this state endothelial cells may release various cytokines, chemokines, and growth factors that promote the proliferation, migration, and permeability of endothelial cells.These processes initiate the inflammation processes of the vessel walls and cause endothelial dysfunction [*Nguyen H C et al., 2020, Yamagata K, Yamori Y, 2020*].

Health benefits of polyphenols also have been linked to their well-established powerful antioxidant activity [*Lv Q et al., 2021; Hu W et al., 2022*].

From the point of view of the structure-activity relationship, the hydroxyflavones are more effective than their corresponding methoxyflavones, considering that the hydroxyl group position also influences platelet function. As it is known methylation changes the electrical charge of the flavonoid and so decreases the action on TXA_2 receptors [*Ravishankar D et al., 2018*].Glycosylation also decreases the activity of flavonoids and complicates the binding process of flavonoids platelets due to enlargement of the molecule size. The double bond in C2–C3 and/or 4-C=O in the C-ring of flavonoids has also a key importance for the antiplatelet activities. It was also observed that not only the phenyl group of a B ring plays a critical role in antiplatelet activity, but the heteroatoms of the B ring also largely influence this activity [*Salehi B et al., 2020*].

Most active flavonoids possess hydroxyl groups at position 6. Catechins are the most potent class of flavonoids, while isoflavonoids show the lowest antiplatelet activity [*Sharifi-Rad J. et al., 2021*].

The mechanisms of antiplatelet action of individual flavonoids have been studied and include: bilayer function change, change in ROS concentrations and oxidative stress, change of intracellular Ca^{2+} concentration, inhibition of enzymes (phospholipase C, cAMP phosphodiesterase, cyclooxygenase, thromboxane A_2 synthase) [*Bojić M et al., 2019; Masselli E, 2020*].

Experiments on flavonoids, anthocyanins and their antiplatelet effects, show that most of the flavonoids inhibit platelet aggregation through the inhibiting COX-1 enzyme. It's fact that mostly non-glycosylated flavonoids have more affinity toward COX- 1 enzyme.Only hidrosmin shows high affinity toward COX-1 enzyme in glycosylated form [*Zaragozá C et al., 2022*].

Recent investigations demonstrate that such plants as tomato, pomegranate, apple, orange, berries can inhibit platelet aggregation.Currently the soluble extract of tomato, which is known as FRUITFLOW® (Provexis, UK) is widely used in Europe, as a "safest antiplatelet agent'' [*O'Kennedy N et al., 2016*]. Some literature sources evidence that apple and its enzymated forms due to inhibiting PAF and ADP are potential sources of antiplatelet drugs [*Tsoupras A et al., 2021*].Pomegranate inhibits platelet aggregation via antioxidant and anti-inflammatory properties [*Riaz A, Khan R A, 2016*]. Daily consumption of 70 *mg/kg* strawberries can also inhibit thrombin induced platelet aggregation [*Alarcón M et al., 2014*].Berries inhibit platelet aggregation by blocking P-selectin in ADP-stimulated platelet aggregation [*Aboonabi A et al., 2020*].

Not only the above-mentioned plants, but also different fruits, vegetables and medicinal herbs have large amounts of anti-platelet substances, but unfortunately there is no evidence based data insisting on their antiplatelet activity.

Based on experiments on antiplatelet effects of anthocyanins it becomes clear that pure anthocyanins compared with the anthocyanins contained in the plants show less antiplatelet and other pharmacological effects. All these things are conditioned with the pharmacokinetic properties of anthocyanins [*Mattioli R et al 2020*].

It can certainly be argued that plant based antiplatelet agents are the drugs of the future, but considering that polyphenolic substances, particularly anthocyanins become inactive in high temperature, environmental pH changes, under the sunlight, it becomes clear that not only the amount of the anthocyanins in the plant is important, but also it is important to find optimal technological ways of developing new drugs.

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