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REVIEW

Role of flavonoids in thrombotic, cardiovascular, and inflammatory diseases

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Abstract

The failure of mechanisms of natural anti-coagulation either due to genetic impairment or due to severe external injuries may result in a condition called thrombosis. This is believed to be the primary cause for a variety of life-threatening conditions such as: heart attack, stroke, pulmonary embolism, thrombophlebitis, and deep venous thrombosis (DVT). The growing number of these incidents requires an alternative anti-coagulant or anti-thrombotic agent that has minimal side effects and improved efficiency. For decades, plant polyphenols, especially flavonoids, were known for their vital role in preventing various diseases such as cancer. Mitigating excessive oxidative stress caused by reactive oxygen species (ROS) with anti-oxidant-rich flavonoids may reduce the risk of hyper-activation of platelets, cardiovascular diseases (CVD), pain, and thrombosis. Furthermore, flavonoids may mitigate endothelial dysfunction (ED), 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 (TF) availability in the endothelium. Although the role of flavonoids in CVD is widely discussed, to the best of our knowledge, their role as anti-thrombotic lead has not been discussed. This review aims to focus on the biological uses of dietary flavonoids and their role in the treatment of various coagulation disorders, and may provide some potential lead to the drug discovery process in this area.

Keywords Flavonoids · Thrombosis · Cardiovascular diseases · Reactive oxygen species · Tissue factor

Abbreviations

AA	Arachidonic acid
ACS	Acute coronary syndrome
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
CEP 350	Centrosome-associated protein 350
COX-1	Cyclooxygenase-1
CVD	Cardiovascular diseases
DNBS	Dinitrobenzene sulfonic acid
DVT	Deep venous thrombosis
ED	Endothelial dysfunction
HNE	4-Hydroxy-2-nonenal
MAPKs	Mitogen-activated protein kinases
NAC	*N*-acetylcysteine
NO	Nitric oxide
PMQ	Pentamethylquercetin
PON2	Protein paraoxonase 2
PT	Prothrombin time
ROS	Reactive oxygen species
SNI	Spared nerve injury
SOD	Superoxide dismutase
TBARS	Thio-barbituric acid reactive species
TF	Tissue factor
TiO_2	Titanium dioxide
TxA_2	Thromboxane A2
VTE	Venous thromboembolism

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Introduction

Thrombosis, one of the leading causes of morbidity and mortality all over the world, is defined as the formation of blood clot within the blood vessel that leads to reduced blood flow (Mackman 2012; Wendelboe and Raskob 2016). The formation of clot may lead to myocardial infarction, stroke, or deep vein thrombosis (DVT) depending upon the vessel and the organ affected. Hemostasis is a physiological process that ensures proper repairing of injured blood vessels by the formation of physiological thrombus to limit bleeding (Gale 2011). This process comprised of platelet aggregation, coagulation, and associated fibrinolysis (Chen et al. 2015a). A balance between procoagulant and anti-coagulant systems is essential to maintain hemostasis that will ensure the formation of physiological clot when needed. Imbalance between these systems will result in different pathological conditions characterized by bleeding or thrombosis (Gale 2011). This condition characterized by excessive thrombus formation will lead to partial or total blockage of blood vessels (Furie and Furie 2008). Thrombosis can be initiated in the arteries causing coronary myocardial infarction, ischemic stroke, mesenteric artery embolism, and limb arterial thrombosis. It can also be initiated in the venous system causing venous thromboembolism (VTE) (Prandoni 2009).

Oxidative stress and thrombosis

Various kinds of stress and pathological conditions may lead to thrombosis, one of them being oxidative stress (Dong et al. 2015; Förstermann et al. 2017). Oxidative stress is defined as the imbalance between the generation of reactive oxygen species (ROS) and anti-oxidative defense of the biological system (Betteridge 2000). ROS, a collective term used for both oxygen radicals and certain non-radical oxidizing agents such as hydrogen peroxide, are generated in the cells during regular biological processes such as mitochondrial electron transport chain, signal transduction, gene regulation, and also during antimicrobial activity (Sugamura and Keaney 2011). However, an aberrantly elevated level of ROS leads to oxidative stress-induced pathological conditions such as neurodegeneration, cancer, atherosclerosis, sepsis, diabetes, as well as aging. There are various emerging reports that demonstrate the role of oxidative stress in the development of thrombotic complications (Madamanchi et al. 2005; Reuter et al. 2010). Thrombus formation could be a result of platelet activation or activation of other prothrombotic proteins. The role of platelets has emerged as one of the major causes of thrombosis under oxidative stress. Strong evidence of data in literature illustrates the various mechanisms involved in platelet-induced thrombosis (Violi and Pignatelli 2012). The activation of platelets is associated with redox changes and the generation of ROS (Freedman 2008). However, in addition, elevated levels of oxidative stress leads to the prothrombotic transformation leading to thrombus formation. Studies on isolated human platelets have shown that superoxide increases platelet aggregation (Handin et al. 1977). In another study, Begonja et al. showed that inhibition of platelet-dependent ROS using NAD(P)H oxidase inhibitors and superoxide scavengers also reduced platelet aggregation and thrombus formation (Begonja et al. 2005).

Furthermore, it has been hypothesized that tissue factor (TF) can also serve as a trigger for thrombosis. TF is a transmembrane glycoprotein that initiates the extrinsic pathway of blood coagulation and has been speculated to be involved in some form of VTE (Giesen et al. 1999). For the earlier discoveries made to test this hypothesis, please refer to the excellent review by Mackman (2012). Here, we will highlight the recent discoveries made on this proposal that have not been discussed elsewhere. In general, TF is expressed in the extravascular cells sequestered from the blood and other clotting factors including its ligand, factor (F) VIIa. However, several infections lead to the expression of TF on the surface of the immune cells such as monocytes, macrophages as well as endothelium and microvesicles. A mere expression of TF on the cell surfaces, however, may not be sufficient to induce the clot formation (Ansari et al. 2017). Various mechanisms operate to transform these less thrombotic TFs into highly procoagulant TF, a process called decryption (Rao et al. 2012). One such factor is oxidative stress that has recently been shown to transform the inactive TF into active TF (Vatsyayan et al. 2013). Induction of oxidative stress by the lipid peroxidation product, 4-hydroxy-2-nonenal (HNE) has recently been shown to transform cryptic TF into procoagulant TF on the surface of blood-derived macrophages and the monocytic cell line, THP-1 (Ansari et al. 2017). It has been further shown that deficiency of the anti-oxidative protein paraoxonase 2 (PON2) leads to increased oxidative stress and endothelial dysfunction in mice. These PON2 knockout mice exhibited reduced coagulation times and increased platelet activity compared to wild-type mice. These coagulation related abnormalities were diminished upon treatment with the anti-oxidant *N*-acetylcysteine (NAC) or anti-TF antibody, suggesting a critical role of oxidative stress and TF in systemic coagulation activation (Ebert et al. 2018).

Therefore, several mechanisms have been documented and are still emerging that demonstrates the critical role of oxidative stress in promoting thrombotic complications. Platelets or other prothrombotic proteins that play pivotal roles in regulating hemostasis have been shown as one of the

key targets of oxidative stress. Therefore, measures to prevent elevated levels of oxidative stress via different chemical or naturally occurring compounds could serve as a major therapeutic strategy for the treatment of thrombotic complications (Phang et al. 2011).

Flavonoids in thrombotic diseases

In recent years, a plethora of research has been carried out to develop an efficient promising therapeutic compound for effective anti-thrombotic/anti-platelet treatments. The use of existing medications is limited by their side effects and efficacy in some patients (Çakarer et al. 2013). As a result, efforts are directed to study and discover natural compounds with anti-thrombotic effect. Amongst these, plant flavonoids received huge attention not only to being developed and used as an effective regimen against various disease conditions as anti-thrombotic agents, but also to maintain a healthy life and to prevent cancer (George et al. 2017; George and Rupasinghe 2017).

A few studies have been conducted to investigate the anti-thrombotic effects of different flavonoids. A flavone derivative, known as pentamethylquercetin (PMQ), a polymethoxylated version of quercetin, inhibits the thrombus formation in mice that have acute pulmonary thrombosis, resulting in survival of 90% of the mice compare to the control group (Liang et al. 2015). In addition to that, PMQ significantly improves the blood flow of the mice suffering from an injury to the carotid artery, further indicating its inhibiting effect on thrombus formation. In another study, pycnogenol (antioxidant extracted from *Pinus pinaster*) was studied against the risk of DVT and thrombophelibitis conditions and found with improved effects when compared to a control group (Belcaro et al. 2004). Furthermore, Ryu et al. evaluated the anti-thrombotic effects of Persimmon leaf extract and its major flavonoid constituents (catechin, epicatechin, and epicatechin gallate) through an in vitro monitoring of activated partial thromboplastin time (aPTT), the prothrombin time (PT), and the platelet aggregation. It was found that the extract and its major components were able to prolong aPTT and PT, indicating anti-coagulant effects. Furthermore, it was concluded that the extract and major flavonoids inhibit platelet aggregation by inducing arachidonic acid (AA), ADP, and collagen levels (Ryu et al. 2015). This result is consistent with a recent study that confirms the effect of propolis and its major flavonoids (caffeic acid, phenethyl ester, galangin, apigenin, quercetin, kaempferol, and ferulic acid) on inhibiting platelet aggregation. Moreover, propolis and its major flavonoids inhibited the platelet aggregation in a dose-dependent manner leading to the inhibition of thrombus formation (Zhang et al. 2017). Furthermore, nobiletin, a bioactive polymethoxylated flavone isolated from citrus fruits, inhibits the activation of platelets by inhibiting PLCγ2/PKC cascade and formation of hydroxyl radicals by suppressing Akt and mitogen activated protein kinases (MAPKs) activation. This in turn was found to reduce the calcium [Ca^{2+}] levels and ultimately inhibited the aggregation of platelets. This finding suggested that nobiletin can be a potential therapeutic agent in preventing or treating thromboembolic disorders (Lu et al. 2016).

Among the flavonoids, isoflavonoids also have vital role to play as anti-platelet agents. Studies on isoflavonoids (genistein and daidzein) revealed potential to act as cyclooxygenase-1 inhibitors as well as functional antagonists at thromboxane A2 receptors (TxA_2), affecting the AA-based platelet aggregation cascade. The blocking of COX-1 by these isoflavonoids was comparable to acetylsalicylic acid (ASA) effect and hence may have a positive inhibitory effect on the aggregation of human platelets, and on cardiovascular diseases (CVDs) associated with enhanced platelet activity (Karlíčková et al. 2016). Similarly, the anti-thrombotic effect of diosmin extracted from *Galium verum* was studied by Cheng et al. and found that it could well modulate the uneven spindle assembly formation by regulating a centrosome-associated protein 350 (CEP 350) and thereby bringing improvement in venous thrombosis condition (Cheng et al. 2017). Furthermore, flavonolignans (silybin and silychristin) showed preventive primary and secondary thrombotic events, mainly acute coronary syndrome (ACS), wherein the excessive blood platelets respond to a physiological agonists by inhibiting its aggregation (Bijak et al. 2018).

In addition, a few studies demonstrated the TF inhibitory effects of flavonoids from the fruits of *Chaenomeles sinensis* (Lee et al. 2002). Polyphenols such as resveratrol, green tea catechins, and quercetin are also found to inhibit lipopolysaccharide-induced TF procoagulant activity in peripheral blood mononuclear cells (Kaur et al. 2007). These studies implicated that the flavonoids can prevent thrombotic diseases by various mechanisms (Fig. 1).

Flavonoids in cardiovascular diseases

Disorders in the blood vessels and the heart contribute to one of the major health problems faced by humanity. CVDs are a collection of diseases some of which includes heart attack, stroke, and hypertension. Despite several medical and pharmacological advancements in the last decade, many patients with CVD reach the final stages of the disease and eventually end up with heart attack or heart failure. While there have been many presumed mechanisms of action explaining the possible cardiovascular protective interactions between the cardiovascular system and flavonoids, that exert anti-oxidant, anti-inflammatory, anti-platelet aggregation as well as recovery of endothelial functions, the exact effect and mode

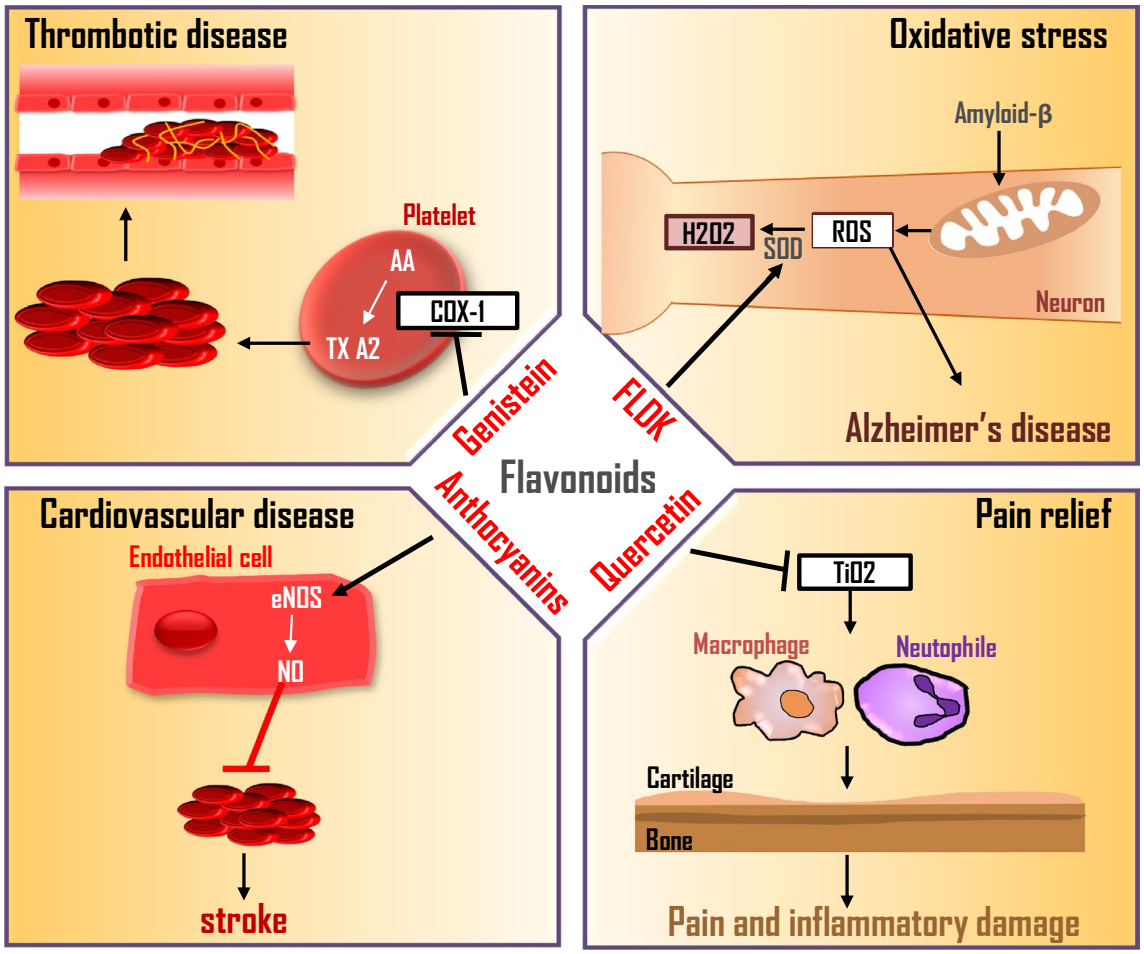

Fig. 1 Flavonoids impact on thrombosis, cardiovascular diseases, pain and oxidative stress: Flavonoids and/or isoflavonoids such as genistein have protective role against thrombotic diseases. Pycnogenol has strong anti-oxidant effect to inhibit thrombosis, while genistein acts as a cyclooxygenase-1 (COX-1) inhibitor to block the formation of thromboxane A2 (TxA_2) and subsequently prevent platelet aggregation. In cardiovascular diseases, anthocyanins regulate nitric oxide (NO) levels derived from endothelial cells and thus may reduce the chance of stroke. Flavonoids like quercetin reduces the inflammatory damages and pain associated with chronic arthritis through inhibiting titanium dioxide (TiO_2), which induces the recruitment of macrophages and neutrophils. Flavonoid extract from *Diospyros kaki* (FLDK) has a protective effect against Alzheimer's diseases. FLDK restores the activities of anti-oxidant enzymes such as superoxide dismutase (SOD) resulting in lowering the level of ROS and subsequent reduction in oxidative stress in neurons

of action of flavonoids in CVD is poorly studied (Vita 2005; Voelter-Mahlknecht 2016). However, growing evidence suggests that the intake of isoflavones and flavonols may play a role in explaining these effects (Grosso et al. 2017). Over the past decade, particular attention was given as to understand the link between reduction in CVD and the intake of flavonoids. A number of experimental studies showed that flavonoids, that are present in red wine, tea, many fruits and vegetables in considerable amounts, possess anti-thrombotic characteristics as well act as anti-oxidants (Hooper et al. 2008; Peterson et al. 2012). Such bioactive polyphenols are found mostly in plants and cannot be synthesized chemically (Chacko et al. 2010). The available literature reports, related to the effects of flavanols and anthocyanins and their effects on the prevention or reduction of CVDs, provides a promising future, although most of the results are from in vitro studies (de Pascual-Teresa et al. 2010). Moreover, clinical trials followed the same trend and further indicated a correlation between the intake of flavonoids and a reduction in CVDs (Wang et al. 2014; Ponzo et al. 2015).

Strokes, ischemic or hemorrhagic, are the second highest source of disability in the world as well as being the second most common cause of death (O'Donnell and Yusuf 2009). Amongst the many factors linked to the risk of stroke, an important one is the dietary, with particular interest in the flavonoid intake in the normal diet. Though the exact mode of action of flavonoids against stroke remains unclear, possible explanations could include blood pressure regulation, specifically by anthocyanins, that can regulate endothelial-derived nitric oxide (NO) level or by reducing the

peroxidation of mitochondrial lipids (Cassidy et al. 2016). The loss of electric potential in mitochondrial transmembrane-induced oxidative stress may well help to reduce the chance of stroke (Cassidy et al. 2012; Ferreira et al. 2016). Although few in vitro and in vivo studies are reported for flavonoid's effectiveness against stroke, they lacked much of potential, as the doses that were used were too high or low and may thus lead to hormetic effects (George et al. 2017). For instance, catechin and proanthocyanidins were able to show protective effects in both in vitro as well as in vivo studies, but their effects on cardiovascular health was not due to their strong anti-oxidant properties, rather due to different mechanisms and doses involved with CVDs (de Pascual-Teresa et al. 2010; Vauzour et al. 2010). Some of these mechanisms included, cellular proliferation, hypertension, thrombogenesis, inflammation as well as hypercholesterolemia and hyperglycemia (Hollman and Katan 1999). The pathogenesis of heart attack (myocardial infarction) as well as ischemic strokes is thought to be initiated by the activation and aggregation of platelets. Therefore, reducing the activity by altering dietary components is an interesting strategy for maintaining cardiovascular health and thus helps to prevent CVDs. In addition, a meta-analysis cohort studies confirmed the lower risk of stroke with an improved dietary flavonoid intake (Tang et al. 2016). More detailed mechanisms about how dietary components reduce CVDs were discussed elsewhere (Perez-Vizcaino and Duarte 2010; Majewska-Wierzbicka and Czeczot 2012).

Flavonoids reduces oxidative stress, inflammation and pain

Flavonoids and oxidative stress

Anti-oxidant-rich flavonoids may exert their mitigating ROS effects and thereby reduce platelet aggregation/function or prothrombotic effects (Freedman 2008). Plant flavonoids may well inhibit platelet activity by different methods, of which inhibition of the AA-based pathway is the most representative mechanism (Faggio et al. 2017). A TxA_2 receptor is a potent vasoconstrictor and platelet agonist and Guerrero et al. demonstrated the role of flavonoid to inhibit the platelet receptor through binding to TxA_2 and inhibit aggregation (Guerrero et al. 2005). The dietary beneficial effect of flavonoid is not limited to oxidative stress-mediated thrombosis or CVDs, rather associated with many diseases. For instance, investigating the effect of cocoa phenolic extract (CPE) and epicatechin (EC) in hepatic hepG2 cells, revealed their protective effect against oxidative stress induced by a high-glucose challenge, causing insulin resistance in type-2 diabetes mellitus. The beneficial effects of CPE on redox balance and insulin resistance were shown to be enhanced in the presence of selective MAPKs inhibitors, suggesting that CPE-induced protection is mediated by MAPKs (Cordero-Herrera et al. 2015; Ramos et al. 2017). A study by Fusco et al. has shown that the flavonoid-rich extract of orange juice (OJe) could prevent dinitrobenzene sulfonic acid (DNBS) induced colonic pathological damage and ameliorate the typical signs of inflamed colon in mouse experimental colitis. Oje decreases the oxidative stress by diminishing the expression of nitric oxide synthase (iNOS) and increases the activity of superoxide dismutase (SOD), thereby counteracting the accumulation of nitrotyrosine and lipid peroxidation that accompanied inflammatory events (if any) (Fusco et al. 2017). Flavonoids also play a commendable role in reducing the oxidative stress in Alzheimer's diseases (Thapa and Carroll 2017). Studies on the flavonoid-rich ethanol extract from leaves of *Diospyros kaki* (FLDK) on a APP/presenilin 1 (PS1) mutated mouse model, proved its effectiveness in restoring the activities of anti-oxidant enzymes, thus reducing lipid peroxidation, malondialdehyde formation, and inflammatory mediators levels (Ma et al. 2018). A detailed mechanism by which flavonoids exert their protective effects on oxidative stress-mediated diseases was discussed elsewhere (Suen et al. 2016).

Flavonoids, inflammation and pain

Flavonoids have also been widely studied for their anti-inflammatory and analgesic effects. The flavonoid extracted from the traditional Chinese herb *Sanguis draxonis* (SD) was found to have an antinociceptive effect against the neuropathic pain induced by spared nerve injury (SNI) model in rats. This effect is partly due to the inhibition of pro-inflammatory cytokines release from astrocytes by FGFR3/GFAP and NO/GFAP pathway in the spinal dorsal horn. Moreover, SD was found to play a role in the repression of signal amplification of pro-inflammatory cytokines by inhibiting NO/p-CREB pathway in neuropathic pain (Chen et al. 2015b). A study by Borghi et al. has shown that the flavonoid quercetin can inhibit chronic arthritis in mice induced by titanium dioxide (TiO_2), a common component of orthopedic prosthesis. A dosage of 30 mg/kg of quercetin could successfully inhibit TiO_2-induced knee joint mechanical hyperalgesia and edema, further demonstrating its potential in reducing pain as well as the inflammatory damages associated with prosthesis wear process-induced arthritis (Borghi et al. 2018). On studying three varieties of *Allium cepa*, which is otherwise known as onions, the NHRDF-Red (L28) was found to have the highest amount of flavonoids and quercetin, wherein the flavonoid-rich fraction (FRF) of L28 not only significantly reduced the thermal and mechanical hyperalgesia, but also ameliorated cold allodynia. Moreover, an increased chronic constriction injury (CCI) by thio-barbituric acid reactive species (TBARS) and decreased glutathione (GSH) levels,

which are the oxidative stress markers, can be attenuated by L28 and thereby making it as a potential candidate in managing neuropathic pain (Kumar et al. 2016). All this evidences further suggest that the flavonoids can reduce oxidative stress-mediated diseases and can regulate inflammation and pain associated with disease.

Conclusions

The naturally occurring plant flavonoids are vastly studied for their beneficial effects against various diseases. Nevertheless, their effective role in thrombotic and/or blood disorders has not been discussed well. This review briefly discussed the possibility of developing flavonoids as antithrombotic agents that was not known well before. Various examples from this review showed that the flavonoids can reduce the risk of blood related disorders by many mechanisms, most importantly, by reducing the excessive ROS level. Several studies are now underway aimed at identifying anti-thrombotic effects of unique natural compounds. The main focus now is to have new promising anti-thrombotic agents which might address the issues such as toxicity and side effects possessed by some chemically synthesized compounds that are currently used for therapy. However, dose responsive effects and bioavailability of flavonoids still remains one of the limitations and more studies/effective approaches are, therefore, needed to prove their effectiveness as anti-thrombotic agents.

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Compliance with ethical standards

Conflict of interest Authors declare that there is no conflict of interest on this review article.

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