REVIEW

Cardiovascular Therapeutics

Cardiovascular Ion Channels as a Molecular Target of Flavonoids

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SUMMARY

Flavonoids are a class of naturally occurring polyphenols abundant in edibles and beverages of plant origin. Epidemiological studies consistently associate high flavonoid intake with a reduced risk for the development of cardiovascular diseases. So far these beneficial effects have been mainly attributed to nonspecific antioxidant and antiinflammatory properties. However, there is an increasing body of evidence that flavonoids specifically target molecular structures including cardiovascular ion channels. Playing a pivotal role in the regulation of vascular tone and cardiac electric activity, ion channels represent a major target for the induction of antihypertensive and cardioprotective effects. Thus, pharmacological properties of flavonoids on cardiovascular ion channels, ion currents and tissue preparations are being increasingly addressed in experimental studies. Whereas it has become clear that cardiovascular ion channels represent an important molecular target of flavonoids, the published data have not yet been systematically reviewed.

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Introduction

Cardiovascular diseases (CVD) are the leading cause of illness and death in the industrial nations and emerging economies. Due to the rapidly growing older population the prevalence of CVD continues to increase thereby placing a tremendous financial burden on health care systems. The individual risk for the development of CVD is dependent on nonmodifiable risk factors like gender, genetic predisposition, and age as well as modifiable factors such as nutrition and lifestyle habits. It has been shown that dietary intake and food pattern can influence the development and progression of CVD. Within this context, several epidemiological studies suggest that an increased intake of nutritional flavonoids is associated with a reduced risk for the development of CVD including coronary heart disease, stroke, hypertension, and vascular dementia [1–4].

Sharing a common chemical structure, flavonoids are a subset of natural polyphenols and are abundant in vegetables and fruits [5–7]. So far, beneficial effects of flavonoids have been mainly attributed to unspecific antioxidant, antiinflammatory, lipid lowering, and immune modulatory properties as well as inhibition of platelet aggregation [8]. These effects have been studied extensively and have been reviewed elsewhere in detail [8–11].

However, there is an increasing body of evidence that flavonoids can affect vascular tone and cardiac function by directly targeting cardiovascular ion channels. These effects have been repeatedly associated with antihypertensive and cardioprotective actions of flavonoids and might account for part of the beneficial effects of flavonoids. This is the first review focusing on direct effects of flavonoids on cardiovascular ion channels. Data were identified by searching PubMed with the search phrase: "(flavonoid OR flavonoids) AND channel AND (heart OR cardiac OR vascular OR cardiovascular OR endothelial OR myocardial)."

Effects of Flavonoids on Vascular Ion Channels

Systemic blood pressure is a result of the resistance of the vascular system to blood flow. The main determinant of vascular resistance is the contractile activity of vascular smooth muscle cells located in the walls of resistance arteries and arterioles. The activity of these cells is precisely controlled by vasodilator and vasoconstrictor stimuli mediated by circulating hormones, neurotransmitters and local endothelium-derived factors.

Vascular Electrophysiology

Ion channels located in the plasma membrane of vascular smooth muscle cells play a central role in the regulation of

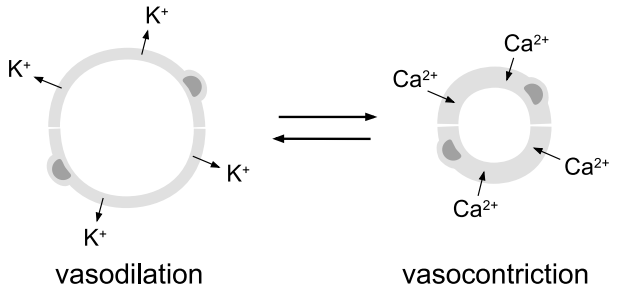

Figure 1 Ion conductance and vascular tone. The contractile activity of vascular smooth muscle cells is dependent on the membrane potential. Potassium efflux via potassium channels hyperpolarizes the membrane potential leading to vasodilation (left figure). Closing of potassium channels in turn depolarizes the cells thereby activating voltage gated calcium channels. Calcium influx triggers calcium release from intracellular stores that initiates contraction (right figure).

contractile activity [12,13]. The contractile status of each muscle cell is finely regulated by the amount of cytosolic calcium that in turn is controlled by the cellular membrane potential. Calcium influx through calcium channels located in the plasma membrane initiates vasoconstriction by triggering the release of calcium from intracellular stores (Figure 1). In contrast, activation of potassium channels hyperpolarizes smooth muscle cells due to an efflux of potassium ions thereby closing voltage gated calcium channels and leading to vasodilation [13]. Vascular smooth muscle cells express a variety of potassium, calcium, chloride, and stretch-activated cation channels that govern membrane potential thereby regulating muscular activity [12].

Effects of Flavonoids on Vascular Calcium Current

Calcium influx through vascular calcium channels depolarizes vascular smooth muscle cells and initiates vasoconstriction. Thus, inhibition of vascular calcium currents is a well-established therapeutic concept in antihypertensive pharmacotherapy. Inhibitory effects on vascular calcium currents have been described for several flavonoids. Wijetunge et al. reported that the isoflavone and tyrosine kinase inhibitor genistein dose-dependently inhibits vascular calcium currents in myocytes isolated from rabbit ear arteries [14]. Similar results could be obtained by Figtree et al. showing that the phytoestrogens genistein, phloretin, and biochanin A relax rabbit coronary arteries by inhibition of vascular calcium currents in an endothelium-independent mechanism [15]. Interestingly enough, vasorelaxant effects were observed at concentrations that were in the same range as flavonoid plasma levels measured in volunteers after oral ingestion of soy protein drinks [15]. Only recently, Pan et al. found that the flavonoid scutellarin dose-dependently relaxes both endothelium-intact and endothelium-denuded rat aortic rings [16]. The authors suggested that inhibition of calcium influx might be involved in the observed vasorelaxant effect. Inhibition of vascular calcium current has also been reported for the natural flavonoid calycosin isolated from *Astragali* radix, the flavonoid containing extract of *Sarcococa saligna*, and the plant-flavonoid catechin [17–19]. Effects of the main green tea flavonoid epigallocatechin (EGCG) on vascular preparations have been studied in detail. EGCG exerts biphasic effects resulting in an initial vasoconstriction by calcium influx and a late vasorelaxation by inhibition of vascular calcium channels [20–23]. Fusi et al. showed that the flavonoid myricetin exerts similar complex effects on calcium channels resulting in a net reduction of calcium current in cells isolated from rat tail main arteries [24,25]. Contradicting its reported vasodilatory effect, activation of vascular calcium channels has been reported for quercetin and its rutinoside rutin, [26–28]. However, this obvious discrepancy seems to be explained by a second hierarchically prevailing vascular target of quercetin that might be represented by protein kinase C [27,28].

Effects of Flavonoids on Vascular Potassium Currents

To date four main potassium channels have been identified in vascular smooth muscle cells including calcium activated potassium channels (BK_{Ca}), ATP-sensitive potassium channels (K_{ATP}), voltage-gated potassium channels (K_V), and inward rectifier channels (K_{ir}) [29]. Activation of any type of potassium current in vascular smooth muscle cells leads to membrane hyperpolarization thereby inducing vasodilation (Figure 1).

Activation of the Vascular Calcium Activated Potassium Channel BK_{Ca}

Under physiological conditions, BK_{Ca} channels answer the rise of intracellular calcium with increasing potassium efflux as a kind of feedback mechanism in certain vascular beds [30]. Hence, activation of BK_{Ca} channels is a well-established vasorelaxant mechanism. Effects of flavonoids on calcium activated potassium channels have been studied in large detail. Xu et al. reported that kaempferol exerts part of its vasodilatory activity via activation of BK_{Ca} channels [31]. Similar effects have been shown for the isoflavone puerarin [32]. Dioclein, a flavonoid isolated from the root of *Dioclea grandiflora*, a legume of the native Americans, causes hypotension in normotensive rats [33]. Using preparations of isolated rat mesenteric arteries, the authors showed that the vasorelaxant effect is mainly due to hyperpolarization caused by an opening of BK_{Ca} channels [33]. Saponara et al. found that the citrus flavonoid naringenin also dilates endothelium denuded rat aortic rings by activation of BK_{Ca} channels [34]. Similar effects could be obtained for the flavonoids quercetin, puerarin, EGCG, and proanthocyanidines, and the nonflavonoid polyphenol resveratrol [35–40]. Taken together, activation of calcium activated potassium channels seems to be a key mechanism in flavonoid induced vasorelaxation and might account for a good portion of the observed beneficial effect of flavonoids in CVD.

Effects of Flavonoids on the Vascular ATP-Sensitive Potassium Channel K_{ATP}

Effects of flavonoids on ATP-sensitive potassium channels have been studied to a far less extent. Ogata et al. reported that genistein inhibits ATP-sensitive potassium channels in rabbit portal vein

Table 1 Effects of flavonoids and other polyphenols on vascular electrophysiology

Affected ion current/ ion channel	Flavonoid	Reference
I_{Ca}	Amentoflavone, biochanin A, calycosin, cardamonin, catechin, earalanone, epigallocatechin, genistein, koalviron, luteolin, myricetin, phloretin, pinocembrin, quercetin, rutin, *Sarcococa saligna* extract, scutellarin	[14–28,49–53]
I_K	Amentoflavone, cardamonin, kolaviron, luteolin, pinocembrin	[49–53]
BK_{Ca}	Dioclein, epigallocatechin kaempferol, naringenin, proanthocyanidines, puerarin, quercetin, resveratrol	[31–40]
K_{ATP}	Chrysoeriol, epicatechin, genistein, epigallocatechin	[41–43]
K_V	Delphinidins, genistein, procyanidins, tilianin	[44–48]

I_{Ca}, vascular calcium current; I_K, vascular potassium current; BK_{Ca}, calcium activated potassium current; K_{ATP}, ATP-sensitive potassium channel; K_V, voltage gated potassium channel.

muscle in a dose-dependent manner [41]. They state that current inhibition might be due to a combination of direct channel inhibition together with tyrosine kinase activation [41]. Jin et al. showed that green tea flavonoids EGCG and epicatechin reduce the activity of K_{ATP} channels [42]. Interestingly, they found that high EGCG concentrations directly inhibit K_{ATP} channels, whereas modest EGCG concentrations seem to result in a current reduction by uncoupling phosphoinositides and ATP from the channel [42]. The exact functional role of K_{ATP} channel inhibition in the regulation of vascular tone has not been completely understood yet. Analyzing effects of the Rooibos tea flavonoid chrysoeriol, Khan and Gilani showed a vasodilation in anesthetized rats that might be due to an activation of vascular K_{ATP} channels [43].

Effects of Flavonoids on other Vascular Potassium Channels

Effects of flavonoids on voltage-dependent (K_V) potassium channels were analyzed by several groups. Ko et al. reported that genistein inhibits K_V channels independently of protein tyrosine kinase activation [44]. Analyzing effects of procyanidins, Kim et al. showed that vasodilatory effects might be due to activation of voltage-gated potassium channels [45]. Iwasaki-Kurashige et al. reported that blackcurrant concentrate exerts vasodilatory effects via activation of diverse potassium channels [46]. They further suggested that two distinct delphinidins that are abundant in blackcurrants might be causative for the observed effect [46]. The flavonoid tilianin isolated from *Agastache mexicana* similarly induces an antihypertensive effect and a relaxation of isolated aortic rings possibly due to an endothelium-independent opening of potassium channels [47]. Only recently, Matsui et al. reported that apple procyanidins relax rat aortic rings possibly by activation of several potassium channels [48]. Vasodilation via synergistic effects of potassium current activation and calcium current reduction has been suggested for amentoflavone, kolaviron, pinocembrin, luteolin, and cardamonin [49–53]. Effects of flavonoids on vascular electrophysiology have been summarized in Table 1.

Effects of Flavonoids on Cardiac Ion Channels

Cardiac action is precisely controlled by an ordered generation and propagation of excitatory stimuli through the cardiac tissue. Specialized cells located in the sinus node form the primary pacemaker of the heart. After depolarization of the atria, excitation passes the atrio-ventricular node and spreads out over the Purkinje system and subsequently the ventricular myocardium. Activation of the myofilaments via intracellular calcium release closely couples mechanical to electric activity during systole. Cellular repolarization terminates myocardial contraction and initiates diastole.

Cardiac Electrophysiology

Myocardial cells respond to an excitatory stimulus with a characteristically long (few hundreds of milliseconds) action potential, which can be further divided into five characteristic phases [54]. Under resting conditions, membranes of myocytes are highly permeable to potassium ions and almost impermeable to sodium ions. Small rises in intracellular voltage levels caused by a propagating electrical wave front result in a fast opening of voltage gated sodium channels (I_{Na}), inducing cellular depolarization (phase 0) (Figure 2B). Initial depolarization may be followed by a brief phase of repolarization caused by transient potassium outward current (I_{to}) in some but not all regions of the ventricles (phase 1) [55]. Depolarized membrane potentials during phase 0 and 1 activate L-type calcium channels (I_{Ca}) that maintain the depolarized voltage level during plateau phase (phase 2). This phase lasts for a few hundreds of milliseconds and is characterized by a continuous interplay between depolarizing calcium and repolarizing potassium currents conducted by delayed rectifier potassium channels (I_{Kur}, I_{Kr}, I_{Ks}) [56]. Phase 3 repolarization is then terminated by increasing potassium and inactivating calcium currents. Final repolarization is accomplished by the inward rectifier potassium current (I_{K1}) that reestablishes the resting membrane potential (phase 4). Whereas the resting membrane potential is stable in most cardiac cells, specialized "slow response" cells located in the sinus and atrio-ventricular node exhibit unique characteristics (Figure 2A). Slow depolarization of these cells causes rhythmic firing that is driven by a hyperpolarization-activated cation current, termed funny current (I_f). Furthermore, rapid action potential upstroke (phase 0) is absent in these "slow response" cells and depolarization is accomplished by calcium channels.

Inhibition of Cardiac Pacemaker Current I_f

The pacemaker current I_f is a nonspecific cation current that is activated at hyperpolarized membrane potentials [54]. Inhibition

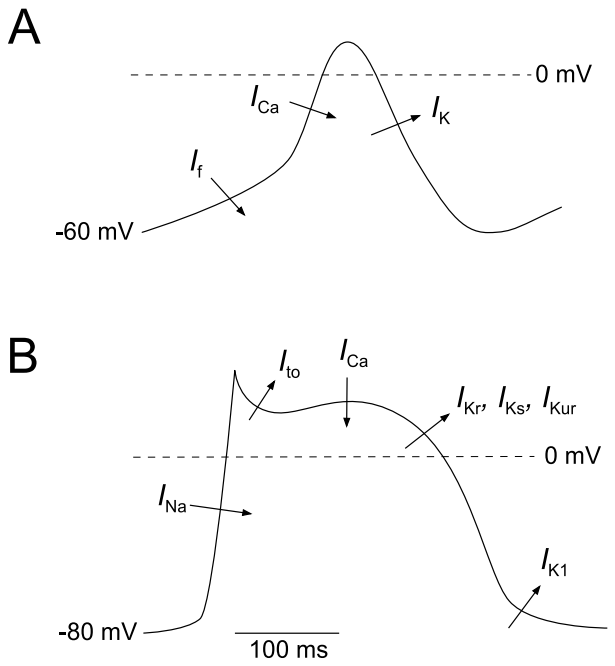

Figure 2 Action potentials and underlying ion currents of slow response cells and cardiomyocytes from the working myocardium. (**A**) Pacemaker activity of "slow response" cells is dependent on spontaneous diastolic depolarization via a hyperpolarization-activated cation current (I_f). (**B**) Myocytes from the working myocardium exhibit characteristically long action potentials that are maintained by calcium influx. See text for detailed description.

of I_f prolongs the slope of the diastolic depolarization of "slow response" cells, thereby reducing the rate of spontaneous rhythmic firing. Ma et al. found that the isoflavone and natural tyrosine kinase inhibitor genistein exerts negative chronotropic effects on isolated rabbit sinoatrial node cells [57]. Whereas pharmacologic effects on isolated ionic currents have not been further analyzed in their study, the authors assumed that inhibition of calcium influx and potassium efflux might contribute to the observed effect [57]. However, a few years later, Altomare et al. demonstrated that genistein directly inhibits I_f in a voltage-independent manner by interacting with the intracellular side of the underlying ion channel protein [58].

Inhibition of Cardiac Sodium Current I_{Na}

The rapid upstroke of the cardiac action potential is dependent on inward sodium current through voltage gated sodium channels [54]. Prolonged sodium influx during the plateau phase is considered a proarrhythmic mechanism causing early afterdepolarizations and ventricular tachycardia. Accordingly inhibition of I_{Na} has been shown to effectively suppress fibrillatory activity [59]. Using patch-clamp techniques, Zhang et al. showed that among other ion currents the isoflavone puerarin directly inhibits I_{Na} in a dose- and rate-dependent manner [60]. The authors state that the nonselective inhibition of cardiac ion currents by puerarin including I_{Na} might exert antiarrhythmic effects especially in cases of myocardial reperfusion injury [60]. Wallace et al. found that the red grape flavonoids quercetin and catechin, as well as the nonflavonoid polyphenol resveratrol inhibit cardiac sodium channels [61]. Interestingly, they showed that resveratrol exerts part of its effects by specifically inhibiting late I_{Na}. This current is thought to be a key feature in the development of early-afterdepolarizations as well as the induction of ventricular tachyarrhythmia and Torsade-de-Pointes tachycardia [61].

Effects of Flavonoids on Cardiac Calcium Current I_{Ca}

The cardiac calcium current consists of two major components, the L-type (long lasting) and the T-type (tiny) calcium current [54]. Calcium influx via L-type calcium current maintains the characteristic long plateau phase of cardiomyocytes. Furthermore, calcium influx triggers the release of intracellular calcium that couples electric to mechanical activity. However, excessive calcium influx has been associated with the development of early and delayed afterdepolarizations and proarrhythmia [54,62]. Inhibitory effects on L-type calcium current have been shown for several flavonoids. Chiang et al. reported that the isoflavone genistein directly inhibits I_{Ca} in guinea pig ventricular myocytes [63]. Further analyzing the type of block, Katsube et al. found that genistein reduces the open probability of calcium channels without affecting the mean open time and slope conductance [64]. Similar results could be obtained by other groups [65,66]. Taken together, there is a large body of evidence that the isoflavone and protein tyrosine kinase inhibitor genistein directly inhibits cardiac calcium channels. Using patch-clamp techniques, Quian et al. analyzed effects of puerarin on calcium currents in isolated guinea pig cardiomyocytes [67]. They found that the isoflavone dose-dependently inhibits I_{Ca} with a potency similar to the inhibition of I_{Na} by puerarin [60]. Thus, similar to the isoflavone genistein, puerarin seems to act as a multichannel inhibitor in cardiomyocytes. Analyzing effects of plant derived flavonoid extracts, it has been suggested that extracts of star fruit (*Averrhoa carambola*), stinking nightshade (*Hyoscyamus niger*), and *Ginkgo biloba* inhibit cardiac calcium current [68–70].

Inhibition of Cardiac Potassium Currents

Cardiac potassium currents can be further subdivided in a transient outward (I_{to}), the delayed rectifier (I_K), and an inward rectifier current (I_{K1}) [54,71]. Mainly expressed in epicardial layers of the myocardium, I_{to} conducts a brief outward current following phase 0 depolarization, thereby leading to a characteristic "spike and dome" configuration of the action potential. The delayed rectifier currents can be further divided into an ultrarapidly, a rapidly and a slowly activating current. Whereas the ultrarapidly activating current I_{Kur} represents the main repolarizing current in human atrial cells, the rapidly (I_{Kr}) and slowly (I_{Ks}) activating delayed rectifiers are mainly involved in ventricular phase 3 repolarization of ventricular cells [54,56]. The inward rectifier current I_{K1} potently restores the resting membrane potential in late repolarization. To date, inhibition of the transient outward current has been shown

for only a few flavonoids. Zhang et al. found that the isoflavone puerarin inhibits transient outward current [72]. Similar effects could be obtained for the isoflavone genistein [73,74]. Only recently, the flavone acacetin was be identified as a promising atrial-selective antiarrhythmic drug [75]. Using the patch-clamp technique, Li et al. showed that acacetin prolongs the cardiac action potential by inhibiting the transient outward and the ultrarapid delayed rectifier current with no effect on cardiac depolarizing currents (I_{Na}, I_{Ca}) [75]. Inhibition of I_{Kur} has also been reported for the flavonoid precursor isoliquiritigenin, a component of licorice [76]. Ventricular repolarization strongly depends on the rapidly activating delayed rectifier current I_{Kr} [77]. Inhibition of I_{Kr} is a common side effect of a large number of noncardiac drugs and has been associated with the development of malignant ventricular arrhythmias (Torsade-de-Pointes). However, inhibition of the same current has also been linked to antiarrhythmic properties and several well-known antiarrhythmics, like amiodarone, dronedarone, and ajmaline inhibit I_{Kr} [78–80]. Only recently, we screened a broad spectrum of flavonoids and showed that among others, the citrus flavonoids hesperetin and naringenin potently block hERG potassium channels, which form the molecular basis of I_{Kr} in humans [81–83]. Similar results could be found for EGCG, the active component of green tea [84]. However, it has to be further elucidated whether these effects are associated with proarrhythmic or antiarrhythmic effects. The inward rectifier current I_{K1} is the main determinant of final repolarization and the stabilization of the resting membrane potential [54,56]. Analyzing potassium currents in guinea pig ventricular myocytes, Chiang et al. found that the tyrosine kinase inhibitor genistein blocks inward rectifier currents within the micromolar range, thereby depolarizing the resting membrane potential and causing abnormal automaticity [85]. Inhibition of cardiac $K_{ir}2.3$ channels could be identified by Zhao et al. as a molecular basis for the observed reduction of I_{K1} [86]. Analyzing the basis of action potential prolongation by *Crataegus*, Müller et al. found that both, inward and delayed rectifier potassium currents are blocked by *Crataegus* extract [87]. Effects of flavonoids on cardiac electrophysiology have been summarized in Table 2.

Miscellaneous Effects

There are several studies reporting pharmacological effects of flavonoids on ion currents and ion transporters other than the main determinants of the cardiac action potential. Bidasee et al. showed that the isoflavones tectoridin and 3′-hydroxy tectoridin isolated from an Ayurvedic herbal preparation bind to and modulate ryanodine receptors which represent the main intracellular calcium-release channels and are mainly involved in mechano-electrical coupling [88]. Lorenz et al. found that the green tea component EGCG activates cardiac Na^+/H^+ and Na^+/Ca^{2+} exchangers, thereby modulating myocardial contractility [89]. The multichannel inhibitor puerarin has been shown to also inhibit the mitochondrial permeability transition pore opening and activate the mitochondrial ATP-sensitive potassium channel, thereby possibly reducing ischemia and reperfusion injury [90].

Conclusion and Clinical Implications

In summary, cardiovascular ion channels are increasingly recognized as important molecular targets of natural occurring flavonoids. Currently, a considerable body of evidence indicates that many flavonoids exhibit antihypertensive effects by either inhibiting calcium channels or activating potassium channels or both. Whereas the pathophysiological link is rather straightforward in the vascular system, the impact of altered ion channel function has remained somewhat obscure in the heart. Whereas several groups were able to show in single-cell measurements that flavonoids directly interact with ion currents, the influence of these effects on cardiac function has to date been only rudimentarily analyzed. Furthermore, many of the analyzed compounds act as multichannel inhibitors, thereby exerting almost unpredictable pharmacological effects. Thus, for the vast majority of flavonoids with reported effects on cardiac ion channels, it remains largely unclear whether they exert anti- or proarrhythmic effects. Further studies are essentially needed in this field.

In conclusion, we show that cardiovascular ion channels represent an important molecular target of flavonoids. These

Table 2 Effects of flavonoids and other polyphenols on cardiac electrophysiology

Affected ion current/ ion channel	Flavonoid	Reference
I_f	Genistein	[57,58]
I_{Na}	Catechin, puerarin, quercetin, resveratrol	[60,61]
I_{Ca}	Genistein, *Ginkgo biloba* extract, *Hyoscyamus niger* extract, puerarin, *Averrhoa carambola* extract	[63–70]
I_{To}	Acacetin, genistein, puerarin	[73–75]
I_{Kur}	Acacetin, isoliquiritigenin	[75,76]
hERG	*Crataegus* extract, epigallocatechin, ethoxycoumarin, flavone, hesperetin, kaempferol, methoxsalen, morin, naringenin, quercetin, scopoletine, umbelliferone	[81–84,87]
I_{K1}	*Crataegus* extract, genistein	[85,87]
$K_{ir}2.3$	Genistein	[86]

I_f, cardiac pacemaker current; I_{Na}, cardiac sodium current; I_{Ca}, cardiac L-Type calcium current; I_{To}, cardiac transient outward potassium current; I_{Kur}, atrial ultrarapidly activating potassium current; hERG, human Ether-à-Go-Go Related Gene potassium channel; I_{K1}, cardiac inward rectifier potassium current; $K_{ir}2.3$, cardiac inward rectifier channel.

effects might account for part of the observed beneficial effects of flavonoids in CVD. Furthermore, selected flavonoids might prove to be promising lead compounds for the development of new cardiovascular pharmaceuticals.

Conflict of Interest

The authors have no conflict of interest.

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