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Cardioprotection and natural polyphenols: an update of clinical and experimental studies

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Myocardial ischemia is the leading cause of death worldwide. Despite better outcomes with early coronary artery reperfusion strategies, morbidity and mortality remain significant. The principal myocardial hallmark of myocardial ischemia is cell death and the associated impairment of cardiac contractility. In this way, the use of extracts from medicinal plants *versus* synthetic drugs to mitigate post-ischemic damage constitutes an alternative. Despite their proven beneficial effects in cardiovascular disorders, the use of many plants is questioned. Our aim is to update the clinical and experimental studies about the actions of medicinal plants and polyphenol-enriched extracts against ischemia–reperfusion injury and the involved mechanisms. A review of the recent scientific literature (last ten years) on cardioprotective medicinal plants was developed using the following bibliographic databases: PubMed, Scopus, Web of Knowledge and Google Scholar. Herein, the clinical and experimental studies on medicinal plants and their phenolic compounds have been reviewed. The second part of this review was centered on the search for medicinal plant extracts and natural products isolated from them as potential cardioprotective agents. The botanical names of the cited plants have been authenticated by searching the Plant List and Royal Botanical Garden, Kew databases. The data collected show that treatment with natural products diminishes post-ischemic damage through an improvement of the mitochondrial functionality mainly mediated by enhanced nitric oxide bioavailability. Despite these results, further studies must be carried out to validate their use to prevent or mitigate ischemia–reperfusion injury in the clinical setting.

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Introduction

Cardiovascular disease, heart failure and cardioprotection

Cardiovascular disease (CVD) is a chronic disease responsible for the highest morbidity and mortality worldwide, with coronary artery disease or ischemic heart disease being the most common type. CVD is the leading cause of death globally. This resulted in 17.9 million deaths (32.1%) in 2015, up from 12.3 million (25.8%) in 1990.[1] Heart failure (HF) is the result of many different cardiac and non-cardiac abnormalities leading to a complex clinical entity and has a significant impact on the prognosis of patients. Adverse left ventricular remodeling after acute myocardial infarction is a precursor to the development of overt HF and heralds increased mortality. Therefore, in order to prevent HF and improve clinical outcomes in patients presenting with acute myocardial infarction, novel therapies are required to protect the heart against the detrimental effects of acute ischemia–reperfusion injury. A wide variety of strategies and pharmacological treatments have been beneficial at the experimental level but its translation to the clinical setting was not always successful. Currently, diet and lifestyle are considered major risk factors for CVD.[2] Also, a growing body of evidence suggests that reactive oxygen species

(ROS) and oxidative stress play a pivotal role in cardiac injury, myocardial remodeling and HF.[3] Therefore, the intake of functional food ingredients in a healthy diet or drugs derived from natural products will be considered as new strategies for the prevention and/or treatment of CVD.

Myocardial ischemia–reperfusion injury pathogenesis

Myocardial ischemia refers to a clinical state characterized by low coronary blood flow arising from various causes but resulting in a lack of myocardial oxygen supply. The absence of oxygen determines that aerobic metabolism ceases and glycolytic anaerobic metabolism occurs. In this scenario, the energy demand of cardiomyocytes exceeds the production from anaerobic glycolysis and ATP decreases.[4] Lactate accumulation produces intracellular acidosis and the Na^+/H^+ exchanger and the reverse mode of the Na^+/Ca^{2+} exchanger are activated,[5] leading to intracellular Na^+ and Ca^{2+} increases. After acute ischemia, the only option available to reduce infarct size and improve clinical outcome is to restore blood flow by thrombolysis, primary percutaneous coronary intervention or cardiac surgery. However, reperfusion exacerbates ischemic damage, a phenomenon known as reperfusion injury.[6]

During the reestablishment of blood flow, the Na^+/H^+ exchanger and the Na^+/Ca^{2+} exchanger are again activated and Ca^{2+} overload takes place. At the mitochondrial level the uncoupling of mitochondrial metabolism produces ROS excess. Between them the superoxide anion ($O_2^{\bullet -}$) has been identified as being responsible for cell membrane peroxidation. Hydroxyl radical ($OH^{\bullet}$), nitric oxide ($NO^{\bullet}$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$) and peroxynitrite ($ONOO^-$) are other reactive species produced during reperfusion.[7] Ca^{2+} overload and ROS have been implicated in the pathogenesis of myocardial ischemia–reperfusion injury through the impact of both factors on the mitochondria contributing to mitochondrial permeability transition pore (MPTP) formation and/or opening (Fig. 1).[8] The exact composition of this pore remains unclear, although it seems to include adenine nucleotide translocase (ANT), cyclophilin D (CyP-D) and voltage-dependent anion-selective channel (VDAC) in the outer membrane.[9] During MPTP formation, CyP-D induces a conformational change of ANT, leading to increased permeability of the inner mitochondrial membrane (Fig. 2).

Other proteins, such as hexokinase and creatine kinase, have been proposed to participate in MPTP formation, but to date, it has not been known whether they are structural or regulator components. Although the molecular composition of the MPTP is still a matter of debate, there are many pieces of evidence showing its contribution to myocardial damage caused by ischemia–reperfusion. In this pathological situation, MPTP formation leads to the rapid collapse of the mitochondrial membrane potential and it can trigger cell death by apoptosis, necrosis or both mechanisms.[10] Then, the MPTP is the end point of multiple pathways involved in cell death or survival.[11] Therefore, the pharmacological interventions able to reduce MPTP formation and/or opening appear as possible tools to protect the myocardium against reperfusion injury.

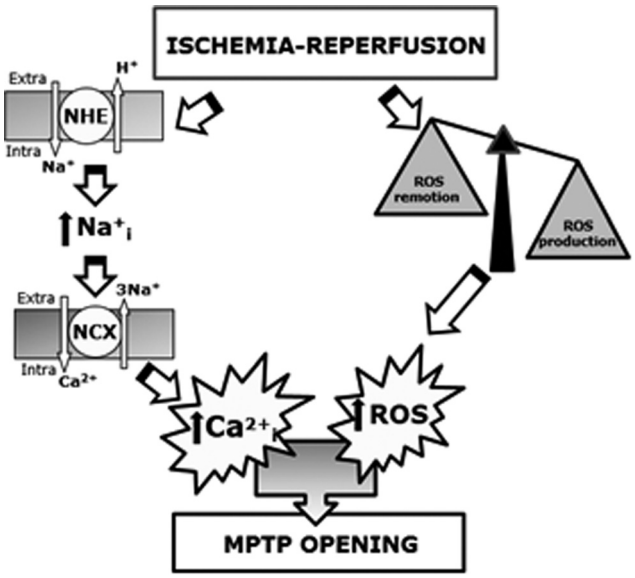

Fig. 1 Events produced during ischemia–reperfusion leading to MPTP (mitochondrial permeability transition pore) opening. NHE = Na^+/H^+ exchanger, NCX = Na^+/Ca^{2+} exchanger, ROS = reactive oxygen species.

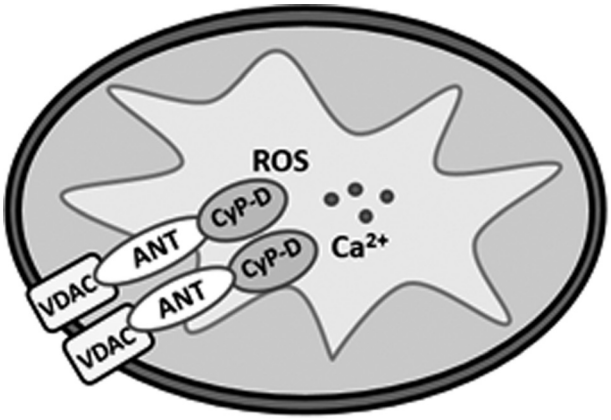

Fig. 2 Principal components of the MPTP (mitochondrial permeability transition pore). ANT = adenine nucleotide translocase; CyP-D = cyclophilin D; ROS = reactive oxygen species; VDAC = voltage-dependent anion channel.

Cardioprotective interventions

Therefore, it is necessary to develop strategies or treatments to improve myocardial function, and to limit the infarction produced by ischemia–reperfusion. In 1986, Murry *et al.*[12] described a cardioprotective intervention called 'ischemic preconditioning' (IP). IP is based on the fact that brief episodes of ischemia followed by reperfusion, applied prior to longer lasting ischemia, reduce disturbances caused by ischemia–reperfusion.[13] As IP has to be implemented before the onset of severe ischemia, its clinical application has been largely restricted to specific situations, such as heart surgery, heart transplantation or angioplasty.

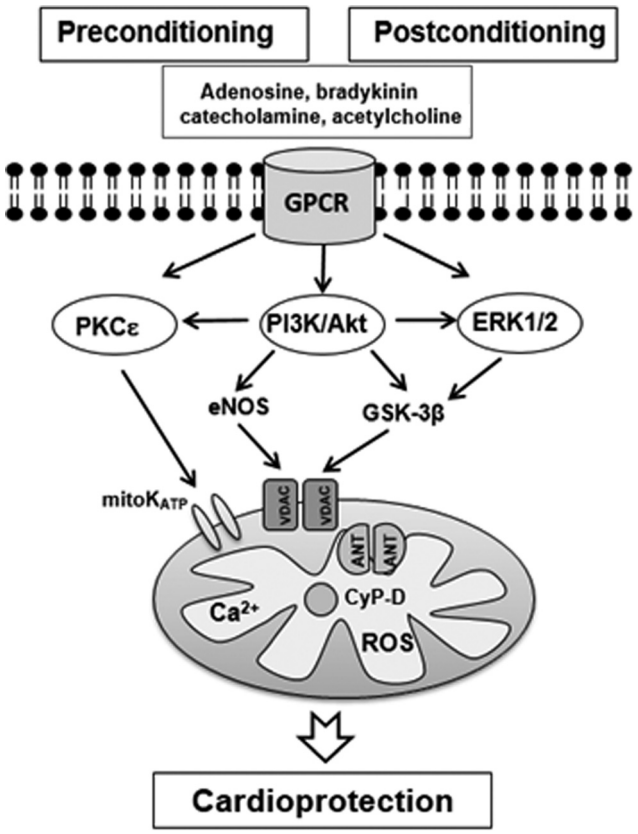

Fig. 3 Some signaling pathways of ischemic pre- and post-conditioning leading to cardioprotection. GPCR = G protein-coupled receptor; PKC = protein kinase C; PI3K = phosphatidylinositol 3-kinase; Akt = protein kinase B; ERK1/2 = extracellular signal-regulated kinase 1 and 2; eNOS = endothelial nitric oxide synthase; GSK-3β = glycogen synthase kinase-3β; VDAC = voltage-dependent anion channel; ANT = adenine nucleotide translocase; CyP-D = cyclophilin D; ROS = reactive oxygen species.

In 2003, Zhao *et al.*[14] demonstrated that the application of short periods of ischemia–reperfusion at the onset of reperfusion was able to reduce infarct size. This phenomenon, called 'ischemic postconditioning' (IPC), provided a tool that can be applied at the time of reperfusion, which facilitates its application to patients with acute myocardial infarction.[15] However, the clinical application of IPC is limited by the fact that it requires an invasive treatment protocol and is restricted to patients with acute myocardial infarction undergoing primary angioplasty.

Regarding protection mechanisms, it is recognized that IP and IPC recruit similar signaling pathways, involving cardioprotective ligands such as adenosine, bradykinin, acetylcholine, and phenylephrine among others (Fig. 3).[16] The interaction of these ligands with membrane receptors leads to the activation of various kinases, such as protein kinase C (PKC), extracellular signal-regulated kinase 1 and 2 (ERK1/2), the complex phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) and glycogen synthase kinase-3β (GSK-3β). NO produced by endothelial nitric oxide synthase (eNOS) has also been considered as an important factor in IP- and IPC-mediated cardioprotection. The activation of cGMP-dependent protein kinases, *S*-nitrosylation, and the interaction with mitochondrial cytochrome c oxidase are some NO-mediated protective mechanisms.[17] Recently, the *S*-nitrosation of Cys39 on the ND3 subunit of mitochondrial complex I by NO has been identified as a new underlying cardiac protection from ischemia–reperfusion injury.[18] Numerous pieces of evidence indicate that the mitochondria is the end target of the different cascades activated by IP and IPC, with the inhibition of MPTP formation and/or opening being a crucial event associated with cardioprotection.[19]

During ischemia–reperfusion, AMP-activated protein kinase (AMPK) activation restores energy homeostasis, inhibits protein synthesis, decreases endoplasmic reticulum stress, reduces ROS generation and attenuates MPTP opening. Thus, it was demonstrated that the pharmacological activation of AMPK prevents cell death and contractile dysfunction during ischemia–reperfusion.[20,21] AMPK can be activated by several compounds present in plants, such as epigallocatechin-3-gallate and theaflavin (green tea), resveratrol (grape-wine), catechin and epicatechin (cocoa) or ginsenoside Rg1 (ginseng). However, the efficacy of this action in cardiovascular disease has not been fully demonstrated.[22]

Medicinal plants as cardioprotective agents

Until the 1990s, different authors studied the cardioprotective effect of several plant species, and a most interesting controversy arose in 1996–1997 in which after analyzing the clinical trials carried out to date it was established that the bulb of garlic has no cardioprotective properties.[23] However, the observation starts from an erroneous concept, in which the lowering of lipid levels was established as the only evaluable parameter. Indeed, the general concept of cardioprotection must encompass other parameters and effects, in addition to the effect on lipids.[24–26] In later years, other pathophysiological parameters were established to determine the cardioprotective properties of agents external to the organism. With the advent of studies on the cardioprotective action of plants and their active principles, new species were incorporated into folk medicine. Some of these studies are supported by increasing epidemiological evidence on the relationship between diets rich in fruits and vegetables and health, including cardiovascular health.[27] Numerous studies have demonstrated that flavanol-rich foods and medicinal plant extracts exert beneficial effects on lipid metabolism, vascular function and platelet reactivity.[28–32] In this sense, polyphenols from cocoa[33] and green tea,[34] and medicinal plants used in folk medicine such as motherwort[35] and hawthorn[36] have been studied.

Hawthorn

Hawthorn leaves and flowers consisting of the whole or cut, dried, flower-bearing branches of *Crataegus* species (Rosaceae)

were used as medicinal plants. Some of them are included in the European Pharmacopoeia, such as *Crataegus monogyna* Jacq. and *C. laevigata* (Poiret) D.C., but other species are also accepted for the treatment of heart diseases, such as *C. pentagyna* Waldst. & Kit. ex Willd., *C. azarolus* L. and *C. nigra* Waldst. & Kit., as well as their hybrids.[37] Other used names, such as *C. oxyacantha* L., are not accepted at present.[38] In addition, the German Commission E approved the use of hawthorn leaf with flower extracts in the case of patients with heart failure graded stage II according to the New York Heart Association (NYHA).[39]

Hawthorn is used in China and North America for the treatment of heart problems since the 1800s.[40,41] The leaf extracts have different properties with a direct relationship with cardiac protection: positive inotropic and antiarrhythmic effects, protective effect against ischemia–reperfusion injury, anti-inflammatory and antioxidant effects, vasodilation and endothelial protective effects, lipid-lowering and antiplatelet aggregation effects, and arterial blood pressure decreasing effect.[40,41] The chemistry of all the species is quite similar, with flavonoids and anthocyanins as the principles responsible for their pharmacological activity, and hyperoside, vitexin, and glycosylated derivatives being the main flavonoids. In the group of catechin/epicatechin derived oligomeric procyanidins there is a variation in the degree of polymerization, from 1% to 3% (B2-, B4-, B5-dimers, C1 trimer, D1 tetramer, E1 pentamer). Other compounds such as organic and phenolic acids (quinic, protocatechuic, salicylic and syringic acids), terpenes (ursolic, oleanolic, and crataegolic acids), essential oils and phenylpropanoids – such as hydrocinnamic acids (coumaric, caffeic, chlorogenic and ferulic acids) – and lignans (pinoresinol, lariciresinol and matairesinol) are also implicated in the pharmacological effects.[37,40]

Clinical studies. Previous studies in humans indicated that standardized extracts has potential for the treatment of left ventricular dysfunction because they improve left ventricular performance, as measured by the ejection fraction.[42] Recent clinical trials with hawthorn extracts (hydroethanolic extracts from leaves and flowers) in 4000 patients confirm their effectiveness in the treatment of NYHA stage II and III chronic heart failure and might be applied as cardioprotective agents in different disorders, such as endothelial dysfunction, atherosclerosis and coronary heart disease.[37] The hawthorn extracts are effective for symptom control based on short-term studies, but there is no evidence of decrease in mortality.[43] The results suggest that there is a significant benefit in symptom control and physiological outcomes as an adjunctive treatment for chronic heart failure.[39] However, clinical trials involving hawthorn preparations are in general inconsistent in terms of the criteria used, but have been largely consistent with regard to positive outcomes.[44]

Experimental studies. On the other hand, experimental studies demonstrated that these extracts have cardioprotective efficacy in a crystalloid perfused heart model of ischemia–reperfusion injury. Indeed, hearts treated with the extract showed a significant recovery in cardiac contractile function, reduction in infarct size, and decrease in creatine kinase and lactate dehydrogenase activities.[36]

As a conclusion, hawthorn preparations have an excellent safety profile and on the basis of the lack of herb–drug interactions detected in clinical trials could have high potential for inclusion in future treatment strategies for the early stages of cardiovascular disease.[44]

Motherwort

Leonurus cardiaca L. (Lamiaceae) has similar chemical composition and pharmacological activity to those of hawthorn and it is included in the European Pharmacopoeia. It contains phenolic compounds, such as chlorogenic acid, orientin, quercetin, hyperoside, and rutin, and has cardioprotective effects.

Clinical studies. Previous studies performed in patients demonstrated that different preparations of motherwort (tincture, alcoholic liquid extract, dry extract and infusion) exerted antihypertensive and heart-strengthening effects such as the facilitation of coronary blood flow, and attenuation of functional heart disorders.[45]

Experimental studies. Intracoronary administration of a motherwort refined extract to isolated rabbit hearts reduced left ventricular pressure, increased coronary blood flow, increased the basic cardiac cycle and lengthened the duration of the action potential in the pacemaker cells of the heart conduction system.[46] Bernatoniene *et al.*[35] demonstrated that phenols of motherwort uncouple mitochondrial oxidation from phosphorylation, inhibit the mitochondrial respiratory chain, and reduce the generation of ROS in mitochondria. These effects can be considered as the mechanisms of motherwort-mediated cardioprotection. These mechanisms can be considered useful to the motherwort-mediated cardioprotection against the pathogenic processes.[35]

Arjun tree

Terminalia arjuna (Roxb.) Wight & Arn. (Combretaceae) is a medicinal plant used in Ayurveda for treating heart disease with the property of reversing heart failure. It contains phytosterols, lactones, flavonoids, phenolic compounds, tannins and different kinds of glycosides.[47]

Clinical studies. A previous trial demonstrated that patients receiving 500 mg of a hydroalcoholic extract of *Terminalia arjuna* barks each 8 h for 3 months showed improvement in the left ventricular ejection fraction, reduction in left ventricular mass (echocardiography) and symptomatic relief in coronary heart failure moving from NYHA class III to NYHA class I.[48]

Experimental studies. Another study demonstrated that oral pre-treatment with a hydroalcoholic extract of the bark of *Terminalia arjuna* (100–400 mg kg^{-1}, 30 days) was able to decrease the biochemical and apoptotic changes induced by isoproterenol in rats.[49] The prevention of oxidative stress and apoptosis by a standardized aqueous extract of the stem bark of *Terminalia arjuna* (125 and 250 mg kg^{-1} day^{-1} for 25 days) was also detected in a pulmonary artery hypertension model.[50] As in other similar species, the phenolic compounds appear to be responsible for the beneficial effects of this plant.

Searching cardioprotective medicinal plants and natural products

Numerous experimental studies show that antioxidants present in herbal extracts exert a cardioprotective effect against ischemia–reperfusion injury.[51,52] Unfortunately, most of the clinical trials carried out to test the *in vivo* efficacy of the antioxidants could not measure any benefit of their administration.[53] Thus, recent studies indicate that the radical scavenger property is unlikely to be the only reason for their cardioprotective actions and in fact, a wide spectrum of cellular signaling events may well account for their biological actions.[54,55]

Several thousand active principles have been identified in different medicinal plant extracts, as well as edible fruits, leaves and seeds. These compounds cover a diverse range of chemical entities such as flavonoids (isoflavones, flavonols) and other phenolic compounds (proanthocyanidins, epigallocatechin-3-gallate, resveratrol), steroids (diosgenin, saponins), carotenoids, organosulfur compounds and vitamins. Previous studies demonstrated the ability of these phytochemicals to reduce the risk of cardiovascular disease and to attenuate ischemia–reperfusion damage.[56,57] Independently of the use of medicinal plants, different foods and diets, such as the Mediterranean diet, have been used as potential cardioprotective agents. Indeed, a compilation of the data from experimental, epidemiological and clinical studies indicates that dietary nutrients have beneficial effects in the prevention of coronary heart disease. Experimental data also present evidence about the cardioprotective effect against ischemia–reperfusion injury caused by some herbal extracts.[51,52]

Although there are many reports focusing on the cardioprotective mechanisms or direct targets of natural compounds, the acknowledgment of them is far from being definitive. Unfortunately, most of the clinical trials carried out to test the *in vivo* efficacy of antioxidants could not measure any benefit of their administration.[53] Thus, different studies indicate that the antioxidant property is unlikely to be the only reason for their cardioprotective actions and in fact, a wide spectrum of events including the linkage of that molecule with targets for the regulation of cell signaling and gene modulation may well account for their biological actions.[54,55,58–61] On the other hand, we must consider that the actions of 'antioxidants' could be due to their degradation products as previously described.[62] In addition, and supported by multiple pieces of evidence, the physiological role of redox signaling in cellular homeostasis should be taken into account.[63] Therefore, in this review, we gather evidence on the molecular mechanisms of some natural products involved in their cardioprotective action against ischemia–reperfusion injury, providing arguments to link plant polyphenol consumption and health improvement.

The active compounds of plants are phenols from grapes, red wine, coffee, green tea and cocoa, citroflavonoids, oils and fatty acids (olive, omega-3), and others.[34] Among them, phenolic compounds have been widely studied. The antioxidant, vasodilator, anti-inflammatory, anti-fibrotic, anti-apoptotic and metabolic properties have been the mechanisms involved in their cardioprotective effects.[64] However, the precise targets of natural products as anti-ischemic agents have not been fully elucidated. This review summarizes the evidence about the protective effects of some natural products against ischemia–reperfusion injury, analyzing the responsible mechanisms.

Tea leaves

Camellia sinensis (L.) Kuntze (Theaceae) is one of the most popular beverages; approximately three billion kilograms of tea are produced and consumed yearly throughout the world. There are different types of tea dependent on the manipulation and degree of fermentation: green, black, red (pu-erh), blue (oolong), yellow (huángchá) and white tea (báichá). They have different concentrations and phenolic compositions, but green tea has the most number of studies.

Although evidence from epidemiological and clinical intervention studies regarding the potential beneficial health effects of green tea polyphenols is inconclusive and sometimes conflicting, green tea extracts have had increasing use as ingredients of dietary supplements, beverages, and (functional) foods, which may lead to a higher consumption of green tea by the general populace.

The major catechin present in green tea extracts is (−)-epigallocatechin-3-gallate (Fig. 4). This compound and several related catechins are believed to be responsible for the health benefits of green tea.

Clinical studies. A previous review summarizes the studies that demonstrate the efficacy of green tea extracts and purified products in patients.[65] Antioxidant action, cancer chemoprevention, protection against skin damage caused by ionizing radiation, and improvement of cardiovascular health are some of their beneficial effects.

Experimental studies. Townsend *et al.*[66] demonstrated that epigallocatechin-3-gallate reduced cardiomyocyte death and improved hemodynamic recovery and ventricular function in the ischemic-reperfused rat heart through a reduction of the signal transducer and activator of transcription (STAT)-1 phosphorylation. In 2008, Dreger *et al.*[67] showed that the activation of prosurvival signaling kinases (Akt, ERK1/2) and the upregulation of antioxidant enzymes did not play a major role in epigallocatechin-3-gallate-mediated cardioprotection. Two years later, Song *et al.*[68] demonstrated that this compound reduced myocardial infarction in a dose-dependent manner and this effect was abrogated by K_{ATP} channel blockers, indicating the participation of these channels in epigallocatechin-3-gallate-induced cardioprotection. Similar results were obtained with theaflavin (Fig. 4), a phenolic derivative present in black tea, which protected against ischemia–reperfusion injury through the opening of K_{ATP} channels and inhibition of MPTP opening.[69] Also, epigallocatechin-3-gallate and theaflavin activate AMPK,[22] and this effect could be implicated in the cardioprotective effects.

Green tea (1 μM) and epigallocatechin-3-gallate (10 μM) significantly reduced reperfusion-induced cardiac necrosis.[70] In a

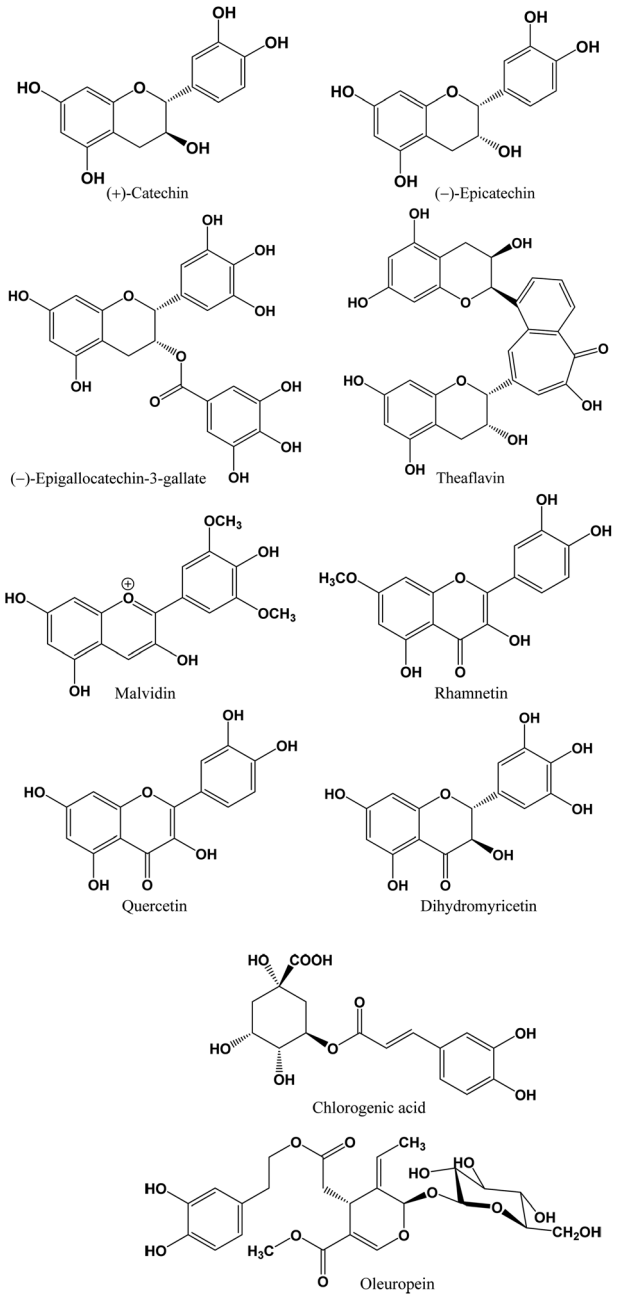

Fig. 4 Chemical structure of active phenolics: (+)-catechin and (–)-epicatechin derivatives, flavonoids, chlorogenic acid and oleuropein.

similar experiment, Yanagi *et al.*[71] demonstrated that the oral administration of epigallocatechin-3-gallate to rats for 2 weeks preserved the cardiac function after ischemia–reperfusion involving the antioxidant and anti-apoptotic properties of the drug. However, Bao *et al.*[72] studied the effects of epigallocatechin-3-gallate at different doses and observed that at a low dose (20 μM) it conferred cardioprotection but at a high dose (50 μM) it increased the incidence of arrhythmia. Another investigation also showed that a green tea extract is able to protect myocytes against oxidative stress induced by ischemia–reperfusion.[73] Recently, Yao *et al.*[74] have demonstrated that epigallocatechin-3-gallate alleviated doxorubicin-induced cardiotoxicity in sarcoma 180 tumor-bearing mice, possibly by increasing MnSOD and $\tilde{N}^{\circ}_{m}$, reducing myocardial calcium overload and subsequently attenuating apoptosis and lactate dehydrogenase release. For that, the co-administration of epigallocatechin-3-gallate and doxorubicin could be a possible strategy to reduce the cardiotoxicity of doxorubicin without affecting its chemotherapeutic value.

Yerba mate

Yerba mate – trivial name of the species *Ilex paraguariensis* A. St.-Hil. (Aquifoliaceae) – has a social and almost ritualistic role in Argentina, Uruguay, Brazil and Paraguay. It is used both as a source of caffeine, in lieu of or in parallel with tea and coffee, and as a therapeutic agent for its purported pharmacological properties. The folium contains caffeine (0.3–1.7%) as the principal xanthine, tannins, essential oils, triterpenes, saponins, resin, and phenolics, principally flavonoids and caffeoyl derivatives, with chlorogenic (Fig. 4), isochlorogenic and neochlorogenic acids being the most relevant compounds of the last group.[75] These components are responsible for the well-characterized antioxidant properties of *Ilex paraguariensis*.[76] Yerba mate beverages have many beneficial biological activities.

Clinical studies. Although it was demonstrated that the consumption of *Ilex paraguariensis* improves serum lipid parameters in healthy dyslipidemic subjects and provides additional LDL-cholesterol reduction in individuals on statin therapy,[77] its use as a possible therapy in patients suffering from cardiovascular disease has not yet been assessed.

Experimental studies. Several studies demonstrated its anti-obesity action, anxiolytic, stimulant and neuroprotective effects and anti-inflammatory actions in both local and systemic inflammatory processes. Anti-hypertensive, hypo-cholesterolemic, anti-thrombotic, anti-mutagenic and vasodilation actions have also been described after *Ilex paraguariensis* extract administration.[78] Although these effects are contributing to the reduction of the risk factors of cardiovascular disease, the use of *Ilex paraguariensis* as a possible therapy in patients suffering from that pathology has not yet been assessed. In this sense and at the experimental level, in a previous study using an *ex vivo* model of rat heart we described an improvement of the post-ischemic recovery of myocardial function and an attenuation of oxidative damage by treatment with an aqueous extract of *Ilex paraguariensis*.[79] Recently, we have also shown that the administration of the extract at the onset of reperfusion was protective, diminishing the infarct size generated by a longer ischemic period leading to irreversible damage.[80] Additionally, the yerba mate extract produced a preservation of heart antioxidant capacity, an increase of PI3K/Akt cardioprotective kinase expression, and a diminution of mitochondrial permeability. Moreover, these experimental data highlight the essential role played by NO as a mediator of the beneficial actions of the *Ilex paraguariensis* extract against ischemia–reperfusion injury.

Grape-wine extract

Epidemiological studies have consistently shown that, when compared with non-drinkers, light-to-moderate consumers of alcoholic beverages have a lower risk of cardiovascular disease, whereas heavy drinkers show a greater risk than moderate drinkers as well as non-drinkers describing the known 'J-shaped curve'. This curve was demonstrated in relation to red wine consumption (*Vitis vinifera* L., Vitaceae). The first data were collected from a resident of France in whom was observed an inverse relationship between red wine consumption and incidence of coronary heart disease, despite it being rich in saturated fats, a phenomenon called 'French Paradox'.[81,82] Although there are many epidemiological pieces of evidence of this phenomenon, the advantages or benefits of light-to-moderate red wine consumption are still being questioned and a consensus has not yet been reached. However, great effort is made to isolate and identify the bioactive compounds of red wine and to elucidate the action mechanisms. In this sense, a recent paper summarizes all the information about red wine composition and the effects of its components on chronic cardiovascular disease.[83]

Clinical studies. Clinical studies demonstrated that red wine was able to decrease the inflammatory markers of atherosclerosis, increase serum antioxidant activity and prevent cardiovascular disease.[84] The data obtained from the European project 'Wine and cardiovascular disease' showed that red wine polyphenol extracts improve vascular function mainly through NO-mediated mechanisms, interfere with hemostatic and oxidative processes involved in the progression of vascular damage, and modulate the early events of atherosclerosis.[85] These results contributed to the establishment of a biological plausibility to the epidemiological association of moderate wine consumption with the prevention of cardiovascular disease. More recently, a clinical trial in patients hospitalized following a cardiovascular event has shown that moderate red wine consumption provided some benefits to various blood parameters of lipid and oxidative status, decreasing plasma total and low-density lipoprotein (LDL) concentrations and increasing erythrocyte membrane fluidity.[86] However, the experimental basis for such health benefits of red wine consumption is not fully understood. The cardioprotective effect of wine has been attributed to both components of wine: the alcoholic portion and, more importantly, the alcohol-free portion containing polyphenols. Thus, closer to our days, it was shown that polyphenol-rich grape-wine extract (high content of catechins and procyanidins), but not grape juice, consumption decreased the ambulatory blood pressure in mildly hypertensive subjects and contributed to the healthy Mediterranean lifestyle.[87,88] Therefore, wines or enriched grape juice can attenuate cardiac diseases and/or risk factors of ischemic heart disease. Despite these pieces of evidence more long-term clinical trials are needed to elucidate the mechanisms involved in these protective effects.

Experimental studies. Experimental studies demonstrate that the hearts of the rats fed with a standardized grape extract are resistant to myocardial ischemia–reperfusion injury, suggesting a cardioprotective role of grapes.[89] Previous *in vitro* studies performed in our laboratory revealed that acute treatment with a non-alcoholic red wine extract or its polyphenolic compounds was able to improve the post-ischemic ventricular function, and reduce the myocardial infarct size, cardiomyocyte apoptosis and oxidative stress.[90,91] It was also demonstrated in hypercholesterolemic swine that a moderate consumption of red wine reduced post-ischemic damage by improving collateral-dependent perfusion *via* the activation of eNOS and sirtuin-1/antioxidant Forkhead box protein O1 (FoxO1).[92] By using the Langendorff perfused rat heart, it was shown that a polyphenol-rich red grape extract and malvidin (its principal phenol, Fig. 4) induced cardioprotection against ischemia–reperfusion damage involving PI3K/Akt, eNOS, ERK1/2, and GSK-3β-dependent pathways.[93] Otherwise there are studies which provide evidence about the possible association between the modulation of mitochondrial capacity and the beneficial effects of red wine polyphenols.[94]

Blueberries

The genus *Vaccinium* L. (Ericaceae) provides a group of plants with promising antioxidant properties, such as *V. myrtillus* L., *V. macrocarpon* Aiton, *V. meridionale* Sw. and *V. arctostaphylos* L. It includes about 400 species, which grow principally in the hillside of tropical mountains. Blueberries are particularly rich in flavonoids (principally anthocyanins) in addition to containing significant amounts of micronutrients and fiber. They have the highest antioxidant capacity among fruits and vegetables, and the fermented juice, such as in the case of wine, improves its processing and storage effects on anthocyanin composition, color and appearance.[95]

Clinical studies. Dietary berries have been associated with protective effects against chronic diseases, especially lowering the risk factors of coronary artery disease.[96] Thus, the consumption of berries produces a decrease in blood pressure, lipid peroxidation and LDL oxidation, an increase of plasma antioxidant capacity and high-density lipoprotein-cholesterol and an attenuation of arterial stiffness. By using different species, the ability to reduce microvascular impairments and decrease apoptosis and/or necrosis induced by ischemia–reperfusion was also demonstrated.[97,98] The hypothesis of increased NO production as being primarily for the beneficial effects of berries appears more likely.

Experimental studies. In our laboratory, we demonstrated the beneficial effects of a non-alcoholic extract of berry fruit from *Vaccinium meridionale* against reperfusion injury in an isolated rat heart also showing that the increase of eNOS *via* Akt and the scavenging activity contribute to the cardioprotection.[99] The cardioprotective effects have been recently confirmed by Shen *et al.*,[100] who analyzed the effect of a fermented aqueous extract in ischemia-induced male albino Wistar strain rats. The administration of 1, 10, or 25 mg kg^{-1} d^{-1} of the extract for 15 days produced a reduction of serum marker enzymes, necrosis, and lipid peroxidation and an increase of antioxidant enzymes, reduced glutathione and NOS and Akt

expression. According to these results 'mortiño' could be considered as a potential therapeutic agent for the treatment of ischemia–reperfusion injury.

Cocoa extracts

Cocoa and chocolate are two products derived from the processing of *Theobroma cacao* L. (Malvaceae) tree seeds. The main difference between cocoa and chocolate is the absence or existence of cocoa butter. In cocoa, butter is little or non-existent, but in contrast, chocolate has butter. Therefore, cocoa is considered as a healthy drink because it has less sugar and fat. The earliest use of chocolate dates back to the Olmec civilization in Mesoamerica, and after the European discovery of the Americas, it became very popular in the wider world, due to the highly attractive organoleptic characteristics, and its demand exploded. Cocoa has the highest flavanol content of all foodstuffs on a weight basis and is a significant contributor to the total dietary intake of flavonoids. The main flavanols in cocoa are the monomers catechin and epicatechin (Fig. 4). These monomers can form links between C4 and C8, allowing them to assemble as dimers, oligomers, and polymers of catechins, the so-called procyanidins. Procyanidins are also shown as condensed tannins, which, through the formation of complexes with salivary proteins, are responsible for the bitterness of cocoa.[101] Some of these compounds, such catechin and epicatechin, are AMPK activators, which justify part of the pharmacological properties of cocoa, and could also be implicated in its cardioprotective effects.[22]

Clinical studies. Previous studies show a high degree of risk reduction of about 50% in cardiovascular and all-cause mortality associated with regular cocoa intake,[102] simultaneously with the detection of anti-hypertensive, anti-inflammatory and anti-platelet aggregation actions by cocoa product ingestion.[102–107] Also, the importance of establishing the doses of cocoa flavanols to obtain these cardiovascular benefits has recently been emphasized.[105] The inhibition of 5-lipoxygenase, the reduction of arginase activity and the increase in NO activity are some mechanisms involved in the beneficial actions of cocoa polyphenols.[102,106–109] Taking into account that NO plays an important role in vasodilation, the anti-hypertensive action of cocoa polyphenols could be mediated by that agent.[110,111] No differences of arterial pressure between cocoa treated and untreated groups have also been reported.[112]

In a controlled clinical trial of transplanted patients or patients with heart failure the consumption of chocolate showed an improvement of vascular function and a decrease of platelet function.[113,114] These effects are parallel to the significant reduction of oxidative stress and are positively correlated with the plasma concentration of epicatechin.[115] Given the complex interplay of different cocoa/chocolate constituents, it is very difficult to dissect the mechanisms involved in the benefits of their consumption. However, an enhanced NO bioavailability appears as one of the most important mechanisms.[116]

Experimental studies. González-Arbeláez *et al.*[117] have recently demonstrated that acute treatment at the onset of reperfusion with a polyphenol-enriched cocoa extract ameliorated the infarct size and attenuated the mitochondrial permeability in an isolated rat heart. In the same study, it was demonstrated that PI3K/Akt, GSK-3β and eNOS mediated signaling pathways are responsible for the beneficial actions of the extract.

Olive leaves and oleuropein

Clinical studies. The data emanating from a number of studies suggest that an olive leaf extract may influence cardiovascular disease risk *via* its potential to induce anti-atherosclerotic, hypotensive, anti-inflammatory and hypocholesterolemic effects.[118] Specifically, Susalit *et al.*[119] demonstrated that an olive leaf extract was similarly effective in lowering systolic and diastolic blood pressures in subjects with stage-1 hypertension as captopril.

Experimental studies. Manna *et al.*[120] and Janahmadi *et al.*[121] observed that treatment with oleuropein (Fig. 4) protects against cardiac damage induced by ischemia–reperfusion, limiting the infarct size and improving the post-ischemic recovery of myocardial function. Among the mechanisms proposed the inhibition of apoptosis and the reduction of oxidative stress appear as the most likely.[122] Similar results were obtained by the Andreadou group[123–126] who showed that the administration of oleuropein exerts anti-ischemic and hypolipidemic effects, and prevents the appearance of cardiomyopathy induced by the chronic administration of doxorubicin, through the regulation of pro-apoptotic mediator expression, reduction of nitro-oxidative stress and restoration of NO homeostasis. Recent findings indicate that oleuropein protects against ischemia–reperfusion injury through its antioxidant potential and activation of PI3K/Akt and ERK1/2 signaling pathways.[127,128]

Ginseng and ginsenosides

Clinical studies. Many cardiovascular benefits attributed to *Panax ginseng* include cardioprotection, antihypertensive effects, and attenuation of myocardial hypertrophy and heart failure.[129] However, there is some evidence of patient risk associated with ginseng abuse, describing unfavorable symptoms of its consumption such as morning diarrhea, nervousness and depression with a relatively low frequency of toxic incidence.[130] In this sense, a study from the 1970s contraindicated ginseng in hypertension highlighting the need to use efficacy-based standardized preparations.[131] This topic was also taken into account by a more recent paper, which demonstrated the efficacy of a ginsenoside Rg3 extract to reduce the central and peripheral arterial pressures in healthy adults.[132] Hence, further investigation is required to clarify these issues.

Experimental studies. In relation with these compounds, the negative inotropic effect of ginsenosides Rb1 and Re (Fig. 5)[133] and the vasodilator effect of ginsenoside Rg3 (Fig. 5) have been demonstrated.[134] The suppression of L-type Ca^{2+} current and the activation of K^+ current through eNOS and PI3K/Akt signaling pathways were the mechanisms proposed for the beneficial actions of ginsenosides at the cardiovascular level.[135–138] In the case of ginsenoside Rb1, the activation of AMPK[22] and the suppression of PI3K-mediated MPTP opening

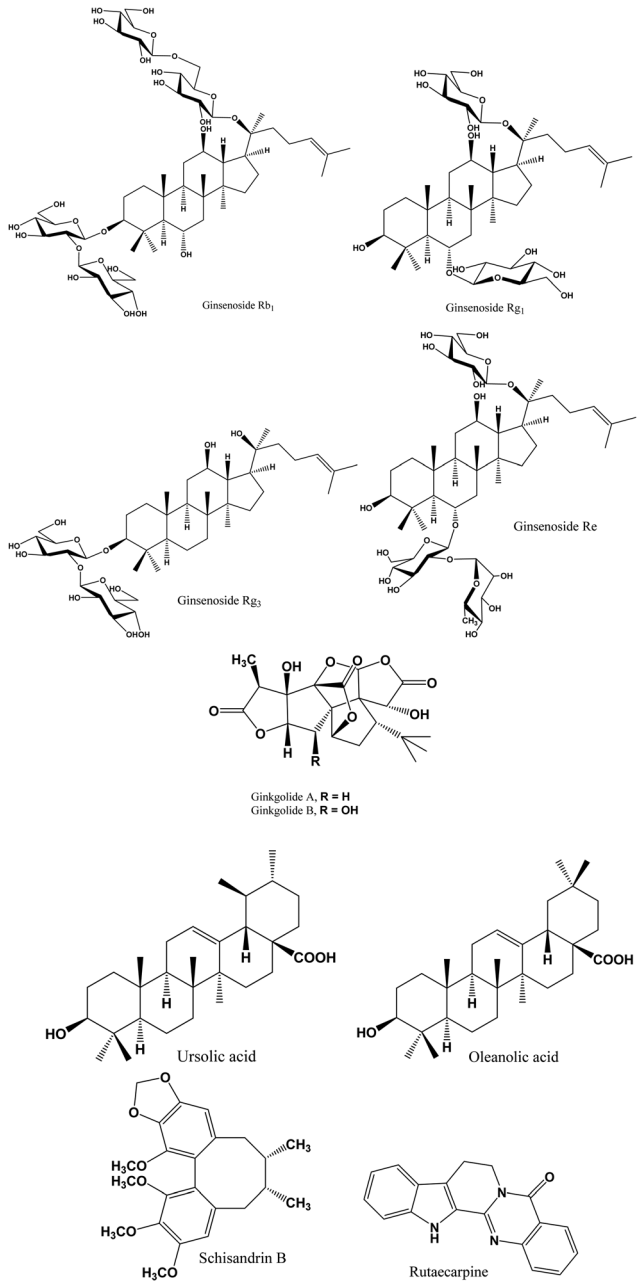

Fig. 5 Chemical structures of some active ginsenosides from *Panax ginseng* and ginkgolides A and B from *Ginkgo biloba*. Chemical structures of ursolic acid, oleanolic acid, schisandrin B and rutaecarpine.

have been included as the mechanisms responsible for its cardioprotective effects.[139,140] The reduction of apoptosis by ginsenoside Re through the decrease of pro-apoptotic Bcl2 protein expression in rats subjected to coronary artery occlusion and reperfusion was also described.[141]

Ginkgo, ginkgolides and flavonoids

Clinical studies. A previous paper[142] summarizes the data about the beneficial effects of an extract of *Ginkgo biloba* L. (Ginkgoaceae) on patients with angina pectoris but the authors indicate that more rigorous clinical trials are needed to provide conclusive evidence.

Experimental studies. At the experimental level many studies demonstrate the beneficial actions of *Ginkgo* on cardiovascular disease.[143] It was previously shown that *in vitro* exposure of hearts to a *Ginkgo biloba* extract (EGb761) or to ginkgolides A and B (Fig. 5), or *in vivo* pretreatment of rats with the terpene-free fraction of EGb761 protects the myocardium against ischemia–reperfusion injury.[144] These authors also showed that the antioxidant effect of flavonoid metabolites (formed *in vivo*) was superior to that of intact flavonol glycosides (present *in vitro*), indicating that part of the cardioprotection afforded by EGb761 involved an antioxidant-independent mechanism.

Other species of interest

The cardioprotective effects of other plant species used in folk medicine have also been demonstrated. Thus, a recent study shows that a phenylethanoid glycoside-rich extract of *Cistanche deserticola* Y.C.Ma (Orobanchaceae) protects the heart against ischemia–reperfusion injury through a reduction of oxidative stress and inhibition of apoptosis.[145]

Ajwa is a special variety of dates (*Phoenix dactylifera* L., Arecaceae) used in Arabian traditional medicine against cardiovascular disease. Al-Yahya *et al.*[146] showed the amelioration of isoproterenol-induced cardiomyopathy achieved by a lyophilized aqueous extract of Ajwa, with the antioxidant, hypolipidemic, anti-inflammatory and anti-apoptotic properties appearing as the responsible mechanisms.

A dry powder of honey mesquite tree, *Prosopis glandulosa* Torr. (Leguminosae), also showed cardioprotective effects, reducing infarction and hypertension through PI3K/Akt pathways.[147] The protective effects of a *Salvia miltiorrhiza* Bunge (Lamiaceae) aqueous extract against ischemia–reperfusion injury have also been previously documented.[51] It was also demonstrated that an upregulation of p-Janus kinase 2 (JAK2) and p-STAT3 protein expression, and a decrease of TNF-α and IL-6 concentrations were the involved mechanisms of *Salvia miltiorrhiza* extract-mediated cardioprotection.

Jiang *et al.*[52] established the antioxidative and cardioprotective relationship of *Dracocephalum moldavica* L. (Lamiaceae). These authors observed that after pretreatment with 5 μg mL^{-1} of that extract, the infarct size became smaller, the SOD activity and GSH/GSSG ratio increased and lipid peroxidation decreased.

Isolated compounds: flavonoids, terpenoids and alkaloids

The principal cardioprotective actions described above have been attributed to phenolic compounds. However, in the bibliography, there exists evidence about the ability of no phenolic compound to protect the myocardium against ischemia–reperfusion injury. In this sense, the isolated flavonoids, rhamnetin,

dihydromyricetin and quercetin (Fig. 4), were the principal studied compounds.

Park *et al.*[148] showed that rhamnetin decreased H_2O_2-induced cell death, inhibited ROS intracellular production and enhanced catalase and MnSOD expression in cardiomyoblasts (H9c2 cells). This flavonoid also increased Akt/GSK-3β and MAPK phosphorylation and decreased apoptosis by the activation of sirtuin-3 and sirtuin-4. Quercetin, an analogous flavonol, had similar properties to those of rhamnetin and PI3K/Akt and MAPKs-dependent pathways are implicated in its cardioprotective effects.[149]

Dihydromyricetin is one of the most abundant components in vine tea, commonly known as the tender stems and leaves of *Ampelopsis grossedentata* (Hand.-Mazz.) W.T.Wang (Vitaceae). The cardioprotective effects of dihydromyricetin were evaluated by Liu *et al.*[150] using a regional ischemia model (left anterior descending coronary artery occlusion) in rats and a protocol of hypoxia–reoxygenation in H9c2 cells. The pretreatment with dihydromyricetin provided significant myocardial protection, enhanced antioxidant capacity and inhibited apoptosis both *in vivo* and *in vitro*. The authors also demonstrated that the beneficial effect on myocardium was correlated with the activation of PI3K/Akt and HIF-1α-mediated signaling pathways. These actions of dihydromyricetin might be important for the clinical efficacy of acute myocardial infarction treatment.

A second group of active metabolites are terpenoids. As stated above, diterpenoids from *Ginkgo* or triterpenoids from ginseng could be cardioprotective agents. However, other common plant metabolites from this group may also be relevant. It is the case of triterpenes such as ursolic and oleanolic acids (Fig. 5). Indeed, ursolic acid – present in commercial herbal preparations – at 1.6–5 ng mL^{-1} concentrations exerted beneficial effects on patients with cardiovascular disorders. Improvement of the mitochondrial functionality appeared as a possible mechanism explaining the cardioprotective action of ursolic acid. Thus, Liobikas *et al.*[151] demonstrated that ursolic acid (0.4–200 ng mL^{-1}) induced a significant uncoupling of oxidative phosphorylation and a decrease of H_2O_2 production in cardiac mitochondria. In the case of oleanolic acid, the pretreatment of the myocardium with 0.6 and 1.2 mmol kg^{-1} for 3 days protected against ischemia–reperfusion injury, improving the contractile force recovery. The maximum cardioprotection was associated with parallel increases in mitochondrial GSH and α-tocopherol levels.[152]

Schisandrin B (Fig. 5), a dibenzocyclooctadiene derivative from *Schisandra chinensis* (Turcz) Baill. (Schisandraceae), also protected against myocardial ischemia–reperfusion injury.[153] A later study, performed by Chiu *et al.*,[154] demonstrated that the increased resistance of calcium-stimulated MPTP opening could be the mechanism responsible for the schisandrin B-mediated cardioprotection.

In the case of alkaloids the number of studies is limited. Among them, the principal research was performed by Hu *et al.*,[155] who analyzed the effects of rutaecarpine (Fig. 5) on an isolated guinea-pig heart in a protocol of ischemia–reperfusion injury. These authors demonstrated that rutaecarpine at a concentration of 1.0 μM significantly improved the recovery of cardiac function and reduced the release of creatine kinase. However, at 3.0 μM, rutaecarpine reduced creatine kinase release, increased the coronary flow, but only caused a slight improvement of left ventricular pressure during reperfusion. Because a vanilloid receptor antagonist and a calcitonin gene-related peptide receptor antagonist abolished the cardioprotective effects of rutaecarpine, the authors affirm that its protective effects are due to the stimulation of endogenous calcitonin gene-related peptide release *via* activating vanilloid receptors.

Summary, discussion and conclusion

Although there are a large amount of plants used as food, the number of such plants with evident cardioprotective effects is limited. Only motherwort and hawthorn are cited in the European Pharmacopoeia and accepted in cardioprotective phytotherapy. On the other hand, all the information summarized here highlights the fact that the beneficial effects of natural products on ischemia–reperfusion injury are not only due to their antioxidant properties. The attenuation of mitochondrial permeability – consequently to a low MPTP opening – through PI3K/Akt/PKC/ERK1/2/eNOS-dependent pathways activated by the interaction of natural products with membrane receptors appears as the main mechanism of cardioprotection. Therefore, these findings suggest a potential role for natural products – phenolic compounds and other kinds of chemicals – as a possible therapy for the limitation of post-ischemic damage. However, the high dose of extracts or their constituents used in *ex vivo* or *in vivo* experimental models and the low intestinal absorption of these products when they were orally administered determine that the results obtained cannot be extrapolated directly to humans. Further pharmacological studies, clinical trials and epidemiological studies must be carried out to address the mechanisms of the multi-target actions of natural products and to validate the benefits for safe translation to clinical therapy.

Abbreviations and symbols

Akt	Protein kinase B (serine/threonine-specific protein kinase)
AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
ANT	Adenine nucleotide translocase
BAX	Gene encoded Bax protein
Bax	Bcl2 associated X protein
BCL2	Gene encoded Bcl2 protein
Bcl2	B-cell lymphoma 2 protein
CVD	Cardiovascular disease
CyP-D	Cyclophilin D
EGb761	*Ginkgo biloba* extract 761
eNOS	Endothelial nitric oxide synthase

ERK1/2	Extracellular signal-regulated kinase 1 and 2
FoxO1	Forkhead box protein O1
GPCR	G protein-coupled receptor
GSH	Reduced glutathione
GSK-3β	Glycogen synthase kinase-3β
GSSG	Oxidized glutathione
HF	Heart failure
IP	Ischemic preconditioning
IPC	Ischemic postconditioning
JAK	Janus kinase
LDL	Low-density lipoprotein
MAPK	Mitogen-activated protein kinase
MPTP	Mitochondrial permeability transition pore
NCX	Na^+/Ca^{2+} exchanger
NHE	Na^+/H^+ exchanger
NO	Nitric oxide
Nrf2	Nuclear factor erythroid 2-related factor
NYHA	New York Heart Association
PI3K	Phosphatidylinositol 3-kinase
PKC	Protein kinase C
ROS	Reactive oxygen species
SOD	Superoxide dismutase
STAT	Signal transducer and activator of transcription
VDAC	Voltage-dependent anion channel.

Conflicts of interest

There are no conflicts of interest to declare.

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