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Review

A review on pathophysiology of ischemic-reperfusion injury of heart and ameliorating role of flavonoids and polyphenols

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Ischemia-reperfusion (IR) syndrome is defined as injury caused by the restoration of coronary flow after a period of ischemia. The pathophysiology of ischemia-reperfusion injury involves cellular effect of ischemia, reactive oxygen species and inflammatory cascade. Flavonoids and polyphenols possess unique antioxidant properties and other protective activities which are beneficial for ischemia-reperfusion injury. It is found that flavonoids and polyphenols prevent production of reactive oxygen species and thereby inhibit oxidation of cellular components and also block propagation of oxidative reactions. They also increase the activity of endogenous antioxidant enzymes such as superoxide dismutase and catalase during ischemia-reperfusion injury. Flavonoids also possess anti-inflammatory, anti-platelet aggregation and vasodilatory effects through different mechanism. This review scrutinize to what extent flavonoids and polyphenols play a role in moderating ischemia-reperfusion mediated injury with special emphasis on pathophysiology of heart ischemic-reperfusion injury.

Key words: Ischemia, reperfusion, heart, flavonoids, polyphenols, antioxidant.

INTRODUCTION

Heart diseases are the major causes for most of the mortalities in the developed countries. World Health Organization (WHO, 1969) described heart disease as the greatest epidemic. In India, heart ailment has become the third greatest killer (Rajasekhar et al., 2004). According to the World Health Report (2002), cardio-vascular diseases (CVD) will be the largest cause of death and disability in India by 2020. Much of these are attributed to rapid acquisition adverse lifestyle which includes smoking, alcohol, physical in-activity, improper diet, stress, etc. Cardiovascular diseases killed nearly 17 million people in 2011, which are 3 in every 10 deaths. Of these, 7 million people died of ischemic heart disease and 6.2 million from stroke (Figure 1 and Table 1).

Ischemia comprises not only insufficiency of oxygen (hypoxia), but also reduced availability of nutrient and inadequate removal of metabolite. Ischemic heart disease (IHD) is due to narrowing or occlusion of one or more branches of coronary arteries. When a tissue is deprived of oxygenated blood flow followed by re-establishing the blood flow (reperfusion), the reintroduction of oxygen can result in tissue damage and is known as ischemic-

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Table 1. Top 10 leading causes of death in the world in the year 2011.

Disease	Death (million)
Ischemic heart disease (IHD)	7
Stroke	6.2
Respiratory infection	3.2
Chronic obstructive pulmonary disease (COPD)	3
Diarrhoeal disease	1.9
Acquired immune deficiency syndrome (AIDS)	1.6
Diabetes mellitus	1.5
Lung cancer	1.4
Road injury	1.3
Prematurity	1.2

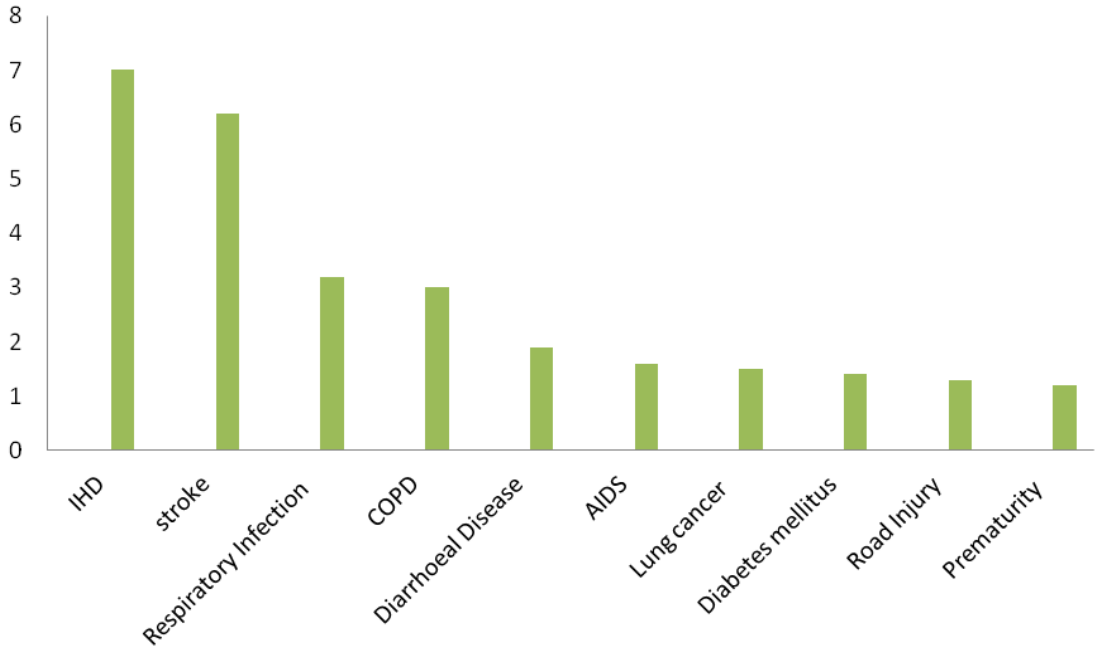

Figure 1. Leading cause of death in the year 2011.

ischemic-reperfusion (IR) injury. In case of heart, IR injury is due to restoration of coronary blood flow after a period of myocardial ischemia. The main pathology for IR injury is over production of free radical, that is, reactive oxygen species (ROS) in the heart especially during the period of reperfusion. Reperfusion of ischemic heart is associated with vascular and micro-vascular injury, endothelial cell dysfunction, increased myocyte edema, necrosis, apoptosis and cardiac contractile dysfunction (Simon and Gregory, 1996). Conditions under which IR injury is encountered include the different forms of acute vascular occlusions (stroke, myocardial infarction) with their respective reperfusion strategies (thrombolytic therapy, angioplasty, operative revascularization, cardiopulmonary bypass, etc.) and major trauma/shock (Biagi et al., 2000). The endogenous antioxidants such as glutathione peroxides, superoxide dismutase and catalase act as primary defence mechanism whereas others, including vitamin E play a secondary role in attenuating the IR injury. But compared to other major organ, heart has low antioxidant defences and is highly vulnerable to free radical mediated damage (Pragada et al., 2004).

Several medicinal plants and their phytoconstituents (such as flavonoids and polyphenols) have been found to possess antioxidant properties and have beneficial effects in myocardial ischemia (MI) and reperfusion injury (Bhattacharya et al., 2002). A considerable number of these plant-based products have been widely used in India for the treatment of cardiovascular disease, as they are inexpensive, efficacious and safe (Mohanty et al., 2009).

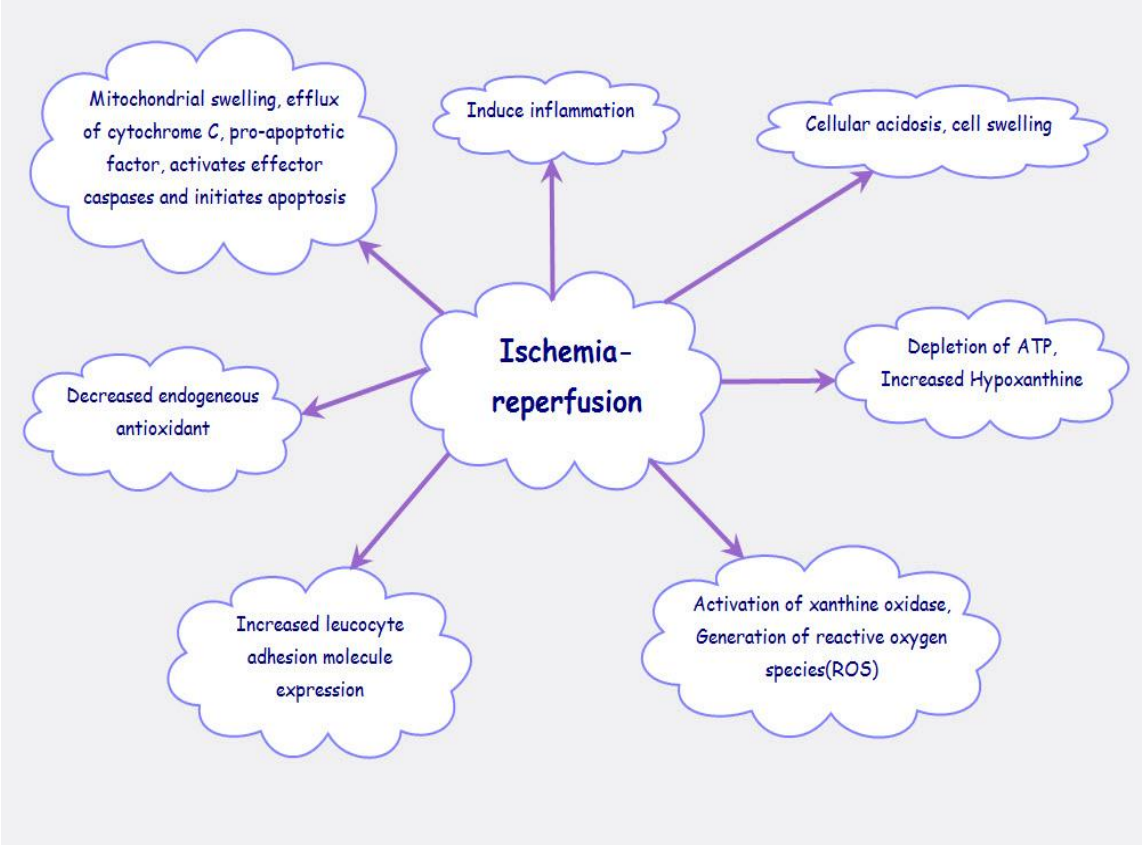

Figure 2. Pathophysiology of ischemia-reperfusion injury.

PATHOPHYSIOLOGY OF ISCHEMIC-REPERFUSION INJURY

Reperfusion of the previously ischemic myocardium is often followed by the detrimental changes in coronary arteries and myocardial tissues, which ultimately lead to cardiac dysfunction, known as ischemia-reperfusion injury (Figure 2).

Pathological changes associated with IR injury

Contractile dysfunction and reperfusion arrhythmias

The deleterious effects of ischemia-reperfusion injury are reversible contractile dysfunction known as myocardial stunning and impairment of blood flow at microvascular level. Myocardial stunning is the contractile dysfunction of heart that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or nearly normal coronary flow.

Reperfusion arrhythmias may be a cause of sudden death after relief of coronary ischemia and are frequent in patients undergoing thrombolytic therapy or myocardial surgical revascularization (Holger and Charles, 2004). Study demonstrates that reperfusion of the ischemic myocardium in animals with normal coronaries often lead to the occurrence of ventricular tachycardia, ventricular fibrillation, or an accelerated idioventricular rhythm, particularly if performed abruptly after 15 to 20 min of ischemia. The occurrence of reperfusion arrhythmias may partly be a result of rapid and sudden alterations in ion concentrations within the ischemic region on reperfusion (Mahmood and Stephen, 2008).

No-reflow phenomenon

The detrimental effect of prolonged post-ischemic reperfusion is no-reflow phenomenon in which no blood flow occurs through coronary blood vessels due to increased leukocyte-endothelial cell adhesion, platelet-leukocyte aggregation, interstitial fluid accumulation and loss of endothelium-dependent vasorelaxation, which all together result in mechanical blood flow obstruction (Rezkalla and Kloner, 2002).

Energy depletion

Energy depletion is other harmful consequences of ischemia as a result of defective synthesis of adenosine

triphosphate (ATP) and degradation of energy rich phosphates, that is, ATP via adenosine diphosphate (ADP) and adenosine mono phosphate (AMP) to adenosine and finally hypoxanthine. Normally, hypoxanthine is converted to xanthine by the enzyme xanthine dehydrogenase in the presence of nicotinamide adenine dinucleotide (NAD). However, under ischemic conditions, xanthine dehydrogenase undergoes a conformational change to xanthine oxidase which is capable of producing highly ROS. This conformational change is also promoted by increased intracellular calcium (Ca^{2+}) (Rezkalla and Kloner, 2002; Buja, 2005).

Cellular acidosis, calcium overload and apoptosis

During ischemia, the reduced O_2 supply causes an increase in the rate of glycolysis, generating H^+ and lactate and decreasing intracellular pH (pHi). The Na^+/H^+ exchanger (NHE) overloads the cytosol with Na^+ as the excess H^+ are extruded, causing the reversal of the Na^+/Ca^{2+} exchanger, which extrudes excess Na^+, but overloads the cytosol with Ca^{2+}. The depletion of ATP during ischemia prevents the activity of pumps such as the Na^+/K^+ ATPase, as well as active Ca^{2+} excretion which prevents the re-establishment of normal cellular ionic homeostasis (Buja, 2005; Karmazyn et al., 1999). Furthermore, there is an increase in ROS production if the first minute of reperfusion is very high as O_2 is re-introduced into damaged mitochondria. Mitochondrial Ca^{2+} overload and increased ROS can result in opening of the mitochondrial permeability transition pore and initiates the translocation of BAX (apoptosis regulator also known as Bcl-2 like protein), from the cytosol to the outer mitochondrial membrane. This causes mitochondrial swelling and induces the efflux of cytochrome C and other pro-apoptotic factor via opening of the permeability transition pore into the cytosol where cytochrome C activates effector caspases and initiates apoptosis (Halestrap et al., 2004).

ROS generation and lipid peroxidation

Under physiological conditions, 95% of oxygen is reduced in the mitochondrium to H_2O via tetravalent reduction without any free radical intermediates, whereas 5% is reduced by univalent pathway in which free radicals like superoxide anion ($^{\cdot}O_2^-$) and hydrogen peroxide (H_2O_2) are produced and are safely metabolized to H_2O by dismutase, catalase and the glutathione peroxidase system. With ischemia, antioxidant defenses become eroded and thus increasingly generates the highly destructive hydroxyl radical ($^{\cdot}OH$) and superoxide ($^{\cdot}O_2^-$) ion that causes direct damage to cellular membranes as well as proteins and induces lipid peroxidation (Braunersreuther and Jaquet, 2012). Following restoration restoration of oxygen supply, the production of ROS by dysfunctional mitochondria rises dramatically and directly damage cellular membranes through lipid peroxidation (Simpson and Lucchesi, 1987).

Leukocyte activation

ROS stimulate leukocyte activation and chemotaxis by activating synthesis of eicosanoids such as thromboxane A_2 and leukotriene B_4 (Buja, 2005). ROS also stimulates leukocyte adhesion molecule and cytokine gene expression via activation of transcription factors such as nuclear factor kB (NF kB) (Zingarelli et al., 2003). Leukocyte activation release proteases and elastases, which result in increased microvascular permeability, edema, thrombosis, and cell death. Various signaling systems such as tumor necrosis factor-α (TNF-α), mitogen activated protein kinase (MAPK), caspases, interleukin-1 (IL-1) and IL-6 are also involved in the pathophysiology of IR injury (Simpson and Lucchesi, 1987; Toyokuni, 1999).

Nitric oxide

Nitric oxide (NO) can also be a mediator of tissue damage during ischemia-reperfusion injury, as it reacts with the abundantly prevalent superoxide anion to form peroxynitrite ($ONOO^-$) and subsequently dissociates into the highly cytotoxic species NO_2 and $^{\cdot}OH^-$. However, as NO also exerts cytoprotective effects, the exact role of NOS enzymes in IR injury is yet to be confirmed (Schulz et al., 2004).

Acute inflammatory response and chemotaxis

Cardiac ischemia-reperfusion injury triggers an acute inflammatory response in which neutrophils via chemotactic attraction infiltrate the myocardium and worsen the condition of the already injured tissue. Endothelial cells, in response to specific stimuli like ROS release chemoattractants. These includes leukotriene B_4, monocyte chemoattractants protein (MCP), adhesion molecules such as intercellular adhesion molecule 1 (ICAM 1), vascular cell adhesion molecules (VCAM) and selectins, leading to neutrophil attraction (Kukielka et al., 1993), sequestration and adhesion to the microvasculature. Accumulation and sequestration of neutrophils in the coronary microcirculation can lead to the occlusion of the microvasculature and thereby interferes with blood flow in the reperfused region (Seal and Gewertz, 2005).

Activation of compliment system

Ischemic-reperfusion results in local activation of

compliment system and leads to production of compliment factors C3a, C5a, and membrane attack complex (MAC). C5a exerts numerous pro-inflammatory effects such as chemotaxis of neutrophils, release of proteases, production of oxygen radicals which may further amplify the inflammatory response by initiating production of TNF, IL-1, and IL-6 and monocyte chemo-attractants protein (MCP-1). Predominant role of C5b-9 is also indicated in IR mediated tissue injury (Kukielka et al., 1993; Seal and Gewertz, 2005).

AMELIORATING ROLE OF FLAVONOIDS AND POLYPHENOLS

Polyphenols are natural substances with variable phenolic structures and are elevated in vegetables, fruits, grains, bark, roots, tea, and wine. Polyphenols are the most abundant antioxidant in the diet (Manach et al., 2004). Their total dietary intake could be as high as 100 mg/day to 1 g/day, which is much higher than all other classes of phytochemicals and dietary anti-oxidants even much higher than Vitamin C and vitamin E (Rice-Evans, 2001). About 8000 different polyphenols are known to be widely present in plants, and their structure can range from simple compounds to highly polymerized structures, such as tannins (Ghasemi et al., 2009). It is reported that antioxidant activity fruits and vegetables significantly increases with the presence of high concentration of total polyphenols content (Fantinelli et al., 2005).

Flavonoids are a subgroup of the more extended family of polyphenols with a basic structure containing two benzene rings with a pyrane ring in the middle. Flavonoids are outstanding antioxidants and because of their antioxidant activity as well as their abundance in fruit and vegetables, they may partly contribute to the currently-known health benefits of plant foods (Aneja et al., 2004; Ikizler et al., 2007; Modun et al., 2003).

Experimental findings of some flavonoids and polyphenols against ischemic-reperfusion injury

(1) The administration of crataegus flavonoid by oral route protects the brain against delayed cell death caused by ischemia-reperfusion injury and also found to increase the antioxidant level in the brain (Zhang et al., 2004).
(2) The garlic-derived flavonoids also have a protective effect against ischemic brain injury. The neuroprotective effect of garlic might be associated with control of the free-radical burst and preservation of antioxidant enzyme activity (Aguilera et al., 2010).
(3) Epigallocatechin-3-gallate (EGCG), that is, the most prominent catechin polyphenols found in green tea is beneficial for the treatment of reperfusion induced myocardial damage. Experimental evidence showed that EGCG reduced myocardial damage by decreasing plasma IL-6, creatine phosphokinase levels and myeloperoxidase activity in rats. The beneficial effect of EGCG was also said to be associated with reduction of nuclear factor-κB and activator protein-1 DNA binding (Aneja et al., 2004).
(4) Quercetin when administered before ischemia reduced malondialdehyde levels in heart tissues after reperfusion (Ikizler et al., 2007). Similarly, 30 days feeding of rats with red grapes also attenuated formation of malondialdehyde in ischemic-reperfused hearts (Pataki et al., 2002).
(5) Salvianolic acid A, constituent of *Salvia miltiorrhiza* has potent antioxidant activity against peroxidized damage to biomembranes. This beneficial effect protects vascular walls from oxidation, inflammation, thrombus formation, etc., (Zhang et al., 2010).

PLAUSIBLE PROTECTIVE MECHANISMS OF FLAVONOIDS AND POLYPHENOLS

Antioxidant and free radical scavenging activity

Flavonoids, polyphenols and their metabolites display antioxidant activity (Pietta, 2000), also potent scavengers (Chun et al., 2003) of ROS such as superoxide, peroxide radicals, and peroxynitrite. Their ability to increase the plasma antioxidant status and preservation of erythrocyte membrane polyunsaturated fatty acids has been proved experimentally. They inhibit the lipid peroxidation, thereby prevent peroxidized damage of biomembranes and formation of malondialdehyde. Flavonoids exert cardiovascular protection by decreasing oxidative stress and increasing NO bioavailability (Maulik et al., 1996). Polyphenols, especially, the flavonols such as kaempferol, quercetin and their derivatives may inhibit the oxidation of low density lipoprotein (LDL) cholesterol, reduce platelet aggregation, or reduce ischemic damage. Polyphenols such as apple polyphenols acts by suppressing mitochondrial superoxide production, thus prevent mitochondrial damage. Flavonoids at relatively low concentrations can be important antioxidants in microenvironments that are less accessible to vitamin C and vitamin E. Interestingly, it has been suggested that specific flavonoids upon binding metals may behave as a superoxide dismutase, scavenging superoxide more potently than the parent flavonoids, while devoid of catalytic activity for the Fenton conversion of hydrogen peroxide to hydroxyl radicals (Vanisha et al., 2010; Malesev and Kuntic, 2007) (Figure 3).

Antioxidant in microenvironment and intermediate antioxidant

Flavonoids are proposed to act as intermediate antioxidants

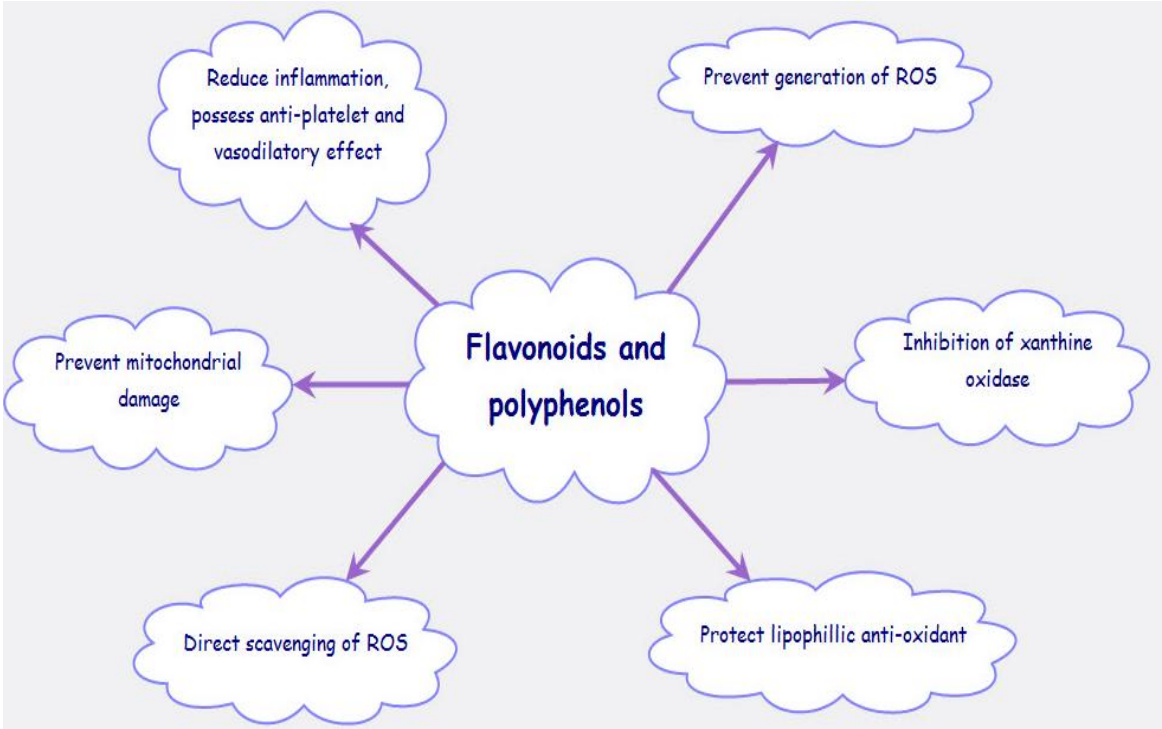

Figure 3. Plausible protective mechanisms of flavonoids and polyphenols.

antioxidants, where protecting lipophilic antioxidants (Vitamin E) and being protected by hydrophilic antioxidants (Vitamin C). Flavonoids also possess the ability to chelate iron ions known to catalyze many free radical-generating processes. This property probably also contributes to their antioxidant effectiveness (Lotito and Fraga, 2000) (Figure 3).

Inhibition of xanthine oxidase and nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase

These may be other mechanisms by which flavonoids at physiological concentrations can mitigate ischemia-reperfusion injury (Cos et al., 1998). Several flavonoids including luteolin, apigenin, quercetin, myricetin, and kaempferol have been shown to inhibit xanthine oxidase. Inhibition of the NADPH oxidase of endothelial cells has recently been proposed as a mechanism by which catechins improve vascular function, which could be of benefit in protecting against ischemia-reperfusion injury (Schewe et al., 2008) (Figure 3).

Vasodilatatory effect

A variety of flavonoids and polyphenols have shown the capacity to dilate blood vessels (vasodilatation). Their mechanism of action is various and may be exerted in endothelium-dependent and/or independent manners. The endothelium-dependent relaxation effect of polyphenols is mediated by nitric oxide. Flavonoids may also promote vasorelaxation by stimulating production of prostacyclins by endothelial cells (Ajay et al., 2003; Novakovic et al., 2006) (Figure 3).

Anti-inflammatory and anti-platelet effect

Flavonoids inhibit the enzymes involved in eicosanoids pathways, including phospholipase A_2 (Kim et al., 2004), cyclooxygenases and lipoxygenases, thus limits the production of inflammatory mediators such as prostaglandins and leukotrienes (Kim et al., 1998). Flavonoids and polyphenols can inhibit the expression of inflammatory mediators such as ICAM-1, by acting on NFkappaB activation. Flavonoids can also inhibit production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and interferon-γ (Rimbach et al., 2001). Flavonoids have also been shown to inhibit platelet activation and aggregation (Gallego et al., 2007). The anti-platelet effect of flavonoids may be because of increased production of prostacyclin or by increased cyclic adenosine monophosphate (cAMP) through inhibition of phosphodiesterases responsible for degradation of cAMP (Bertelli et al., 1995) (Figure 3).

Inhibition of matrix metalloproteinases

Matrix metalloproteinases (MMP) are a family of proteases that play a major role in protein degradation and tissue remodeling. It is confirmed experimentally that flavonoids, at physiologically relevant concentrations, inhibit matrix metalloproteinases (especially two members of this enzyme family, namely MMP-2 and -9) (Ende and Gebhardt, 2004) (Figure 3).

CONCLUSION

Research on the effect of dietary polyphenols and flavonoids on human health developed considerably in past 10 years. It strongly supports a role for polyphenols and flavonoids in the prevention of cardiovascular disease. It has become clear and evident that the flavonoids and polyphenols exert myocardial protective effects via antioxidant activities, preservation of nitric oxide, anti-inflammatory activities and modulation of matrix metalloproteinases.

There have been many studies in various systems on the polyphenols and flavonoids, however more depth study about their source and the way they protect the heart from ischemia-reperfusion injury is highly appreciated and warranted. This will establish much more effective correlations between isolated polyphenols, flavonoids and their cardioprotective effect.

CONFLICT OF INTEREST

The authors have declared that there no conflict of competing interest.

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