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REVIEW

Flavonoids in modulation of cell survival signalling pathways

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Abstract Flavonoids, a family of polyphenols, generally found in various fruits and vegetables, as well as in many plant beverages such as tea, pomegranate juice, raspberry, blueberries, and red wine. Recently, studies on flavonoids have attracted scientific attention as a potential nutritional strategy to prevent a broad range of chronic disorders. Many studies suggest that consumption of these flavonoids in sufficient amount plays neuroprotective, cardioprotective, anti-inflammatory, and chemopreventive roles. While there has been a major focus on the antioxidant properties, there is an emerging view that flavonoids and their in vivo metabolites do not act only as conventional antioxidants but may also exert modulatory actions on cellular system through direct action on various signalling pathways. These pathways include phosphoinositide 3-kinase, Akt/protein kinase B, mitogen-activated protein kinase, tyrosine kinases, and protein kinase C. Various inhibitory or stimulatory actions of flavonoids on these pathways greatly affect cellular functions by altering the phosphorylation state of targeted molecules. In addition, flavonoids also modulate various gene expressions through activation of various transcription factors. Thus, the present review will bestow a breathing overview regarding the prime role of flavonoids in modulation of survival signalling pathways at cellular system.

Keywords Plant polyphenols · Phosphoinositide 3-kinase · Akt/protein kinase B · Mitogen-activated protein kinase · Protein kinase C · Cell survival

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Introduction

Flavonoids are a subclass of polyphenols, derived from plants secondary metabolism. They play important roles in the plant biology and human health. Flavonoids have been referred to as "nature's biological response modifiers" because of the strong experimental evidence of their inherent ability to modify the body's reaction to allergens, viruses, and carcinogens. They show anti-allergic, anti-inflammatory, anti-microbial, and anti-cancer activities. Evidences strongly support the contribution of flavonoids in the prevention of cardiovascular diseases (Mursu et al. 2008), neurodegenerative diseases (Scalbert et al. 2005), coronary heart disease (Knekt et al. 2002), cancers (Belguise et al. 2007; Hazgui et al. 2008), and osteoporosis (Choi 2011). There is also a growing interest in the potential of flavonoids to improve memory, learning, and general cognitive ability (Spencer 2008). Many studies have shown that this contribution is mainly due to the antioxidant power of particular flavonoids and flavonoid-rich extracts (Chen et al. 2000; Rice-Evans 1995, 2001).

Flavonoids are characterized by possessing two or more aromatic rings, each bearing at least one hydroxyl group and connected with a carbon bridge (Clifford 2001). Depending on structural features, flavonoids can be subdivided into following subclasses; (1) flavones (e.g., apigenin, luteolin, and tangeretin), (2) flavonols (e.g., kaempferol, quercetin, myricetin, and rhamnazin), (3) isoflavones (e.g., daidzein, genistein), (4) flavanones (e.g., hesperetin, naringenin, and eriodictyol), (5) flavonols (e.g., silibinin, taxifolin, and dihydrokaempferol), (6) flavonols [e.g., (+)-catechin, (−)-epicatechin, epigallocatechin, and epigallocatechin gallate (EGCG)], (7) anthocyanidins (e.g., pelargonidin, cyanidin, delphinidin, and malvidin) (Vauzour 2012). The widespread distribution of flavonoids, their variety, and their

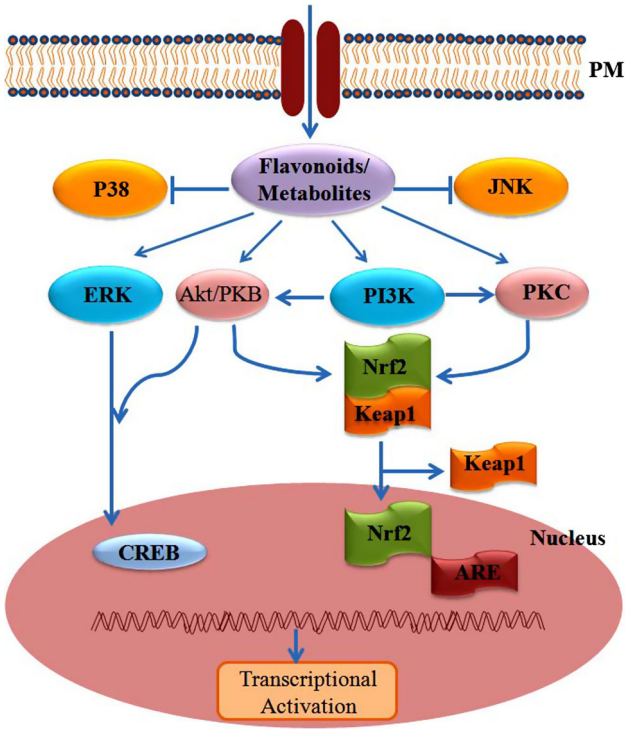

Fig. 1 Schematic representation of interaction of flavonoids with cell signalling pathways. As shown in figure, flavonoids activate various signalling pathways such as ERK, Akt/PKB, PI3K, and PKC to improve the cell survival. The symbol *arrows* show the activation, and the symbol *box drawings light up and horizontal* show deactivation of various signalling pathways. *ERK* extracellular signal-regulated protein kinase; *JNK* c-Jun N-terminal kinase; *PI3K* phosphatidylinositol-3 kinase; *PKC* protein kinase C; *Akt/PKB* protein kinase B; *ARE* antioxidant response element; *CREB* cAMP response element-binding protein; *Nrf2* nuclear factor (erythroid-derived 2)-like 2; *PM* plasma membrane

relatively low toxicity compared to other active plant metabolites (for instance alkaloids) had led to consumption by human beings in significant quantities (Isaac et al. 2011). The main dietary sources of flavonoids are fruits, vegetables, and plant-derived beverages such as tea, coffee, and red wine. However, there is still a difficulty in determining the dose for the daily intake of flavonoids because of the complexity of existence from various food sources and the occurrence of a large amount of flavonoids itself in nature.

The molecular actions of flavonoids are largely dependent on their bioavailability at the target tissue, and now it has been clear that the concentrations of flavonoids and their metabolite forms accumulated in vivo (Manal et al. 2006) are lower than those recorded for small-molecule antioxidant nutrients such as ascorbic acid and α-tocopherol (Halliwell et al. 2005). There is a new emerging view that if flavonoids have any preventive or curative activity through their ingestion, this effect must involve not only their antioxidant potential, but also the modulation of multiple cellular pathways that are crucial in the pathogenesis of various diseases (Williams et al. 2004). Evidences are mounting to show that flavonoids and their metabolites may exert modulatory actions in cells through actions on protein kinase and lipid kinase signalling pathways. The signalling pathways which are targets of flavonoids include phosphatidylinositol-3 kinase (PI3K) (Choi 2011; Kyoung et al. 2010; Lin et al. 2012), protein kinase B (Akt/PKB) (Hwang and Yen 2009; Kyoung et al. 2010; Vauzour et al. 2007), protein kinase C (PKC) (Luo et al. 2012; Levites et al. 2002), and mitogen-activated protein kinase (MAPK) (Huang et al. 2007; Hwang and Yen 2009; Kyoung et al. 2010; Park et al. 2011; Vauzour et al. 2007) (Fig. 1). Inhibitory or stimulatory actions on these pathways by flavonoids greatly affect cellular functions by altering the phosphorylation state of target molecules and by modulating gene expression (Table 1). In this review, we provide thorough overview of role of various flavonoids on different cell survival signalling pathways.

Signalling pathways targeted by flavonoids

During the last decade, important advances have been made in our understanding of the molecular events underlying cellular responses to extracellular signals. The cell signalling is a critically important mechanism for the multicellular organisms including human beings particularly for inflammatory, cardiac, and neurological functions. In many diseases, the signal transduction mechanisms responsible for inducing cell survival and apoptosis (cell death) have been identified. In recent years, there is much emphasis on the role of flavonoids in modulation of signalling pathways especially during various diseases (Fu et al. 2010; Hwang and Yen 2009; Kyoung et al. 2010; Rainey et al. 2008; Vauzour et al. 2007). Evidences indicate that cell signalling continuously declines with ageing (Miyamoto et al. 2013; Naidoo et al. 2008) and these processes are subjected to alterations during cardiovascular diseases, neurodegenerative diseases, etc. (Lakatta and Levy 2003a, b; Rice and Curran 1999). Thus, there is a new emerging view to cure such diseases by modulating the intracellular signalling pathways by use of various natural compounds. It is for this reason that cell signalling pathways have come to be appreciated as attractive targets for drug development. We discuss here the role of flavonoids in targeting various cell survival signalling pathways including PKC, MAPKs, and PI3K/Akt.

PKC pathway

Protein kinase C is an integral part in the cell signalling machinery. Members of this enzyme family play distinct

Table 1 Showing cell signalling pathways targeted by different flavonoids. Shows the effect of flavonoids observed in various cell signalling pathways. The activation of ERK, Akt/PKB, PI3K, and PKC is important to improve the cell survival, and the down-regulation of P38 and JNK is preventing the apoptosis. The activation of signalling pathways is shown as up arrow (↑) and down-regulation of signalling pathways by flavonoids is shown in down arrow (↓)

S. no.	Flavonoids	Activation (↑), deactivation (↓)	Signalling pathways	Cell line	Response	References
01	ECG	↓	P38	HaCaT keratinocytes, endothelial, rat primary hepatocytes, Chinese hamster lung fibroblast (V79-4) cells, BV2 microglial cells, neuronal cells	Prevent apoptosis, oxidative stress, and endothelial barrier dysfunction, as neuroprotective, for treatment of chronic pain and neuroinflammatory diseases, improve cognitive function, and mitochondrial functions	Choi et al. (2005), Huang et al. (2007), Yang et al. (2010), Hwang and Yen (2009), Huang et al. (2013), Meottia et al. (2007), Park et al. (2011), Liu et al. (2012)
	EGCG	↓				
	Quercetin	↓				
	Hesperetin	↓				
	Luteolin	↓				
	Myricitrin	↓				
	Myricetin	↓				
	Kaempferol	↓				
	Pinocembrin	↓				
	Narirutin	↓				
02	ECG	↓	JNK	HaCaT keratinocytes, endothelial, neuronal, Chinese hamster lung fibroblast (V79-4) cells, BV2 microglial cells	Prevent oxidative stress and apoptosis, neuroprotective, for treatment of neuroinflammatory diseases	Huang et al. (2007), Choi et al. (2005), Hwang and Yen (2009), Park et al. (2011)
	EGCG	↓				
	Quercetin	↓				
	Hesperetin	↓				
	Myricetin	↓				
	Kaempferol	↓				
03	EC	↑	ERK1/2	Neuronal, HaCaT keratinocytes, endothelial cells	Improve brain function, prevent oxidative stress, apoptosis	Schroeter et al. (2007), Huang et al. (2007), Choi et al. (2005)
	ECG	↑				
	EGCG	↑				
04	EC	↑	Akt/PKB	Neuronal, epithelial, (MCF10A, pancreatic, Chinese hamster lung fibroblast (V79-4) cells PAECs, MC3T3-E1	Improve brain function, antioxidant defence, neuroprotective, prevent oxidative stress-induced apoptosis, stimulate eNOS activity, antidiabetic, regulate mitochondrial function	Schroeter et al. (2007), Na et al. (2008), Hwang and Yen (2009), Fu et al. (2010), Vauzour et al. (2007), Yang et al. (2010), Zhanga and Liu (2011), Choi (2011)
	EGCG	↑				
	Hesperetin	↑				
	Myricetin	↑				
	Genistein	↑				
	Kaempferol	↑				
05	EGCG	↑	PKC	Brain cell	Neuroprotective	Levites et al. (2002)
06	EGCG	↑	PI3K	Brain cell, Chinese hamster lung fibroblast (V79-4) cells, PC12, endothelial, PAECs	Neuroprotective, prevents oxidative stress-induced apoptosis, protect oxidative damage, stimulate eNOS activity, promote the activity of eNOS	Levites et al. (2002), Luo et al. (2012), Xi et al. (2012), Yang et al. (2010), Zheng et al. (2012)
	Quercetin	↑				
	Myricetin	↑				
	Genistein	↑				
	Kaempferol	↑				
	Naringenin	↑				

MAPK mitogen-activated protein kinase, *Akt/PKB* protein kinase B, *ERK* extracellular signal-regulated protein kinase, *JNK* c-Jun N-terminal kinase, *PI3K* phosphatidylinositol-3 kinase, *PKC* protein kinase C, *EC* (−)epicatechin, *ECG* (−)-epicatechin-3-gallate, *EGCG* (−)-epigallocatechin-3-gallate, *PAECs* porcine aortic endothelial cells, *Nrf2* nuclear factor erythroid 2-related factor 2

roles for the control of major cellular functions. PKCs are activated in specific intracellular compartments in different ways, depending on various membrane lipid metabolites. The coordinated regulation of PKC activation is critical for normal cell functions, whereas the unusually persistent activation of this enzyme may lead to uncontrollable growth. The PKC activation is necessary for the signal transduction pathways by which many hormones, growth factors, and other extracellular ligands that activate phospholipases mediate their effects on target cells. PKC isoforms are categorized into three groups based on their regulatory properties: conventional PKCs (cPKCs; α, β, and γ), novel PKCs (nPKCs; ε, η, δ, and θ), and atypical PKCs (λ and ζ) (Newton 2001). Conventional PKC isoforms are activated by phospholipids, in particular phosphatidylserine (PS), diacylglycerol (DAG), and Ca^{2+}, whereas novel PKCs

lacking a Ca^{2+} binding site require PS and DAG for activation (Kohl et al. 2006). However, the atypical PKC activation is not dependent on Ca^{2+} while it can be activated by various lipid components like phosphatidylinositols, phosphatidic acid, arachidonic acid, and ceramide (Xiao and Liu 2013). PKC is activated by two coordinated mechanisms: first phosphorylation of three distinct sites within the activation loop, the turn motif, and the hydrophobic domain is required for catalytic competence. Second, binding of DAG as well as PS (for conventional PKCs) and membrane targeting promotes conformational activation of the protein (Dutil et al. 1998; Newton 2003).

PKCs are the target of many flavonoids for providing survival signalling. For example, the (−)-epigallocatechin-3-gallate (EGCG) at a dose of 2 mg/kg body weight markedly increased PKCα and PKCε in the membrane and the cytosolic fractions of mice hippocampus (Levites et al. 2002). Preventive role of EGCG against amyloid beta (Aβ)-induced neurotoxicity was exhibited via PKC pathway. This mechanism of EGCG protects neurons and regulates secretory processing of non-amyloidogenic amyloid precursor protein (APP) (Levites et al. 2002) in brain cells. Pre-treatment with genistein significantly increased cell viability via the PKC activation, decreased the levels of intracellular calcium, prevented DNA damage, and blocked caspase-3 activity in Aβ (25–35) treated PC12 cells (Luo et al. 2012). Pre-treatment of myristoylated (Myr), a general PKC inhibitor, significantly attenuated the neuroprotective effect of genistein against Aβ (25–35)-treated PC12 cells indicates that PKC signalling pathway is involved in the neuroprotective action of genistein (Luo et al. 2012). EGCG (1 and 10 μM) exerts potent neuroprotective actions in the mice model of Parkinson's disease by PKC activation (Levites et al. 2002). EGCG restored the reduced PKC and extracellular signal-regulated kinase (ERK1/2) activities caused by 6-hydroxydopamine (6-OHDA) toxicity (Levites et al. 2002) and protects neurotoxicity. Pre-treatment with PKC inhibitor GF 109203X (1 μM) abolished the neuroprotective effect of EGCG on cell survival suggesting that PKC isoenzymes are involved in the neuroprotective action of EGCG against 6-OHDA (Levites et al. 2002).

MAPKs signalling cascade

Mitogen-activated protein kinases are members of distinct signalling cascades in the cell and serve as focal points in response to a variety of extracellular stimuli (Rouse et al. 1994). The MAPKs are an essential part of signal transduction machinery involved in the gene expression associated with the regulation of inflammation, cell survival, proliferation, inducible nitric oxide synthase (iNOS) and cytokine expression, and collagenase production (Hommes et al. 2003). MAPKs have three major classes ERK, c-Jun N-terminal kinase (JNK), and p38, MAPKs (Johnson and Lapadat 2002). The ERK signalling pathway, also known as the p42/p44 MAPK pathway, is a major determinant of cell growth, cell differentiation, cell survival, and motility. ERK1/2 is usually associated with pro-survival signalling (Arany et al. 2005; Vauzour et al. 2007) through mechanisms that may involve activation of the cAMP response element-binding protein (CREB) (Arany et al. 2005), the up-regulation of the anti-apoptotic protein Bcl-2, and non-transcriptional inhibition of Bcl-xL/Bcl-2-associated death promoter (Choi et al. 2005; Kyoung et al. 2010; Zhanga and Liu 2011). The JNK, or stress-activated protein kinase (SAPK), is an important member of the MAPKs superfamily, the members of which are readily activated by many environmental stimuli. The JNK signalling pathway regulates many cellular events, such as growth control, transformation, and programmed cell death (apoptosis). JNK has been shown to regulate the transcription-dependent apoptotic signalling possibly through the activation of c-Jun (Behrens et al. 1999) and other activated protein 1 (AP1) including JunB, JunD, and activating transcription factor 2 (ATF-2) (Davis 2000). The p38 group of MAPKs serve as a nexus for signal transduction. This signalling pathway has been implicated in cellular responses including inflammation, cell cycle, cell death, development, cell differentiation, senescence, and tumorigenesis. The activation of p38 occurs by a variety of cellular stresses including osmotic shock, pro-inflammatory, inflammatory cytokines, lipopolysaccharides (LPS), ultraviolet light (UV), and growth factors. Active p38 regulates the phosphorylation of the transcription factors ATF-2, myc-associated factor X (Max), and myocyte enhancer factor-2 (MEF2). These transcription factors are implicated in cellular response to a variety of cellular stress, including genotoxic agents and inflammatory cytokines (Spencer 2007). The p38 pathway involvement in apoptosis has been shown in many studies (Kawasaki et al. 1997) on the basis of concomitant activation of p38 and apoptosis induced by a variety of agents such as nerve growth factor (NGF) withdrawal and Fas ligation (Kummer et al. 1997; Juo et al. 1997). There are strong evidences linking the p38 pathway and inflammation (Hollenbach et al. 2005). In addition, the rheumatoid arthritis, Alzheimer's disease, and inflammatory bowel disease are all postulated to be regulated in part by the p38 pathway (Hollenbach et al. 2005).

Several flavonoids have been shown to interact with ERK, JNK, and p38 pathways of the MAPKs. The flavonoid (−)epicatechin (EC) mainly found in green tea has been shown to stimulate a rapid, ERK, and PI3K-dependent, increase in CREB phosphorylation at 100–300 nmol/L concentrations. EC also stimulated ERK and Akt phosphorylation. The 15-min exposure of EC increases the

mRNA levels of the glutamate receptor subunit (GluR2) by 60 %, after and this translated into an increase in GluR2 protein. This suggests that EC has the potential to increase CREB-regulated gene expression and increase GluR2 levels and thus modulate neurotransmission, plasticity, and synaptogenesis (Schroeter et al. 2007).

The (−)epicatechin-3-gallate (ECG), a polyphenolic compound found abundantly in green tea, has been shown to protect keratinocytes from UV-B-induced photo-damage and H_2O_2-induced oxidative stress at the concentration of 100 μM, through inhibition of p38 and ERK1/2 (Huang et al. 2007). Treatment of ECG at the concentrations of 1, 10, and 100 μM reduced the activation of UV-B irradiation-induced JNK in keratinocytes (Huang et al. 2007).

Quercetin, a most abundant flavonoid found in many fruits and vegetables and EGCG, abundantly found in green tea, both inhibited H_2O_2-induced phosphorylation of JNK and p38 MAPK pathway after 60 min of exposure. Both quercetin and EGCG also inhibit H_2O_2-induced caspase-3 activation at the concentrations between 1 and 50 μM/L (Choi et al. 2005). Thus, MAPK-related signalling may regulate expression of apoptotic genes, preventing apoptosis, and promoting cell survival. Another observation demonstrates that EGCG at the concentrations between 5 and 25 μM/L inhibits angiotensin II-induced endothelial stress fibre formation and hyperpermeability via inactivation of p38/heat shock protein 27 (HSP27) pathway and suggests that EGCG may protect against endothelial barrier dysfunction and injury (Yang et al. 2010).

The treatment of human breast epithelial (MCF10A) cells with EGCG induces the expression of glutamate-cysteine ligase (GCL), manganese superoxide dismutase (MnSOD), and haem oxygenase-1 (HO-1). In addition, EGCG treatment also increased the nuclear accumulation, antioxidant response element (ARE) binding, and transcriptional activity of nuclear factor erythroid 2-related factor 2 (Nrf2). Furthermore, EGCG activated Akt and ERK1/2. These findings suggest that Nrf2 mediates EGCG-induced expression of some representative antioxidant enzymes, possibly via Akt and ERK1/2 signalling, which may provide the cells with acquired antioxidant defence capacity to survive the oxidative stress (Na et al. 2008).

Hesperetin found abundantly in citrus foods has been shown to cause significant increases in the level of ERK1/2 phosphorylation when used at concentrations of 100–300 nM. However, at this concentration, hesperetin did not increase CREB phosphorylation. Administration of hesperetin at 300 nM concentration partially reversed staurosporine-induced cell death in primary neurones (Rainey et al. 2008). Hesperetin has been also shown to act as a neuroprotective compound at concentration of 50 μM where antioxidant effects are unlikely to predominate (Hwang and Yen 2009). However, the effects of hesperetin are cell-type dependent and, unlike the flavonol EC, neuroprotection in vitro is not associated with enhanced CREB phosphorylation or cAMP response element mediated gene expression (Rainey et al. 2008). The study results demonstrate that signalling actions of these flavonoids are involved in their neuroprotection against oxidative stress and that they act more as signalling molecules than antioxidants (Hwang and Yen 2009). Another study demonstrated the potential of the flavanones hesperetin and its metabolite, 5-nitro-hesperetin against oxidative stress-induced neuronal apoptosis. It was found that both hesperetin and 5-nitro-hesperetin when used at the concentration of 100 nM/L were effective in preventing neuronal apoptosis via a mechanism involving the activation/phosphorylation of both ERK1/2 and Akt/PKB. Thus, flavanones may protect neurons against oxidative insults via the modulation of neuronal apoptotic machinery (Vauzour et al. 2007).

Luteolin (3′,4′,5,7-tetrahydroxyflavone), a food-derived flavonoid mainly found in celery, green peppers, and thyme, has been shown to persistently activate ERK1/2 in neurons. This suggests that luteolin through the activation of the ERK signalling pathway induces neurite outgrowth and augments cellular antioxidant defence capacity in the neurons (Lin et al. 2010). In addition, luteolin has been shown to reduce pyrogallol-induced endothelial dysfunction via suppressing the poly (ADP-ribose) polymerase activation, caspase-8 cleavage, and p38 activation, and stimulated the ERK signalling pathway to prevent the pyrogallol-induced apoptosis (He et al. 2012).

Myricetin found in grapes, berries, other fruits, and vegetables is an important flavonoid promotes cell survival via the down-regulation of p38 and JNK, against H_2O_2-induced apoptosis. Flavonoids by selectively inhibitory actions at these kinases can have beneficial effects on many diseases which were caused by up-regulation of p38 and JNK pathway. The myricetin prevents oxidative stress-induced apoptosis via regulation of MAPK and PI3K/Akt signalling pathways (Kyoung et al. 2010). Myricitrin, a metabolite of myricetin, has found to inhibit p38 phosphorylation in response to cytokines stimulation. This finding suggests that myricitrin can be useful in modulations of neuropathic and inflammatory chronic pain conditions (Meottia et al. 2007).

Genistein, one of the major isoflavones mainly found in soy and red clover, has been shown to activate the cAMP/PKA-dependent ERK1/2 signalling pathway at the concentration of 5 μM and modulates the antidiabetic effect (Fu et al. 2010).

Chrysin, a flavonoid found abundantly in many plants, honey, and bee propolis, and apigenin which is found in

many fruits and vegetables including celery and apple activated ERK2, Nrf2- ARE binding activity, and ARE-dependent luciferase activity (Huang et al. 2013). It has been shown that siRNAs of both ERK2 and Nrf2 attenuated the chrysin-induced HO-1, glutamate-cysteine ligase catalytic (GCLC), and glutamate-cysteine ligase modifier (GCLM) protein expression (Huang et al. 2013). Kaempferol treatment has been shown to reduce LPS-induced inflammatory mediators through the down-regulation of p38, JNK, Toll-like receptor 4 (TLR4), nuclear factor κB (NF-κB), and Akt in a model of neuroinflammation protection, suggesting that kaempferol has therapeutic potential for the treatment of neuroinflammatory diseases (Park et al. 2011).

Pinocembrin, a flavonoid found in fruits, vegetables, nuts, seeds, herbs, spices, and propolis, has been reported to possess numerous biological activities beneficial to health. Pinocembrin has been shown to improve the cognitive function and decrease neurodegeneration of the cerebral cortex in Aβ-treated mice when administered at the doses of 20 and 40 mg/kg/day (Liu et al. 2012). Pinocembrin markedly depressed the activation of SAPK/JNK and p38 MAPK-MAPKAP kinase-2 (MK2), HSP27, and downstream NF-κB inflammatory response subsequent to interaction between Aβ and receptor for advanced glycation end products in neuronal cells. In addition, pinocembrin significantly improves mitochondrial membrane potential and inhibiting mitochondrial oxidative stress, and thus preserving mitochondrial functions (Liu et al. 2012).

Kaempferol (100 mg/kg body weight) strongly reduced LPS-mediated overproduction of pro-inflammatory cytokines in broncho-alveolar lavage fluid (BALF), including tumour necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin 6 (IL-6) in the mice (Chen et al. 2012). In addition, kaempferol, via suppression of MAPKs and NF-κB signalling pathways, exhibits a protective effect on LPS-induced acute lung injury which may involve the inhibition of tissue oxidative injury and pulmonary inflammatory process (Chen et al. 2012).

Flavonoid narirutin found mainly in orange, tangor, and lemon inhibited the LPS-mediated activation of NF-κB and MAPKs, which are signalling molecules involved in production of pro-inflammatory factors. Thus, with these properties, narirutin can be used as effective anti-inflammatory agent (Ha et al. 2012).

PI3K/Akt pathway

In addition to MAPKs pathway, flavonoids and its metabolites have been also shown to modulate cell survival signalling due to their interaction with PI3K/Akt pathway (Choi 2011; Kyoung et al. 2010). The PI3K/Akt pathway is one of the strongest intracellular pro-survival signalling systems. Inhibition of PI3K pathway abolishes cell survival and accelerates apoptosis, whereas an activated form of the Akt/PKB, a downstream effector of PI3K, blocked apoptosis (Kennedy et al. 1997). PI3Ks are enzymes that transfer phosphate to position 3 of the phosphoinositide ring, regulating a variety of cell responses including survival, division, and transformation. Based on their primary structure and substrate specificity, PI3Ks are divided into three subclasses, but only the class I enzymes generate phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate (3-poly-PtdIns) products in vivo (Jimenez et al. 2002). Class IA PI3K is a heterodimer composed of a p85 regulatory and a p110 catalytic subunit, of which there are several isoforms (Escobedo et al. 1991; Fruman et al. 1998). Active PI3K catalyses the production of phosphatidylinositol-3,4,5-triphosphate (PIP3) by phosphorylating phosphatidylinositol (PI), phosphatidylinositol-4-phosphate (PIP), and phosphatidylinositol-4,5-bisphosphate (PIP2). PIP3 may then activate phosphoinositide-dependent protein kinase 1 (PDK1), which plays a central role in many signal transduction pathways (Carpenter and Cantley 1990; Simpson and Parsons 2001), activating Akt and the PKC isoenzymes p70 S6 kinase and p90 ribosomal S6 kinase (Neri et al. 2002). Akt/PKB protein kinase is a serine/threonine kinase. It is the member of cAMP-dependent protein kinase, a super family of protein kinases. All members of Akt/PKB family have structural homology within their catalytic domain and have the similar mechanism of activation. Because of its involvement in various cellular functions, the Akt/PKB plays a central role in the signal transduction pathways. Cellular functions regulated by Akt/PKB includes nutrient metabolism, glycogen metabolism, cell transformation, myogenic differentiation, cell growth, and cell survival through transcriptional factors that are responsible for pro-apoptotic as well as anti-apoptotic genes expression (Brazil and Hemmings 2001; Song et al. 2005). Akt/PKB is activated in response to growth factors or insulin, and it is thought to promote growth factor-mediated cell survival and to block apoptosis (Zhanga and Liu 2011). The ability of Akt/PKB to promote cell survival is due to its kinase activity and depends on the activity of its upstream activator PI3K (Kennedy et al. 1997). Inhibition of apoptosis by Akt/PKB is governed by phosphorylation of the pro-apoptotic Bad at Ser136 thus inactivating Bad and block Bad-induced apoptosis (Datta et al. 1999). Data suggest that different flavonoids modulate the activity of PI3K/Akt and prevent various types of human diseases (Kyoung et al. 2010; Rainey et al. 2008; Vauzour et al. 2007). Kaempferol provides beneficial effects for human health by inducing the activation of PI3K/Akt/and CREB. Further studies' results demonstrated

that kaempferol prevents antimycin A-induced toxicity in osteoblast-like MC3T3-E1 cells utilizing the PI3K/Akt/CREB pathway (Choi 2011). Kaempferol (10 μM) treatment improved the Akt expression and anti-apoptotic protein, Bcl-2, that was significantly reduced in pancreatic beta-cells and human islets chronically exposed to hyperglycaemia (Zhanga and Liu 2011). Inhibition of Akt activation ablated the anti-apoptotic effect of kaempferol suggesting that this flavonoid prevents apoptosis through Akt survival signalling mechanism (Zhanga and Liu 2011). Kaempferol (10–100 μM) was able to reduce LPS-induced inflammatory mediators through the down-regulation of AKT, TLR4, NF-kB, p38, and JNK during inflammatory conditions suggesting that kaempferol can be used for the treatment of inflammatory diseases (Park et al. 2011).

The flavonoids hesperetin and its structural counterparts, isorhamnetin, and isosakuranetin differentially activated pro-survival signalling molecules, including PI3K/Akt and other protein kinases. In nervous tissues, the hesperetin (100 nmol/L) and its metabolites 5-nitro-hesperetin were effective at preventing neuronal apoptosis via a mechanism involving both Akt/PKB activation/phosphorylation and also via an activation of ERK1/2 (Vauzour et al. 2007).

Myricetin induces cell survival via signal transduction pathway involving Akt activation. Cells induced with H_2O_2-induced apoptosis were rescued by myricetin (30 μM) treatment, and this survival mechanism was inhibited by the specific PI3K inhibitor (Kyoung et al. 2010). These observations suggest that PI3K/Akt and MAPK are the main signalling pathways by which myricetin prevents oxidative stress-induced apoptosis (Kyoung et al. 2010).

EGCG activated Akt and ERK1/2 signalling cascade in MCF10A cells (Na et al. 2008). Quercetin or naringenin treatment prevents cell death induced by cytokines-mediated damage, and this effect of quercetin or naringenin was mediated partially via the activation of the downstream pAkt and pBad pathways (Lin et al. 2012).

Genistein has been shown to protect cerebrovascular endothelial cells from Aβ (25–35)-induced oxidative damage through the activation of Nrf2 signalling pathway (Xi et al. 2012). In addition, the genistein could promote the activity of endothelial nitric oxide synthase (eNOS) at the concentration of 100 nM/L through increasing phosphorylation eNOS through PI3K/AKT pathway (Zheng et al. 2012).

Conclusions

It is apparent that naturally occurring polyphenols such as flavonoids have potential beneficial effects due to their antioxidant power and most importantly their interactions with a number of cellular signalling pathways, which are important in the normal functioning of cells. These actions of flavonoids include the inhibition of JNK and p38 pathways and the activation of ERK, PI3-K/Akt, and PKC pathways in different type of cell including neuronal, cardiac, endothelial, epithelial, hepatocytes, and macrophages. Such interactions of flavonoids with cell signalling pathways provide various beneficial effects such as improving brain function, preventing oxidative stress, preventing apoptosis, protecting against endothelial barrier dysfunction and injury, improving the cognitive function, decreasing the neurodegeneration, and stimulating eNOS activity. However, in in vivo conditions, the specific dose and bioavailability of flavonoids that target specific survival signalling mechanism are the area that needs further scientific attention.

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