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Flavonoids as anti-inflammatory and neuroprotective agents

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Neuroinflammation is known as the main mechanism implicated in the advancement of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. The main feature of neuroinflammation is associated with the activation of microglia. The activated microglia increase proinflammatory cytokine production and induce progressive neuronal cell death. Citrus flavonoids show neuroprotective effects that are associated with the anti-inflammatory action of flavonoids in neurodegenerative diseases. Among these citrus flavonoids, kaempferol, naringin, and nobiletin show inhibitory effects on nuclear factor-κB and mitogen-activated protein kinase signaling pathways that can modulate inflammatory conditions in microglial cells. In the present review, we present the anti-inflammatory activities of citrus flavonoids and therapeutic potential of flavonoids as neuroprotective agents.

Keywords: Flavonoid, Anti-inflammatory agents, Neuroprotection, Microglia

Introduction

Inflammation of neuronal cell is regarded as a physiological defensive response to protect central nerve system (CNS) against tissue injury and infection [1]. Therefore, inflammation shows beneficial effects that infectious insults and tissue injury have been eliminated and homeostasis has been restored [2]. This inflammation is also associated with various neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and other neuronal pathologies [3,4]. Although the main cellular or molecular mechanism of neurodegenerative diseases are linked with many factors including oxidative stress, inflammation, protein aggregation, there are many evidences *in vitro* and *in vivo* studies shows that inflammatory response of astrocytes and microglia affects neurodegenerative disease progression [2].

Oxidative stress is also known as one of major contributor in neurodegenerative condition. Comparing with other cells, neuronal cells have higher level of metabolic activities and oxygen consumption. Therefore, neuronal cells are more vulnerable to oxidative stress, particularly neuronal cells in aging brains [5–7]. Oxidative stress leads to activate the mitogen-activated protein kinases (MAPKs) by phosphorylation [8]. MAPKs activation is implicated with triggering transcription of various apoptosis genes [9]. Neuronal cell damage caused by inflammatory cyto-

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kines and oxidative stress occurs by c-Jun N-terminal kinase (JNK) and p38 signal pathway activation. In particular, extracellular signal regulated kinase (ERK) signal pathway is more implicated to neuronal cell death under oxidative stress condition [10,11].

Flavonoids are considered as potential neuroprotective compounds which can modulate cellular mechanisms implicated with neurodegeneration. Flavonoids, a group of natural compounds with various polyphenol structures, are found in fruits, vegetable, grains, bark, tea, and wine [12,13]. Flavonoids show characteristics of both antioxidant and signal pathway modulator. It can modulate cellular signal cascades by interacting with enzymes or receptors that are involved in activation and deactivation of signaling pathways [14]. Flavonoids exhibit neuroprotective effects by modulating intracellular signal which is associated with neuronal cell survival, death, and mitochondrial interaction [15,16]. Recent reports suggest that a habitual intake of dietary flavonoids can reduce the risk of dementia, stroke, and PD [17–19]. For instance, flavonoids in fruits, vegetables, grains, and etc. seems to enable to prevent or reverse cognitive related deficits [20–22].

In the current review, we focus on neuroprotective effects of flavonoids against inflammatory and oxidative damage in neuronal cells.

Flavonoids and Anti-neuroinflammation

1. Flavonoids and major structures

Health benefit of citrus flavonoids has been known for many years. Several studies have shown that citrus flavonoids are associate with lower risk of colorectal [23], esophageal [24], stomach cancer [25] and stroke [26], and improved survival of elderly people [27].

Flavonoids have a general structure with 15 carbon skeleton with two phenyl rings (A and B) and a heterocyclic ring (C). Considering the oxidation of heterocyclic ring (C), flavonoids can be categorized into several classes. Based on the structure, flavonoids divided into following subclasses: flavones, flavanones, isoflavones, flavan-3-ols, anthocyanidins, flavanols (Fig. 1)[28]. In addition, flavonoids also include anthocyanines, and proanthocyanidines [29,30]. The main sources of flavonoids are parsley, onions, blueberry, berries, black tea, green tea, bananas, and etc. Flavonoid contents are high in apple, cauliflower, carrot, tomato, soybeans, and citrus fruits. These fruits contain various flavonoids [31,32]. In particular, the chemical composition of citrus flavonoids has been extensively studied by high-performance liquid chromatograph-mass spectrometry, gas chromatography-mass spectrometry and gas chromatography-flame ionization detector. For example,

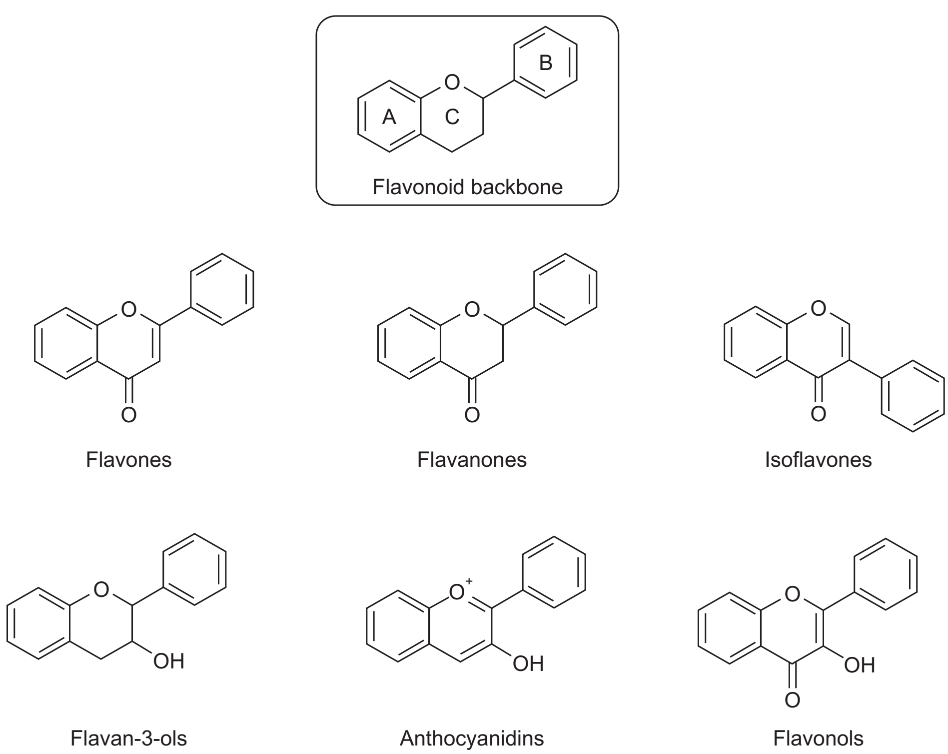

Fig. 1. Basic structures of flavonoids subclasses.

citrus fruits notably contain high level of flavonoids including three major flavonoids; flavanone (mainly di- and tri-O-glycosides), flavone glycosides (mainly di-, tri-O-glycoside, and C-glycoside), and polymethoxyflavones [15]. The O-glycoside citrus flavonoids are mainly rutinosides and neohesperidosides. Rutinosides include hesperidin, narirutin, eriocitrin, isorhoifolin, and diosmin. Neohesperidoses are including naringin, neoericitrin, neodiosmin, and neohesperidin (Fig. 2). In the flavone aglycan, disometin and luteolin are abundant in citrus plants and fruits such as lemon, orange, broccoli, pepper, and celery [15].

2. Anti-neuroinflammatory effects of citrus flavonoids

1) 7-rutinosides

7-rutinosides possess flavone backbone with 7-position of rutinose. These 7-rutinosides include hesperidin, narirutin, eriocitrin, isorhoifolin, and diosmin which are abundantly pre-

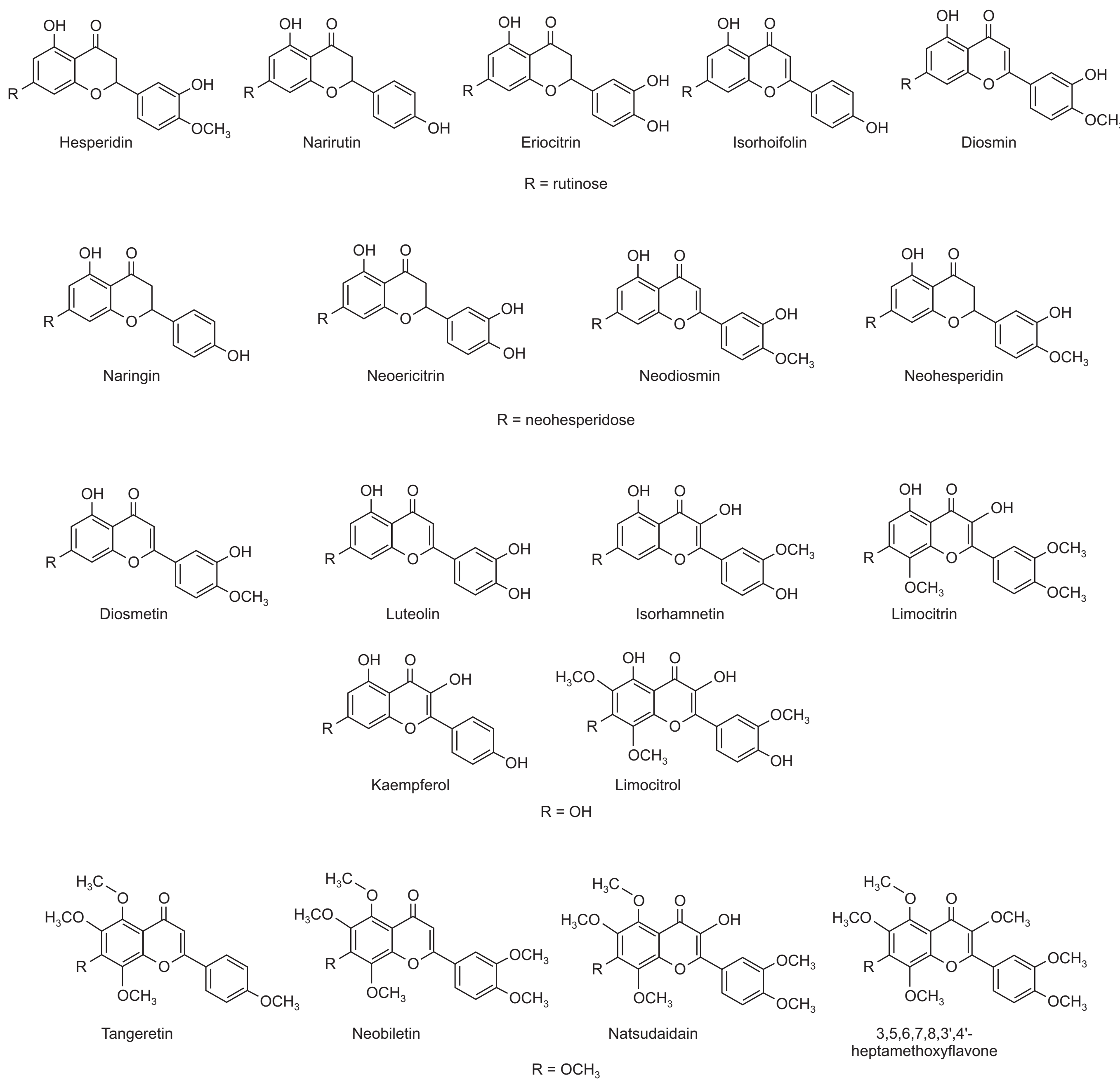

Fig. 2. The chemical structure of citrus flavonoids.

sented in oranges, tangerines, and lemons. Recent literatures show that 7-rutinosides exerts neuroprotective effects or improving cognitive function by reducing neuroinflammation. Among these 7-rutinosides, hesperidin reduces neuroinflammation in the mouse model of MS. Hesperidin increases anti-inflammatory cytokines (interleukin [IL]-10 and transforming growth factor-β) and reduces auto-reactive T cells proliferation and its infiltration into CNS [33]. Diosmin reduces neuroinflammation, Aβ levels, tau phosphorylation, and cognitive impairment in mouse model via inhibition of glycogen synthase kinase-3 proteins. Also, diosmin inhibits microglial proinflammatory activation and enhances Aβ phagocytosis [34].

2) 7-neohesperidosides

7-neohesperidosides include naringin, neoeriocitrin, neodiosmin, and neohesperidin which have bitter taste and mainly found in grapefruit. Recent study shows that naringin has neuroprotective effect and attenuate neuroinflammation in quinic acid induced neurotoxic *in vivo* model. In these studies, naringin reduces anti-inflammatory markers (tumor necrosis factor-α [TNF-α], IL's and nuclear factor-κB [NF-κB]) expression and apoptotic markers (bax-bcl2, caspase-3, and peroxisome proliferator-activated receptor gamma) expression [35].

3) 7-hydoroxy citrus flavonoids

7-hydroxy compounds include diosmetin, luteolin, isorhamnetin, limocitrin, kaempferol, and limocitrol. In recent report of rat pneumococcal meningitis model study, diosmetin prevents the neuroinflammation and apoptotic cell death by controlling phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/NF-κB signal pathway [36]. Neuroinflammatory effects of luteolin have been extensively studied. Johnson and his coworkers reported that luteolin inhibits the LPS stimulated production of cytokine IL-6 by blocking the activator protein-1 binding with IL-6 promoter in microglia cells and mouse model [37]. Lutieolin improves cognitive function by inhibiting neuroinflammation [38]. In addition, cotreatment of luteolin and palmitoylethanolamide decrease neuroinflammation in Parkinson disease animal model [39]. Kaempferol decreases lipopolysaccharide (LPS) induced neuroinflammation by inhibiting of NF-κB, MAPKs and AKT signaling in BV2 microglial cells [40]. Further research also show that kaempferol shows beneficial effects to dementia, ischemic brain injury, and PD by blocking proinflammatory signal cascade [41-43].

4) 7-methoxy citrus flavonoids

7-methoxy compounds include tangeretin, nobiletin, natsudaidain, 3,5,6,7,8,3',4'-heptamethoxyflavone (HMF). Tangeretin decreases the production of nitric oxide (NO), prostaglandin E2, TNF-α, IL-1β, and IL-6 in primary rat microglia and BV2 microglial cell culture models. Further study of tangeretin shows that it exhibits anti-neuroinflammtory effect via the modulation of MAPK signal pathway and the nuclear translocation of p65 [44]. Nobiletin, known as anti-obesity, anti-allergic, and antitumor agent, shows improvement of LPS-triggered memory deficit. Nobiletin suppresses the microglial activation and the production of proinflammatory cytokines (cyclooxygenase2 [COX2], IL-1β, TNF-α, and inducible nitric oxide synthase [iNOS]) via modulation of MAPKs, PI3K/AKT/NF-κB signaling pathways in BV2 cells [45]. HMF inhibits proinflammatory factors including IL-1β, COX2, TNF-α, and iNOS in microglia activation [46].

3. Citrus flavonoids and oxidative stress

Oxidative stress is the disruption of equilibrium between production of reactive oxygen species (ROS) and antioxidant defense in cellular system [47]. Neuronal cells require high level of metabolic activities and oxygen concentration to generate electrical and chemical signals that travel between neurons. These characteristics of neuronal cells can easily give rise to oxidative stress which can damage to neuronal tissue [5,48]. Therefore, neuronal cells are more susceptible to oxidative stress. Recent studies reveal that ROS is crucial in the progression of many neurodegenerative diseases such as AD, PD, Huntington disease (HD), and ALS [49]. ROS generation activates JNK and p38, and deactivates protein phosphatase 2A in AD. The activation of JNK and p38 is known for the increasing expression of Tau protein, which results in aggregation and induction of neuronal cell death [50]. ROS also induces generation of misfolded proteins in PD, HD, and ALS [51-53].

Citrus flavonoids seem to show various bioactivities including reduction of oxidative stress [54]. Antioxidant effects of flavonoids may be attributed by their scavenging effects of oxygen free radical [55,56]. The scavenging effects of flavonoids depend on the hydrogen donation of polyphenol structure in flavonoids [57]. Flavonoids have potentials to enhance the generation of antioxidant enzymes and inhibit harmful oxidases and also have metal chelating activities. These functions of flavonoids show reduction of oxidative stress in neuronal cells.

The citrus flavonoids have strong free radical scavenging activities than other dietary flavonoids. The studies reveal that flavonoids such as kaempfeol, luteolin, rutin, scutellarein, and neoeriocitrin are having strong antioxidant and lipid peroxidation activities than the hesperidin, hesperetin, neohesperidin, naringenin, and naringin. Recently, Hwang et al. [15] reported that flavonoids including hesperetin, isorhamnetin, and isosakuranetin show scavenging effects to ROS, activate AKT signal pathway, and inactivate JNK signal pathway that is implicated with apoptosis. Furthermore, these flavonoids differentially modulate p38 activity that is related with cell survival. Therefore, the treatment of citrus flavonoids could be a promising approach for neuroprotection against oxidative damage.

Molecular Mechanisms Underlying the Anti-neuroinflammatory Effects of Flavonoids

Neuroinflammation is initiated by inflammatory cytokine, COX2 and iNOS expression in active microglia. Inflammatory cytokine production and inflammatory response enzymes such as COX2 and iNOS are regulated by MAPK and NF-κB signaling pathway. MAPK includes ERK1/2, (JNK1/2/3) and p38 kinase (p38 αβγδ). In particular, MAPK signal pathway has a pivotal role for signal cascades from extracellular stimulation into intracellular response. Under the stimulation, these kinases are activated by phosphorylation and the activated kinases phosphorylate both cytosolic and nuclear specific proteins. As result, transcription factors including signal transducer and activator of transcription-1/2/3, NF-κB, are activated. Many activated glia cells show increased proinflammatory cytokine secretion such as iNOS, COX2, IL-1β and TNF-α expression via NF-κB and MAPK activation [58-60].

Many literatures reveal that NF-κB activation is associated with oxidative stress [61] and inflammatory condition [62]. NF-κB signal and its modulators are regarded as good therapeutic targets for modulating inflammatory diseases [63,64]. In neuroinflammatory condition, NF-κB activation is associated with excessive ROS generation in activated microglia. As a result, activated microglia increases production of proinflammatory cytokines (Fig. 3) [45]. Therefore, activated microglia with over-producing proinflammatory cytokines are regarded as risk factors to induce neurodegeneration via activation of MAPK and PI3K/AKT pathway [65].

In microglia activation, NF-κB activation is mediated to production of iNOS production which results in high production of NO and cytokine. NF-κB activation also is implicated with expression of COX2 which results in prostaglandin formation in activated astrocyte (Fig. 4) [1,66]. These activated astrocyte or glia induces production of proinflammatory cytokines (IL-1β, TNF-α), glutamate, NO, ROS and etc. These molecules such as TNF-α may directly trigger neuronal cell death by binding with various TNF receptor families by inducing apoptosis. NO

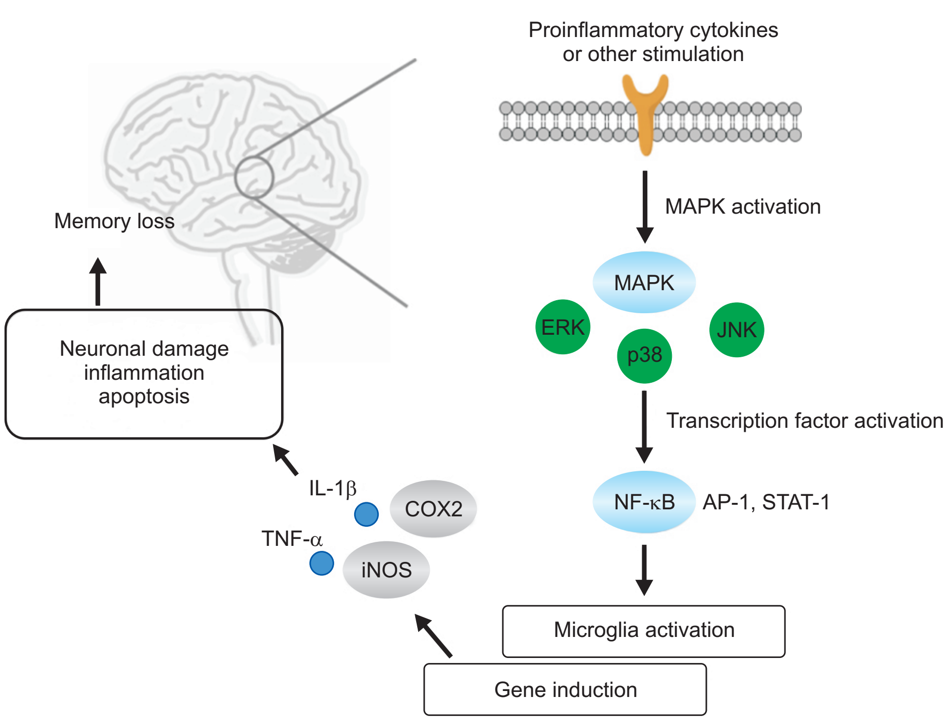

Fig. 3. Mitogen-activated protein kinase (MAPK) signal pathway of neuroinflammation. Cytokines trigger proinflammatory transcription factors (nuclear factor-κB [NF-κB] and signal transducer and activator of transcription-1 [STAT-1]) activation and increase inducible nitric oxide synthase (iNOS), cyclooxygenase2 (COX2), tumor necrosis factor-α (TNF-α), and interleukin (IL)-1β expression through MAPK signal pathway activation. The figure was modified by Qi et al. (J Agric Food Chem 2019;67:5122-34) [45].
ERK, extracellular signal regulated kinase; JNK, c-Jun N-terminal kinase; AP-1, activator protein-1.

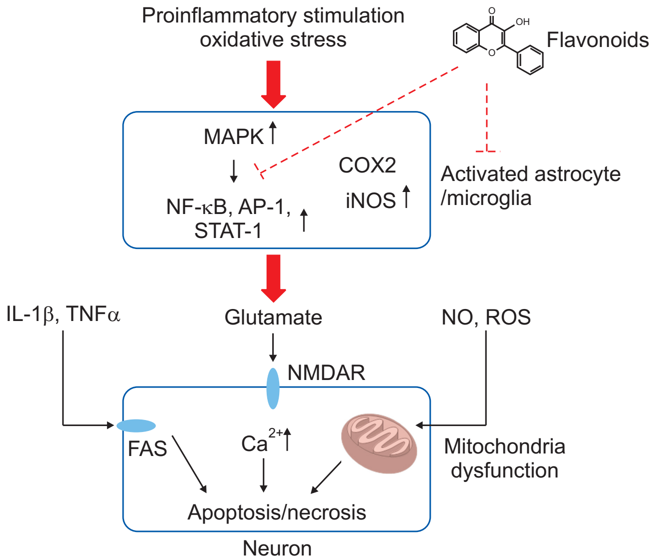

Fig. 4. Neurodegeneration induced by neuroinflammatory signals in activated astrocyte or glia. Flavonoids inhibit neuronal cell death by inhibiting neuroinflammation [1,68]. The figure was modified from Spagnuolo et al. (Eur J Med Chem 2018;153:105-15) [68].
MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; AP-1, activator protein-1; STAT-1, signal transducer and activator of transcription-1; COX2, cyclooxygenase2; iNOS, inducible nitric oxide synthase; IL, interleukin; TNF-α, tumor necrosis factor-α; NO, nitric oxide; ROS, reactive oxygen species; NMDAR, N-methyl-d-aspartate (NMDA) receptor; FAS, CD95, tumor necrosis factor receptor superfamily member 6.

overproduction mediates release of cytochrome c from mitochondria through activation of BCL2-associated X protein (BAX) and BCL2-homologous antagonist killer (BAK1) leading to cell death.

Conclusions

Neuroinflammation is an important mechanism in the progress and advancement of neurodegenerative diseases such as AD, PD, MS, HD, and ALS. Neuroinflammation is mainly associated with glia cell activation, which can cause proinflammatory cytokine over-production and induce neuronal cell death. The *in vitro* and *in vivo* studies indicate that flavonoids can reduce neuroinflammation by inhibiting the NF-κB and MAPK signal pathways in microglia cells.

Flavonoids possess strong antioxidant and anti-inflammatory potentials. Therefore flavonoids contribute to neuroprotective effects against neuronal damage by neuroinflammation. Several flavonoids have known for therapeutic potentials including blood brain barrier penetration, and multiple neuroprotective effects [67,68]. However, bioavailability of flavonoids is still one of main hurdle in their development as drug candidates [69,70]. Recently, formulation technology can help to observe less bioavailable flavonoids to human body.

In summary, flavonoids are suitable candidate for the development of health benefit products for anti-neuroinflammation and neuroprotection.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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