



THE NEUROPROTECTIVE ROLE OF FLAVONOIDS

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ABSTRACT

Flavonoids are antioxidants found in fruits and vegetables and when taken with the diet, they reduce the risk of chronic diseases and even cancer. Flavonoids possess many healthful properties including neuroprotection through the regulation of many pro-inflammatory signaling pathways such as for p38 mitogen-activated protein kinases (MAPK) and nuclear factor kappa B (NF- κ B). Therefore, flavonoids inhibit pro-inflammatory cytokines, reactive oxygen species (ROS), and diverse metalloproteases (MMP)s such as MMP2, MMP3, and MMP9. Here, in this paper, we primarily studied the effect of flavonoids on central nervous system (CNS) inflammation.

KEYWORDS: *Flavonoids, antioxidants, neuroprotection, inflammation, central nervous system*

INTRODUCTION

Flavonoids are a family of polyphenols found in plants such as fruits, vegetables, grains, roots, and plant beverages such as juices and teas. Flavonoids are beneficial for health as they possess anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties. They also interact with the human body by modulating cellular enzyme function. Flavonoids have a polyphenolic structure (Fig.1) and are plant secondary metabolites, with the ability to exert effects on other living organisms besides the plant itself (1).

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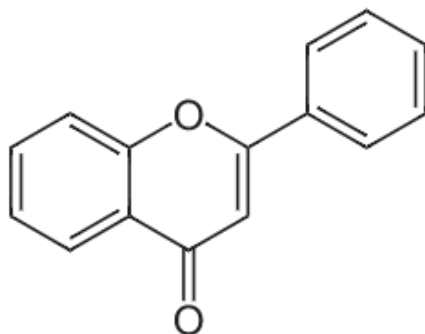


Fig. 1. *Flavonoids are plant secondary metabolites with a polyphenolic structure and exert effects on other living organisms besides the plant itself. They possess anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties and interact with the human body by modulating cellular enzyme function.*

Many medicines and medicinal herbs utilize these secondary plant metabolites. Pharmacology utilizes flavonoids for many purposes due to their broad spectrum of therapeutic activities. Research has shown strong evidence for the preventative role of flavonoids in cardiovascular diseases and coronary heart disease (2-5), osteoporosis (6), and neurodegenerative diseases (7, 8). Flavonoids are neuroprotective due to their role in regulating diverse pro-inflammatory signaling pathways including those of p38 mitogen-activated protein kinases (MAPK) and nuclear factor kappa B (NF-kB).

The role of flavonoids in neuroprotection

In addition to the cardioprotective, anti-inflammatory, and chemopreventive roles played by flavonoids, they also provide neuroprotection. This is due to their modulatory actions on many signaling pathways, such as p38MAPK and NF-kB, and their ability to inhibit the production of proinflammatory cytokines, reactive oxygen species (ROS), and metalloproteases (MMP)s including MMP2, MMP3, and MMP9.

The MAPK families are involved in complex cellular programs such as proliferation, differentiation, development, transformation, and apoptosis. Flavonoids act directly on cellular signaling pathways such as phosphoinositide 3-kinase, Akt/protein kinase B, MAPK, protein kinase C, and tyrosine kinases (9). They can act on these pathways with inhibition or stimulation, which can lead to changes in phosphorylation, and thus, produce effects on cell functions. Flavonoids are also able to activate transcription factors and gene expression that are associated with the inflammatory response, apoptosis, and cell proliferation.

Flavonoids protect against inflammation by exerting effects on MAPK signaling pathways which activate transcription factors such as NF-kB. For example, myricetin, quercetin, and fisetin are dietary flavonoids commonly found in fruits, vegetables, and beverages, including mangoes, apples, berries, onions, tea, grapes, and red wine. Myricetin, quercetin, and fisetin share similar molecular structures (Fig. 2) and have been seen to produce anti-inflammatory effects (10). Through suppression of phosphorylation, these flavonoids inhibit the activation of NF-kB and MAPK pathways, suppressing excessive nitric oxide (NO) production and reducing the levels proinflammatory cytokines tumor necrosis factor (TNF) and IL-6, as well as ROS (11).

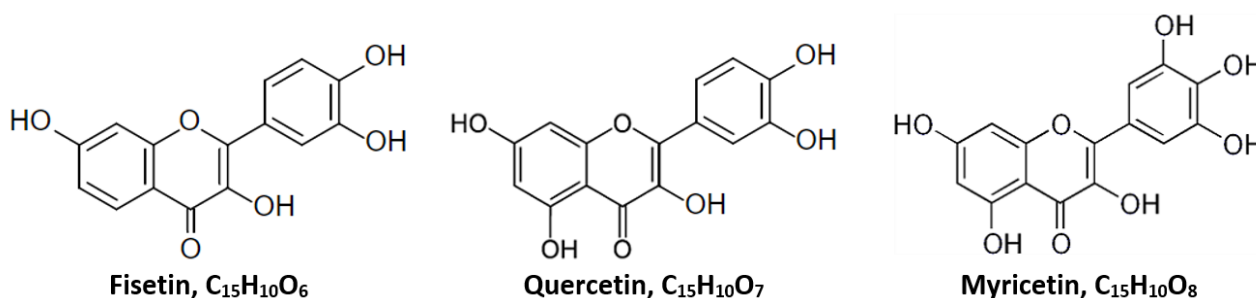


Fig. 2. Myricetin, quercetin, and fisetin are dietary flavonoids commonly found in fruits, vegetables, and beverages such as red wine. They are members of the flavonoid class of polyphenolic compounds that share similar molecular structures to one another and have anti-inflammatory properties.

Myricetin, which is found in many edible plants, was seen to inhibit p38MAPK activation and c-Jun N-terminal kinase (JNK), which prevented oxidative stress-induced apoptosis (12) and decreased the production of NO, iNOS, TNF, IL-6, and IL-12 in mice studies (13).

Quercetin has anti-inflammatory properties (14) that involve different cell types, with an ability to help stabilize mast cells and an immunosuppressive effect on the function of dendritic cells (15,16). Quercetin has been seen to inhibit the production of TNF and IL-1, lowering the rate of apoptotic neuronal cell death induced by microglial activation (17). Additionally, quercetin inhibits MMP-1 and down-regulates MMP-1 expression (18).

In studies, fisetin inhibited the production of proinflammatory mediators including TNF, IL-1, IL-6 by suppressing signaling pathways in macrophages (19, 20). In one interesting study, it was reported that the flavonoid methoxyluteolin significantly dumped gene expression and IL-1 synthesis (21). Methoxyluteolin Inhibited Procaspase 1 Activity, and therefore, IL-1.

Matrix metalloproteinases (MMPs) are zinc-dependent enzymes and inflammatory mediators that mediate tissue remodeling in pathological and physiological processes (22). They are involved in the degradation of the extracellular matrix and tumor invasion, angiogenesis, cancer metastasis, and neuroinflammation (23). In the CNS, MMPs play a role in the formation of myelin, axonal growth, angiogenesis, and regeneration (24). The overproduction of MMPs could be linked to neurological pathologies such as AD, PD, ischemia, and glioma (25), as some MMPs are markedly upregulated in certain disorders (26). In turn, the upregulation of MMPs contributes to the cycle of neuroinflammation by the inflammatory cascade, a series of actions that increase and perpetuate inflammation (27).

MAPK-linked MMP upregulation can be inhibited by flavonoids. In particular, long-chain fatty acids such as epigallocatechin gallate (EGCG) are MMP inhibitors and come naturally from flavonoids and green tea (28), and the flavonoids luteolin and apigenin have inhibitory activity on diverse MMPs (29).

CONCLUSION

Inflammatory events mostly occur in the CNS in glial cells, which produces neuroinflammation. Neuroinflammation is implicated in numerous demyelination and neurodegenerative disorders including multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and virus-associated dementia (30-34). Responding to inflammatory insults, signaling pathways activate proinflammatory transcription factors that initiate gene transcription, resulting in the production of proinflammatory cytokines and ROS.

Flavonoids provide neuroprotection by modulating different signaling pathways and inhibiting the production of inflammatory mediators including TNF, IL-1, and IL-6, ROS, and MMPs such as MMP2, 3, and 9 (29).

The precise biological activity and mechanisms by which flavonoids work is still not completely understood, but much research is being done to isolate, identify, and characterize polyphenols (35). Further understanding of their functions can lead to new therapeutic options and applications.

Conflict of interest

The author declares that they have no conflict of interest.

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