European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2021 vol. 10, ISSUE N. 2, July-December

THE NEUROPROTECTIVE ROLE OF FLAVONOIDS

Al. Caraffa*

School of Pharmacy, University of Camerino, Camerino, Italy.

Correspondence to:
Alessandro Caraffa, MD,
School of Pharmacy,
University of Camerino,
Camerino, Italy.
e-mail: alecaraffa@libero.it

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-kB). 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).

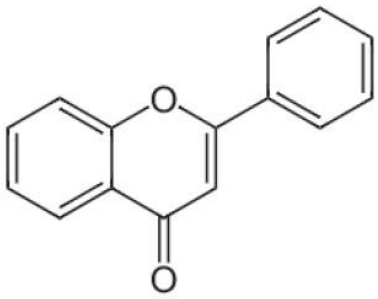

Fig. 1. *Flavonoids are plant secondary metabolites with a polyphenolic structure and exert effects on other living organisms besides the plant itself. They possess anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties and interact with the human body by modulating cellular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

Received: 09 September, 2021
Accepted: 29 October, 2021

2279-5855 (2021)

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).

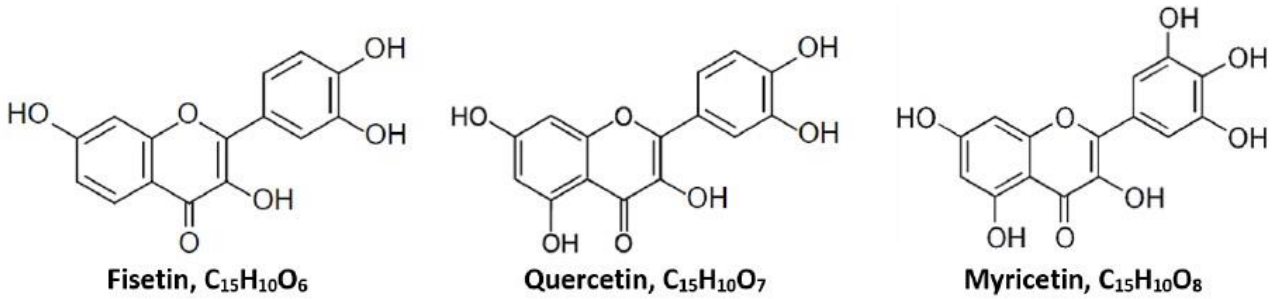

Fig. 2. *Myricetin, quercetin, and fisetin are dietary flavonoids commonly found in fruits, vegetables, and beverages such as red wine. They are members of the flavonoid class of polyphenolic compounds that share similar molecular structures to one another and have anti-inflammatory properties.*

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).

CONCLUSIONS

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.

REFERENCES

1. Teoh ES. Secondary Metabolites of Plants. *Medicinal Orchids of Asia*. Published online November 5, 2015:59-73. doi:10.1007/978-3-319-24274-3_5
2. Ciumărnean L, Milaciu MV, Runcan O, et al. The Effects of Flavonoids in Cardiovascular Diseases. *Molecules*. 2020;25(18):4320. doi:10.3390/molecules25184320
3. Mursu J, Voutilainen S, Nurmi T, Tuomainen TP, Kurl S, Salonen JT. Flavonoid intake and the risk of ischaemic stroke and CVD mortality in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *British Journal of Nutrition*. 2008;100(4):890-895. doi:10.1017/s0007114508945694
4. Knekt P, Kumpulainen J, Järvinen R, et al. Flavonoid intake and risk of chronic diseases. *The American Journal of Clinical Nutrition*. 2002;76(3):560-568. doi:10.1093/ajcn/76.3.560
5. Belguise K, Guo S, Sonenshein GE. Activation of FOXO3a by the Green Tea Polyphenol Epigallocatechin-3-Gallate Induces Estrogen Receptor Expression Reversing Invasive Phenotype of Breast Cancer Cells. *Cancer Research*. 2007;67(12):5763-5770. doi:10.1158/0008-5472.can-06-4327
6. Choi EM. Kaempferol protects MC3T3-E1 cells through antioxidant effect and regulation of mitochondrial function. *Food and Chemical Toxicology*. 2011;49(8):1800-1805. doi:10.1016/j.fct.2011.04.031
7. Scalbert A, Manach C, Morand C, Rémésy C, Jiménez L. Dietary Polyphenols and the Prevention of Diseases. *Critical Reviews in Food Science and Nutrition*. 2005;45(4):287-306. doi:10.1080/1040869059096
8. Ayaz M, Sadiq A, Junaid M, et al. Flavonoids as Prospective Neuroprotectants and Their Therapeutic Propensity in Aging Associated Neurological Disorders. *Frontiers in Aging Neuroscience*. 2019;11. doi:10.3389/fnagi.2019.00155
9. Mansuri ML, Parihar P, Solanki I, Parihar MS. Flavonoids in modulation of cell survival signalling pathways. *Genes & Nutrition*. 2014;9(3):400. doi:10.1007/s12263-014-0400-z
10. Funakoshi-Tago M, Nakamura K, Tago K, Mashino T, Kasahara T. Anti-inflammatory activity of structurally related flavonoids, Apigenin, Luteolin and Fisetin. *International Immunopharmacology*. 2011;11(9):1150-1159. doi:10.1016/j.intimp.2011.03.012
11. Chen GL, Fan MX, Wu JL, Li N, Guo MQ. Antioxidant and anti-inflammatory properties of flavonoids from lotus plumule. *Food Chemistry*. 2019;277:706-712. doi:10.1016/j.foodchem.2018.11.040

12. Kang KA, Wang ZH, Zhang R, et al. Myricetin Protects Cells against Oxidative Stress-Induced Apoptosis via Regulation of PI3K/Akt and MAPK Signaling Pathways. *International Journal of Molecular Sciences*. 2010;11(11):4348-4360. doi:10.3390/ijms11114348
13. Cho BO, Yin HH, Park SH, Byun EB, Ha HY, Jang SI. Anti-inflammatory activity of myricetin from *Diospyros lotus* through suppression of NF-κB and STAT1 activation and Nrf2-mediated HO-1 induction in lipopolysaccharide-stimulated RAW264.7 macrophages. *Bioscience, Biotechnology, and Biochemistry*. 2016;80(8):1520-1530. doi:10.1080/09168451.2016.1171697
14. Kandere-Grzybowska K, Kempuraj D, Cao J, Cetrulo CL, Theoharides TC. Regulation of IL-1-induced selective IL-6 release from human mast cells and inhibition by quercetin. *British Journal of Pharmacology*. 2006;148(2):208-215. doi:10.1038/sj.bjp.0706695
15. Penissi AB, Rudolph IM, Piezzi SR. Role of mast cells in gastrointestinal mucosal defense. *BIOCELL*. 2003;27(2):163-172. doi:10.32604/biocell.2003.27.163
16. Huang RY, Yu YL, Cheng WC, OuYang CN, Fu E, Chu CL. Immunosuppressive Effect of Quercetin on Dendritic Cell Activation and Function. *The Journal of Immunology*. 2010;184(12):6815-6821. doi:10.4049/jimmunol.0903991
17. Bureau G, Longpré F, Martinoli MG. Resveratrol and quercetin, two natural polyphenols, reduce apoptotic neuronal cell death induced by neuroinflammation. *Journal of Neuroscience Research*. 2008;86(2):403-410. doi:10.1002/jnr.21503
18. Lim H, Kim H. Inhibition of Mammalian Collagenase, Matrix Metalloproteinase-1, by Naturally-Occurring Flavonoids. *Planta Medica*. 2007;73(12):1267-1274. doi:10.1055/s-2007-990220
19. Lyu SY, Park WB. Production of Cytokine and NO by RAW 264.7 Macrophages and PBMC In Vitro Incubation with Flavonoids. *Archives of Pharmacal Research*. 2005;28(5):573-581. doi:10.1007/bf02977761
20. Peng HL, Huang WC, Cheng SC, Liou CJ. Fisetin inhibits the generation of inflammatory mediators in interleukin-1β-induced human lung epithelial cells by suppressing the NF-κB and ERK1/2 pathways. *International Immunopharmacology*. 2018;60:202-210. doi:10.1016/j.intimp.2018.05.004
21. Taracanova A, Alevizos M, Karagkouni A, et al. SP and IL-33 together markedly enhance TNF synthesis and secretion from human mast cells mediated by the interaction of their receptors. *Proceedings of the National Academy of Sciences of the United States of America*. 2017;114(20):E4002-E4009. doi:10.1073/pnas.1524845114
22. Chen Q, Jin M, Yang F, Zhu J, Xiao Q, Zhang L. Matrix Metalloproteinases: Inflammatory Regulators of Cell Behaviors in Vascular Formation and Remodeling. *Mediators of Inflammation*. 2013;2013(2013):1-14. doi:10.1155/2013/928315
23. Goetzl EJ, Banda MJ, Leppert D. Matrix metalloproteinases in immunity. *The Journal of Immunology*. 1996;156(1):1-4. doi:10.4049/jimmunol.156.1.1
24. Agrawal S, Lau L, Yong V. MMPs in the central nervous system: Where the good guys go bad. *Seminars in Cell & Developmental Biology*. 2008;19(1):42-51. doi:10.1016/j.semcdb.2007.06.003
25. Yong VW, Forsyth PA, Bell R, Krekoski CA, Edwards DR. Matrix metalloproteinases and diseases of the CNS. *Trends in Neurosciences*. 1998;21(2):75-80. doi:10.1016/s0166-2236(97)01169-7
26. Yong VW. Metalloproteinases: Mediators of Pathology and Regeneration in the CNS. *Nature Reviews Neuroscience*. 2005;6(12):931-944. doi:10.1038/nrn1807
27. Könnecke H, Bechmann I. The Role of Microglia and Matrix Metalloproteinases Involvement in Neuroinflammation and Gliomas. *Clinical and Developmental Immunology*. 2013;2013:1-15. doi:10.1155/2013/914104
28. Kim YS, Joh Tong-H. Matrix Metalloproteinases, New Insights into the Understanding of Neurodegenerative Disorders. *Biomolecules and Therapeutics*. 2012;20(2):133-143. doi:10.4062/biomolther.2012.20.2.133
29. Crascì L, Basile L, Panico A, et al. Correlating In Vitro Target-Oriented Screening and Docking: Inhibition of Matrix Metalloproteinases Activities by Flavonoids. *Planta Medica*. 2017;83(11):901-911. doi:10.1055/s-0043-104775
30. Chavarria A, Alcocer-Varela J. Is damage in central nervous system due to inflammation? *Autoimmunity Reviews*. 2004;3(4):251-260. doi:10.1016/j.autrev.2003.09.006
31. Saha RN, Pahan K. Tumor necrosis factor-α at the crossroads of neuronal life and death during HIV-associated dementia. *Journal of Neurochemistry*. 2003;86(5):1057-1071. doi:10.1046/j.1471-4159.2003.01942.x
32. Caraffa Al. Role of inflammation in Alzheimer's disease: an emphasis on TREM2 and CD33. *European Journal of Neurodegenerative Diseases*. 2020;9(2) July-December e00008

33. Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? *The Lancet Neurology*. 2009;8(4):382-397. doi:10.1016/s1474-4422(09)70062-6
34. Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Translational Neurodegeneration*. 2020;9(1). doi:10.1186/s40035-020-00221-2
35. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. *Journal of Nutritional Science*. 2016;5(e47). doi:10.1017/jns.2016.41