Review Article

Flavonoids as novel neuroprotective nutraceuticals

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ABSTRACT

Dementia/Neurodegenerative disorders result from chronic, progressive loss of neurons involved in cognition. Such disorders are characterized by more long-term care, chronic suffering and lost quality of life than any other disorder. Emerging evidence suggests that flavonoids may retard, block or even reverse such neurodegeneration. The purpose of this review is to assess effects, associations and mechanisms of action of flavonoids on neurons, to describe the recent advancements and to explore some current controversies surrounding the subject. PubMed, Google Scholar and university websites were searched. Additional studies were identified from reference lists.

Key words: Cognition, dementia, flavonoids, learning, memory

INTRODUCTION

The potential impact of diet on health care costs should not be overlooked. According to the latest statistics by WHO worldwide nearly 35.6 million people suffer from dementia. This number is estimated to double by 2030 (65.7 million) and more than triple by 2050 (115.4 million). Treating and caring for people with dementia at present costs the world more than US$ 604 billion per year. This includes the health and social care cost and income loss of people with dementia and their caregivers.[1]

Gone are the days when cognitive decline and neurodegeneration was considered irreversible and a part of aging process. Modern research has revealed that the incidence and onset of these age-related neurodegenerative disorders can be significantly prevented or reversed by certain lifestyle modifications; diet being one of them. These findings provide favorable clues that the development of novel dietary approaches for improving cognitive health as we age is a real possibility.

This review will focus on the potential of flavonoids to influence memory, learning and cognitive performance and will attempt to elucidate the possible mechanisms that underpin such actions in the brain.

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METHODS

Literature search. A search of PubMed, Google Scholar and university websites was performed to identify original research/review articles/randomized controlled trials examining the effect of flavonoids on brain. Furthermore, we hand-searched bibliographic citations from the retrieved papers and from review articles. PubMed was searched using the term "flavonoids" (major subject heading) in combination with memory OR learning OR cognition OR dementia as free terms without any restrictions except language. Then, we screened the titles and abstracts resulting from the search strategies. Articles were rejected on initial screening if titles or abstracts were clearly irrelevant. The full text of potentially relevant articles was retrieved.

Flavonoids in the diet

Flavonoids are the most common group of polyphenolic compounds in the human diet. Major dietary sources of flavonoids include fruits, vegetables, cereals, dry legumes, tea, wine and chocolate.[2] The main dietary groups of flavonoids are (1) flavonols (found in onions and broccoli), (2) flavones (found in parsley and celery), (3) isoflavones (found in soy and soy products), (4) flavanones (found in citrus fruit and tomatoes), (5) flavanols (abundant in green tea, red wine, chocolate), and (6) anthocyanidins (in red wine and berry fruits).

Metabolism

After ingestion, flavonoids are metabolized extensively in the body, resulting in very different forms.[3,4]

Bioavailability of flavonoids in the brain

Flavonoids can cross the blood-brain barrier as many of them have been found in the brain after oral administration.[5,6]

The extent of their blood-brain barrier penetration depend on the lipophilicity of the compound[7] and its interaction with *P* Glycoprotein (a transporter expressed in blood-brain barrier).[8]

Cocoa and Cognition

Dietary intervention studies in a number of mammalian species, including man, using flavonoids have revealed that flavonoids may improve both memory and learning.[9-13] A prospective study of 10-year duration has provided a strong indication that regular dietary flavonoid intake is associated with a better neuro-cognitive performance with aging.[14] A total of 1640 subjects (aged ≥ 65 years) free from dementia at baseline and with reliable dietary assessment data were examined for their cognitive performance with a battery of test four times over a 10-year period. Flavonoid intake was positively associated with better cognitive performance at baseline and over time after adjustment for age, gender and education. Another cross-sectional study revealed that there was a dose-dependent, positive relationship between the intake of flavonoid-containing foods (chocolate, tea, wine) and cognitive performance.[15] A research involving 23 developed countries of the world has shown that dietary flavonoid consumption is linked with reduced incidence of dementia.[16] In accord with this observational data, several dietary intervention studies in both human subjects and animals, particularly those using flavonoid-rich tea,[17-22] cocoa/chocolate[23-25] and blueberry[9,12,26,27] have also confirmed positive effects on memory and learning.

The exact mechanisms by which flavonoids act in the brain remain unclear. Earlier, the biological actions of flavonoids on the brain were ascribed to their antioxidant potentials.[28] Later it was suggested that low concentration of flavonoids found in the brain[29] could not justify for their bioactivity *in vivo* over there. Instead, their neuroprotective potential depends on their ability to lessen neuronal vulnerability, enhance existing neuronal function and induce neurogenesis.[30,31]

A growing number of flavonoid supplementation studies in animal models have provided significant information regarding their functions in brain. Emerging evidence suggests that flavanols improve the retention of rat spatial memory. The latent period to find a platform and the distance swum to a platform in a Morris water maze test are significantly reduced following flavonols supplementation in rats.[32] Reductions in the time taken to make a choice reveal enhanced memory, where rats have quick remembrance followed by a quick response. Investigations have pointed to many potential mechanisms as following:

Improved Cerebrovascular Functions

Cerebral blood flow is vital for optimal brain functions and it decreases with age and in disorders linked with dementia.[33] Brain imaging studies in human subjects have demonstrated that the consumption of flavanol-rich cocoa enhances cortical blood flow[23-25,34] and induces angiogenesis and neurogenesis in the hippocampus.[3] There are several factors behind flavonoid-induced increased cerebral blood flow such as their potential to reduce BP,[35] improve endothelial functions,[36] and inhibit platelet aggregation[37] and inflammatory response.[38,39] Angiogenesis results from flavonoid-induced production of endothelial nitric oxide.[36] Neurogenesis results in response to the vascular growth factors.[40] Hippocampus is a brain region important for memory; therefore, flavonoids may influence memory by improved cortical blood flow, angiogenesis and neurogenesis in the region of hippocampus.

Alleviation of neuroinflammation and oxidative stress-induced injury

Neurotoxic and neuroinflammatory processes in the brain play a central role in the pathophysiology of Alzheimer's disease,[41] Parkinson's disease[42] and injury related with stroke.[43] Activated microglia and/or astrocytes release cytokines and other mediators that lead to the apoptotic death of neurons.

Flavonoids alleviate neuroinflammation by inhibiting (1) iNOS and cyclooxygenase 2 expression; (2) NO production; (3) cytokine release; (4) NADPH oxidase activation and subsequent reactive oxygen species generation in astrocytes and microglia.[44,45] These effects most likely depend on the flavonoids' potential of modulating protein kinase and lipid kinase signaling pathways.[46,47]

Emerging evidence suggests that flavonoids may block oxidant-induced neuronal injury effectively.[48] However, the flavonoids' ability to do so does not depend on direct oxidant scavenging activity.[49] Rather, they act by modulating many protein kinase and lipid kinase signaling cascades, such as the PI3K/Akt, tyrosine kinase, protein kinase C and MAPK signaling pathways.[47]

Interaction with signaling cascade

Flavonoids induce both extracellular signal-regulated protein kinase (ERK) 1/2 and CREB activation in cortical neurons and subsequently increase CREB-regulated gene expression.[50] Owing to their ability to activate CREB, flavonoids may also regulate BDNF (Brain-derived neurotrophic factor), which has a role in synaptic plasticity and long-term memory[51] and is robustly induced in hippocampal neurons on synaptic stimulation.[52] BDNF belongs to the neurotrophin family of growth factors that play a pivotal role in learning and memory by forming new synaptic connections. It also affects the survival and function of neurons in the central nervous system.[53] Decreases in BDNF and pro-BDNF have been reported in Alzheimer's disease;[54,55] genetic[56] as well as pharmacological inhibition[57] of BDNF or its receptor tropomyosin receptor kinase B[58] impairs learning and memory. Conversely, agents that boost BDNF levels lead to enhanced spatial working memory.[59,60]

Mitochondrial modulation

Flavonoids have been reported to bind to mitochondrial ATPase.[61] They may also modulate mitochondrial transition pore, which controls cytochrome c release during apoptosis,[62,63] leading to subsequent inhibition of apoptosis.

Future perspectives

It would be fair to say that current research does provide ample evidence for beneficial effects of flavonoids on neurons. Ongoing research using state-of-the-art recent technology, including functional MRI and transcranial Doppler ultrasound is offering further opportunities to reveal the mechanisms underpinning the effects of flavonoids on neurons. However, although flavonoid consumption may have the potential to forestall or even reverse age-dependent deteriorations in brain function, there are a number of questions still to be resolved. Above all, data in support of a causal relationship between the consumption of flavonoids and cognitive outcomes in human subjects is still lacking. Moreover, the exact chronological nature of flavonoid effects on memory is unclear till date, i.e., when shall we start consuming flavonoids to gain maximum beneficial effects? It is also unclear which flavonoids are most effective in inducing these changes.

In order to clarify and identify such relationships, future intervention studies will be required to utilize better characterized intervention materials, more appropriate controls and more rigorous clinical outcomes. Moreover, except few,[64,65] the majority of the studies investigating the impact of flavonoids on memory, learning and cognition involve the supplementation of whole foods and beverages, rich in a variety of different flavonoids. To establish a causal relationship between individual flavonoids and function, future studies investigating the effects of individual flavonoids shall be encouraged.

CONCLUSION

Development of a treatment that would forestall cognitive deterioration in older persons by only 1% per year would nullify all estimated increases in the long-term care costs for the aging population.[66] Also, there is keen interest in the development of drugs capable of enhancing memory and learning. There is a strong likelihood that in future, flavonoids, might act as precursors for a new class of memory-enhancing drugs.

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