Chapter

# Flavonoids as Modulators of Synaptic Plasticity: Implications for the Development of Novel Therapeutic Strategies for Healthy Lifestyle

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## Abstract

Flavonoids are potential group of phytochemicals found in normal diets capable of mediating improvements in cognition and may reverse age-related declines in memory. Aging is associated with alteration of hippocampal synaptic plasticity and contribute to decline in cognitive functions. The current studies are directed at a greater understanding of how and why the brain modifies synaptic strength with dietary-derived phytochemicals (flavonoids) and age-related declines in cognitive functions (such as learning and memory). Flavonoids modulate neuronal function and thereby influence cognition. In addition, it has been suggested that flavonoids may delay the development of Alzheimer's disease-like pathology, anxiety, and depression disorders, suggesting a novel therapeutic strategy. Emerging evidence suggest that flavonoids are modulators of signaling pathways critical for controlling synaptic plasticity in the brain. For example, phosphatidylinositol-3 kinase (PI3K)/Akt, mitogen-activated protein kinase, protein kinase C, pathways could be involved $Ca^{2+}$ signaling. Significants questions such as: (i) How does flavonoids affect plasticity? (ii) What receptors are modulating by flavonoids and how are they regulated? (iii) Do flavonoids have a neuroprotective effect in aging? are asked.

**Keywords:** flavonoids, synaptic plasticity, health lifestyle, brain

## 1. Introduction

Advances in medicine over the last century have resulted in a considerable increase in human life expectancy. Despite this positive outcome, with increase in age, comes a decline of metabolic and immune functions with impact on the cognitive functions. Although, some decline in cognitive function does occur with normal aging, there is also an increased age-associated risk of neurodegenerative disorders such as Alzheimer's disease (AD) [1]. At the same time, it highlights the need for a more comprehensive understanding of how different aspects of lifestyle such as physical exercise, meditation, musical experience, and diet may influence brain disorders in a preventative manner, affecting long-term neural function that affects cognitive performance [2]. In relation to the diet, flavonoids have been described as promising plant-based bioactives capable of modulating different aspects of neuroplasticity, resulting in improvements in memory in both rodents [2] and humans [3, 4]. For example, flavonoids have been correlated with their ability to modulate the phosphorylation state of intracellular proteins by the activation or inhibition of phosphoinositide 3-kinase (PI3K), protein kinase C (PKC), mitogen-activated protein kinase (MAP), CAMP responsive element binding protein 1 (CREB-1), growth associated protein 43 (GAP-43), brain-derived neurotrophic factor (BDNF), or to alter expression of N-methyl D-aspartic acid (NMDA) receptors (NMDARs), $GABA_A$ receptors ($GABA_A$Rs), and 5-HT receptors (5-HTRs) [5, 6]. In addition, flavonoids can modulate epigenetic modifications [7]. These mechanisms are critical for the neuroplasticity and they are also related with inflammatory processes in the brain.

The aim of this chapter is to highlight the potential of flavonoid-rich food, flavonoid-rich extract, and medicinal plants that act as modulators of neuroplasticity in the central nervous system of mammals. We provide an outline of the neuroplasticity and how flavonoids affect this mechanism, and we will also describe their interaction in the neuroinflammation mechanism that affects the cognition. It will highlight the probable mechanisms that flavonoids promote neuroprotective effect in aging.

## 2. Flavonoids structure and brain bioavailability

Flavonoids are a large group of naturally occurring plant-based compounds that are commonly consumed through a diet rich in fruit, vegetables, tea, wine, and soy-based foods, being of considerable scientific and therapeutic interest. Flavonoids are responsible for numerous functions in plants. Among them, we can mention protection against ultraviolet rays, against insects, fungi, viruses, and bacteria, and the ability to provide the attraction of pollinating animals. In addition to these characteristics, many of these compounds also possess important pharmacological properties, such as antiviral, antitumor, anti-inflammatory, antioxidant, anti-inflammatory activity, and neuroprotective actions.

Flavonoids consist of two aromatic carbon rings, benzopyran (A and C rings) and benzene (B ring) (**Figure 1**). Flavonoids can be subdivided into different subclasses depending on the carbon of the C ring on which the B ring is attached and the degree of unsaturation and oxidation of the C ring on which the B ring is attached and the degree of unsaturation and oxidation of C ring. Thus, they may be divided in seven subclasses as: (1) flavones (e.g. apigenin, luteolin); (2) flavonols (e.g. kaempferol, quercetin); (3) isoflavones (e.g. daidzein, genistein); (4) chalcones (e.g. phloretin, chalconaringenin); (5) flavanones (e.g. naringenin, hesperetin); (6) anthocyanidins (e.g. delphinidin, cyanidin) and, (7) flavanols [e.g. catechin, epicatechin,

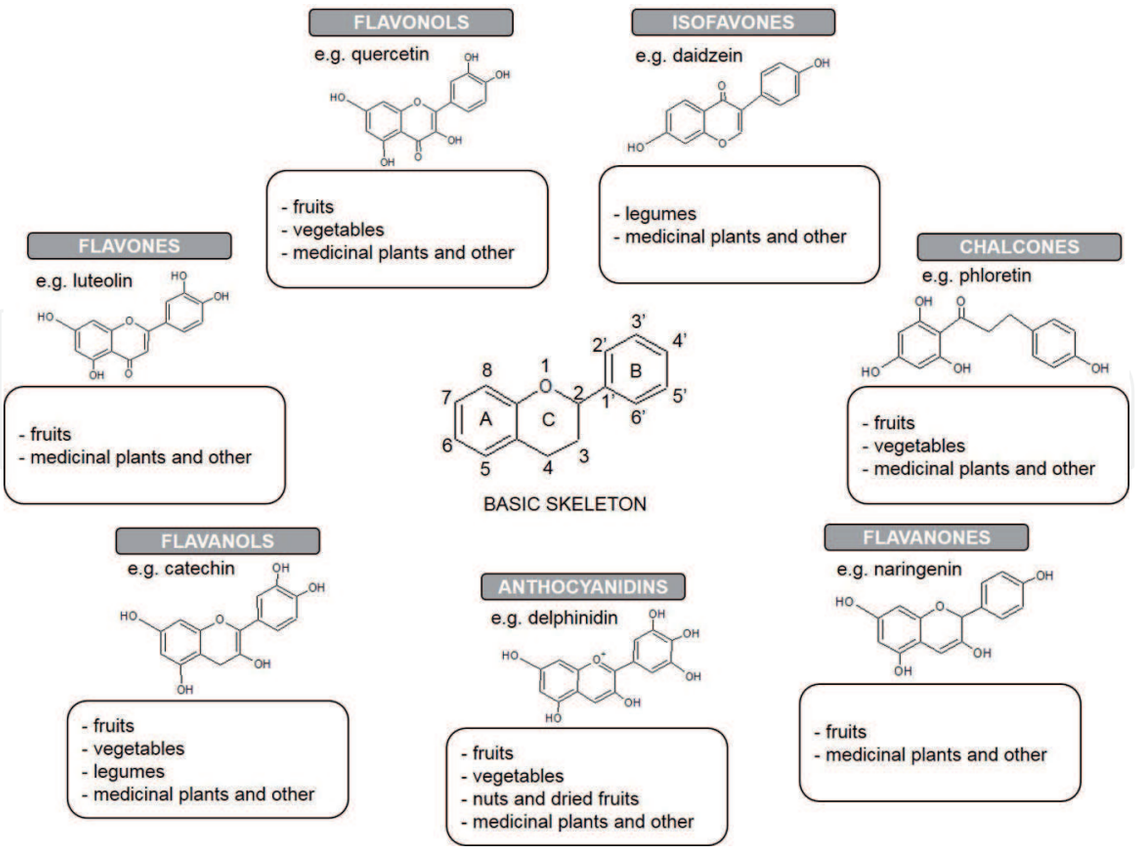


**Figure 1.**
*Basic skeleton structure of flavonoids, subclasses, and their natural sources.*

epigallocatechin, epigallocatechin gallate (EGCG)] [8]. For further information regarding the structure and classes of flavonoids, you can see references Andersen and Markhan [8].

Although flavonoids display directly modulate brain function, during absorption; they are extensive metabolized, resulting in a wide variety of metabolic derivatives. Do flavonoids access the brain?

In order to understand whether flavonoids are capable of modulating brain function, it is important to understand the bioavailability. Bioavailability is a crucial factor determining their biological activity *in vivo*. Therefore, information on the absorption and metabolism of dietary flavonoids in the digestive tract is important for determining their physiological functions, and what if flavonoids and their metabolic derivatives cross the Blood-Brain Barrier (BBB) [9–11]. This point is still a matter of debate, despite a number of studies shows the presence of flavonoids and their metabolites in brain tissue following oral administration of flavonol, e.g. (−) epicatechin [10], flavanones, e.g. hesperetin [11] and flavone, e. g. baicalein [12, 13]. The capacity of flavonoids and their metabolites to cross BBB is dependent on the degree of lipophilicity of each compound, i.e., less polar O-methylated metabolites may be capable of greater brain uptake than the more polar flavonoid glucuronides [14].

Bioavailability studies using flavonoids labeled with radioactive were found in various brain tissues such as hypothalamus, superior colliculus, cerebellum, striatum, and in limbic system structures as cortex and hippocampus [9, 11, 15], both important for memory formation, and are also adversely affected by aging and neurodegenerative diseases. It is a necessary work to discuss bioavailability of flavonoids in brain; however, some studies showed the direct and protective effects of flavonoids in modulating brain function, which will be discussed below.

## 3. Impact of flavonoids on cognition

The common medicine has focused on symptoms and treatment but the majority of chronical diseases are the result of unhealthy habits. The lifestyle medicine has focused on prevention, which means an increase in life quality, well-being, and avoids morbidity conditions [16]. Habitual consumption of dietary flavonoids has been consistently linked with improving cognitive functions [17–19]. For this reason, the flavonoids have been described as a class promised to maintain cognition functions and/or to delay in the progression of age-related cognitive. Despite a growing body of animal studies demonstrating positive effects in learning and memory after flavonoid intake (discussed in the next session), the human clinical trials are somewhat scarcer.

The neurobehavioral effects of phytoestrogens have been the limited data that exist regarding the influence of soy-derived dietary isoflavones on brain structure and function [20]. Clinical trial studies showed the efficacy of isoflavones on cognitive function in postmenopausal women. For example, Long term soy-isoflavone-based supplement (110 mg/d) for 6 months showed better verbal memory than the placebo control group [21]. Similarly, in women aged 50–65 found that intake of 60 mg/d for 3 months resulted in cognitive improvement in several categories related to frontal cortical functions [22]. Another study, involving younger postmenopausal women receiving 160 mg/d isoflavones for 6 months, and results showed an improvement cognitive flexibility [23].

With respect to anthocyanins, blueberry flavonoids supplement (579 mg/d) for 7 days induce cognitive improvements in young and aged adults [24]. Similar results were found after 3 months (long-term supplementation) with blueberry juice in older adults with cognitive impairment in working memory [25]. Some studies address the cognitive impact of a single dose of a blueberry juice in children (8–10 years old) [26]. This study showed for the first time a cognitive benefit for acute flavonoid intervention in children. Another study with 30 g of lyophilized anthocyanins, equivalent to 240 g or 1½ cups of fresh blueberries, demonstrated beneficial cognitive effects on memory and attention, not extending reading ability, in healthy children of 7–10 years of age. These findings increase the growing body of evidence that flavonoids are beneficial to healthy brain function [27].

Finally, precise estimation of nutrient intake is essential for establishing a relationship between diet and cognitive function. However, estimations of dietary flavonoid intake need to take into account their complexity and variability. More recently, a review reported wide range for mean total flavonoid intakes between 209 and 1017 mg/d (mean 435 mg/d) in European, US, and Australian adult populations [28]. In Brazil, the estimate is between 60 and 106 mg/d [29]. There are substantial variations in population estimates of dietary flavonoid intake, which may be associated to true differences in dietary patterns, such as differences in the food supply and cultural eating patterns between countries. Further studies are required to address and to detect effects of dietary interventions on human cognitive functions.

## 4. Mechanisms underpinning the actions of flavonoids as synaptic plasticity modulators

Flavonoid subclass has been extensively studied. For this reason, flavonoids have been recognized as promising agents capable of influencing different aspects of synaptic plasticity resulting in improvements in learning and memory. It is not completely clear how flavonoids affect synaptic plasticity. A growing body of evidence suggests that they can (1) modulate receptor function, and (2) promote

the expression of synaptic plasticity-related genes and proteins (**Figure 2**). The next sections outline the effects of flavonoids in synaptic plasticity and how these may underpin improvements in memory.

### 4.1 Flavonoid-receptor interactions

There are a number of studies that support the flavonoid-receptor interactions. For example, blueberry intake by young rodents increases the levels of GluN2b subunit of N-methy-D-aspartate receptor (NMDAR) in hippocampus [30]. Similarly, in young rodents, acute effect of oral flavonoid-rich fraction (Ff) intake up-regulated mRNA expression of the GluN2b subunit in dorsal hippocampus [5]. The flavonoid-rich fraction (Ff) containing flavones (Vitexin, Isovitexin, and 6-C-glycoside-Diosmetin) and improves learning and memory in young rodents. It is known that NMDARs are centrally involved in synaptic transmission, synaptic plasticity (long-term potentiation – LTP and long-term depression – LTD), and learning and memory [31]. According to this, quercetin resulted in improvements of hippocampal CA1 long-term potentiation in acute hippocampal slice from young rats [32].

The serotoninergic and GABAergic neurotransmissions are involved in learning and memory; the major targets are 5-$HT1_A$Rs and $GABA_A$Rs, and the modulation of these receptors in the hippocampus is essential for the acquisition and consolidation of memory [33–35]. Supporting, acute effect of oral Ff up-regulated mRNA expression of the 5-$HT1_A$R and GABA(A) alpha 5 receptor in dorsal hippocampus from young rats [5]. Molecular docking study showed that flavones such as Isovitexin and 6-C-glycoside-Diosmetin exhibited a strong interaction with the $GABA_A$ BZ binding pocket. Those flavones showed a lack of interaction with α1His101, which may explain the memory-enhancing effect identified in the behavioral test in young rats [36].

Flavonoids can modulate other receptors such as TrKB [37], δ-opioid [38, 39], nicotinic [40, 41], estrogen [42, 43], and adenosine [44–46]. For example, 7,8-dihydroxyflavone, a flavone, was shown high-affinity agonist of the TrKB receptor [47]. In addition, the flavones may improve cognition by modulating the acetylcholine and neurotrophic factors synthesis in hippocampus and frontal cortex [27, 48]. Those flavonoid-binding sites show many possibilities of flavonoids action mechanisms to modulate cognition and brain physiology.

### 4.2 Flavonoid-signaling pathways interactions

Receptor binding by flavonoids is responsible by changes in the up-regulated and down-regulated pathways such as, PI3K, PKC, MAP kinases, and nuclear factor-κB pathway. Their influence on such pathways suggests that they may modulate synaptic plasticity involved in neurodegenerative diseases, and memory acquisition, consolidation, and storage.

Short-term and long-term treatment of oral *Ginkgo biloba* (EGb) extract up-regulated mRNA and protein of the CREB-1 and GAP-43 in dorsal hippocampus

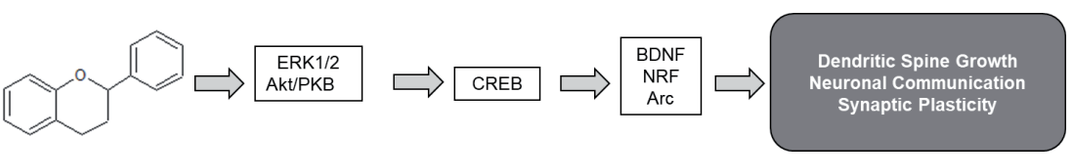


**Figure 2.**
*Mechanisms underpinning the actions of flavonoids.*

from young rats [49, 50]. These molecules are associated with molecular mechanism LTP, and it has been shown that the transcription factor, cAMP response element-binding protein (CREB), may regulate the synthesis of new proteins necessary for the formation of memory. Another potential protein associated with LTP is the protein 43-kDa growth-associated protein (GAP-43), and they dramatically enhances during LTP [51–53]. Quercetin-increased expression of activity-regulated cytoskeletal-associated protein (Arc/Arg3.1) [54] pathway is important for memory.

Flavanols and flavanones activate the ERK pathway [55–58] and ERK modulate cAMP response element binding protein (CREB) activation, which is involved in long-term changes in synapses and memory formation [37–39]. Similarly, acute effect of oral Ff up-regulated mRNA expression of the ERK in dorsal hippocampus from young rats [5].

In addition, the flavonoids may modulate the protein kinases, as MAP-kinase and PI3-kinase [59–62], the alteration on activation of kinase may influence directly on modulation of activity-dependent plasticity and morphological changes in synapses involved in memory acquisition, consolidation, and storage [63].

In summary, the ability of flavonoids to influence receptor activity and synaptic plasticity suggest that these might underpin enhancements in cognitive functions in both health conditions and neurological/psychiatric disorders. Additional approaches are required to understand the molecular mechanisms involved in these processes, for example, electrophysiological studies in rodents and human.

## 5. Prevention of cognitive decline through lifestyle interventions

There is increasing evidence that diet rich in flavonoid or supplements might delay the initiation of and/or slow the progression of cognitive decline related to aging and Alzheimer's diseases (AD). Among existing dietary patterns, adherence to a Mediterranean diet is associated with less cognitive decline, dementia, or AD [64, 65]. For example, a meta-analysis showed that greater adherence to a Mediterranean-style dietary pattern during older adulthood was associated with a lower risk of developing several different health outcomes such as CVD, neurodegenerative disorders, cancer, and overall mortality [66].

With regard to AD, the consumption of food rich in flavonoids such as red wine, fruit juice, and vegetables has been shown to delay the onset of AD [17, 67]. This is in accordance with previous studies linking high consumption of flavonoids to decline related to aging and dementia [19, 68]. A number of studies using animal models of AD have begun to investigate the possible mechanisms involved in these effects. For example, oral administration of the green tea flavonoid EGCG for 6 months to mice overexpressing the Swedish mutation of APP (Tg2576) reduced amyloid β (Aβ) pathology as well as improving cognition [69], and similarly long-term green tea catechin administration improved spatial learning and memory in senescence-prone mice [70]. Furthermore, feeding APP+PS1 double-transgenic mice blueberry from 4 months of age prevented deficits in Y-maze performance at 12 months, without altering the Aβ burden [71]. The myricetin and morin are successful to inhibit the β-sheet of Aβ oligomers. Apigenin, a flavone, and quercetin, a flavonol, have shown promising results with animal model of AD, and quercetin has shown to be benefit to early-stage AD patients [72].

The mechanism underlying these changes is not clear but might be linked to increase α-secretase activity [73] reported in vitro and in vivo after i.p. injection of EGCG [42, 74] or due to disruption of cAbl/Fe65 interactions [75]. Gallic acid and catechin-rich grape seed polyphenolic extract (GSPE) administered for 5 months to Tg2576 mice inhibited cognitive deterioration coincident with reduced levels of

soluble high-molecular-weight oligomers of Aβ [76]. Moreover, GSPE also inhibits tau fibrillization, promotes the loss of preformed tau aggregates, and disrupts paired helical filaments [77–80]. EGCG seems to have broadly similar effects. (−)-Epicatechin and hesperetin hold the potential to inhibit the development of tau pathology through an alternative mechanism relating to their ability to enhance Akt phosphorylation, thereby inhibiting GSK3β-induced tau hyperphosphorylation [55, 56]. Overall, this supports the claim that orally active flavonoids could have the utility in AD beyond anti-Aβ actions. The challenge ahead is to determine if flavonoids have efficacy in individuals affected by dementia.

## 6. Discussion: future directions

The consumption of flavonoid-rich foods and supplements throughout life may have the potential to limit or even reverse the progression of cognitive decline related of aging and potentially delay the onset and progression of dementia. The mechanisms by which flavonoids modulate cognitive functions are yet to be fully established.

In relation to synaptic plasticity, it will be particularly important to investigate the potential effect of flavonoids that mediate the induction of long-term depression (LTD), short-term potentiation (STP), and long-term potentiation (LTP) in hippocampus area. To dementia, it will be important to investigate the potential utility of flavonoids in the modulation of amyloid β pathology in more detail. In addition, it will be important to clearer dietary recommendations on flavonoid intake (including potentially a "recommended daily intake" level). Indeed, there are a number of important questions still to be resolved.

## Conflict of interest

None.

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