Dietary Flavonoid Intake and Risk of Mild Cognitive Impairment in the Elderly: A Case-Control Study

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ABSTRACT

BACKGROUND: This study investigates the association between dietary flavonoid intake and the incidence of mild cognitive impairment (MCI) through a matched case-control design.

METHODS: Dietary intake was assessed using a food frequency questionnaire, comparing the intake of flavonoids between individuals with MCI and those with normal cognitive function. Logistic regression analysis was employed to evaluate the correlation between dietary flavonoid intake and the risk of MCI. Additionally, blood concentrations of S100β, a marker of the blood-brain barrier (BBB) integrity, were measured using electrochemiluminescence immunoassay, and Pearson correlation analysis was conducted to explore the relationship between dietary flavonoid intake and blood S100β levels.

RESULTS: Compared to participants with normal cognition, those with MCI had significantly lower dietary intakes of total flavonoids, isoflavones, daidzein, glycitein, genistein, kaempferol, myricetin, flavonols, and anthocyanidins, while the intake of peonidin was significantly higher. Univariate logistic regression analysis indicated that high dietary intake of total flavonoids, isoflavones, daidzein, glycitein, genistein, kaempferol, myricetin, and flavonols was negatively correlated with MCI, whereas peonidin intake was positively correlated with MCI. Multivariate logistic regression analysis confirmed these findings. Pearson correlation analysis revealed a significant negative correlation between dietary intake of kaempferol and myricetin and blood S100β levels.

CONCLUSION: Increasing the dietary intake of total flavonoids, isoflavones, daidzein, glycitein, genistein, and flavonols appears to be a protective factor against MCI, while higher intake of peonidin is associated with an increased risk of MCI. The protective or adverse effects of these flavonoids may not be related to the permeability of the BBB. Myricetin and kaempferol intake may protect cognitive function by maintaining BBB integrity.

PLAIN LANGUAGE AND SUMMARY:

BRIEF HIGHLIGHTS:

More attention to neurons

Previous studies on the cognitive effects of flavonoid intake have mainly focused on their direct effects on central neurons and glial cells.

Less attention to BBB damage

Few studies have investigated the effects of flavonoid intake on the BBB, which indirectly affects cognitive function.

Negative correlation between BBB damage and Myricetin and Kaempferol

It was found that Myricetin and Kaempferol, two components of flavonoids, were negatively correlated with the risk of MCI and negatively correlated with blood levels of the BBB integrity marker S100β. They may protect cognitive function in middle-aged and elderly people by preserving the integrity of the BBB.

KEYWORDS: Flavonoids, MCI, MoCA, blood brain barrier, kaempferol

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Background

Mild Cognitive Impairment (MCI) represents an intermediate stage of cognitive dysfunction, bridging the gap between normal aging and dementia. Epidemiological studies have shown that over 15% of the global population aged 60 and above suffer from MCI, with prevalence rates reaching up to 50% in individuals aged 80 and above.[1] MCI is particularly concerning due to its potential to precede dementia. Research has demonstrated that individuals with MCI are at a higher risk of developing Alzheimer's disease (AD) compared to those without MCI. Moreover, MCI can impair daily life and social functioning, thereby reducing the quality of life. Consequently, early detection and intervention for MCI are critical in preventing the onset and progression of dementia.[2]

The Blood-Brain Barrier (BBB) is a unique anatomical structure essential for maintaining the stability of the brain's microenvironment. It is primarily composed of microvascular endothelial cells with tight junctions (TJs) formed by proteins such as claudin, occludin, and junction adhesion molecules (JAMs) that seal the intercellular gaps between these cells. The basement membrane beneath the microvascular endothelial cells provides structural support, and pericytes embed into the basement membrane, interacting with vascular endothelial cells through synapse-like contacts to maintain the integrity of the BBB. Astrocytes also tightly connect with microvascular endothelial cells and play a crucial role in the maturation and function of the BBB. Besides these cells, the neurovascular unit includes microglia and neurons, which together constitute the BBB structure and play a role in maintaining its integrity. These cells and structures work together to form a highly selective barrier that protects the brain from harmful substances in the blood while providing the necessary nutrients and metabolic products for the brain. Additionally, the BBB has dynamic regulatory functions that respond to different physiological and pathological conditions.[3] The integrity of the BBB is closely related to neuronal survival and neurologic function. Therefore, identifying accurate, representative, and non-invasive blood biomarkers is crucial. S100β is predominantly synthesized by astrocytes within the BBB and is rapidly released into the bloodstream upon BBB damage. Although S100β can also be found in other tissues, it is present in lower concentrations. The level of S100β in the blood is closely associated with the opening of the BBB and, more importantly, compared to other biomarkers, is more related to BBB integrity than to neuronal injury.[4] Thus, this study uses the level of S100β in the blood to represent the integrity of the BBB.

Studies have identified a connection between BBB damage and the risk of MCI. BBB damage may allow harmful substances, such as inflammatory cytokines, oxidative stress substances, and lipid metabolic products, to enter the central nervous system from peripheral blood, affecting normal neuronal function and leading to MCI's occurrence and progression.[3] Therefore, protecting the integrity of the BBB is crucial for preventing and controlling MCI. Currently, improving lifestyle habits, such as controlling blood pressure, blood sugar, and cholesterol levels, increasing physical exercise, and maintaining healthy sleep, can protect BBB integrity and prevent MCI.[5,6]

Flavonoids are an important class of natural organic compounds, a type of secondary metabolite produced by plants during natural selection.[7] They are widely present in the roots, stems, leaves, flowers, and fruits of plants, with a wide variety and complex structural types. Common flavonoids have unique chemical structures and exhibit many important physiological and biochemical effects on mammalian and other cells. Common flavonoids include isoflavones, flavonols, flavones, anthocyanidins, etc. (Figure 1). Studies have shown that flavonoids can promote human health and prevent various chronic diseases, such as cardiovascular diseases, cancer, and diabetes.[8-10] Therefore, flavonoids have become a hot topic of research in recent years.

Previous studies on the impact of flavonoids on cognitive function in middle-aged and elderly populations have mainly focused on their direct effects on neurons and glial cells, with less attention to their effects on the BBB. Preclinical studies have found that flavonoids can reduce BBB permeability by reducing oxidative stress and inflammatory responses, increasing tight junction proteins, alleviating brain tissue edema, and reducing neuronal damage and inflammation.[11] For example, Xiao Cheng and colleagues found in mice that kaempferol can significantly reduce LPS-induced BBB damage and upregulate the expression of occludin-1 and connexin43 (CX43) in a dose-dependent manner.[12] In vitro studies have shown that luteolin can improve the loss of BBB integrity and increase its permeability caused by amyloid β-protein (Aβ).[13] This suggests that flavonoids may protect the integrity of the BBB, thereby preventing MCI. To investigate the impact of flavonoids on MCI, this study aims to use a case-control study design to collect dietary data from participants who meet the standard and analyze the relationship between flavonoid intake and the occurrence of MCI. This research aims to provide new insights into the nutritional prevention and treatment of MCI.

Methods

Subjects

The study employed a cross-sectional survey design, selecting middle-aged and elderly individuals who underwent health examinations at multiple centers, including Linyi People's Hospital in Shandong Province, from 2017 to 2019. The inclusion criteria were as follows: (1) aged between 50 and 70 years; (2) capable of independently performing daily activities; (3) possessing normal hearing, vision, and communication abilities, enabling them to complete the questionnaire survey; and (4) willingness to participate in the study and sign an informed consent form. The exclusion criteria were: (1) patients with a clinical diagnosis of dementia; (2) patients with severe heart, liver, or kidney insufficiency or advanced malignant tumors; (3)

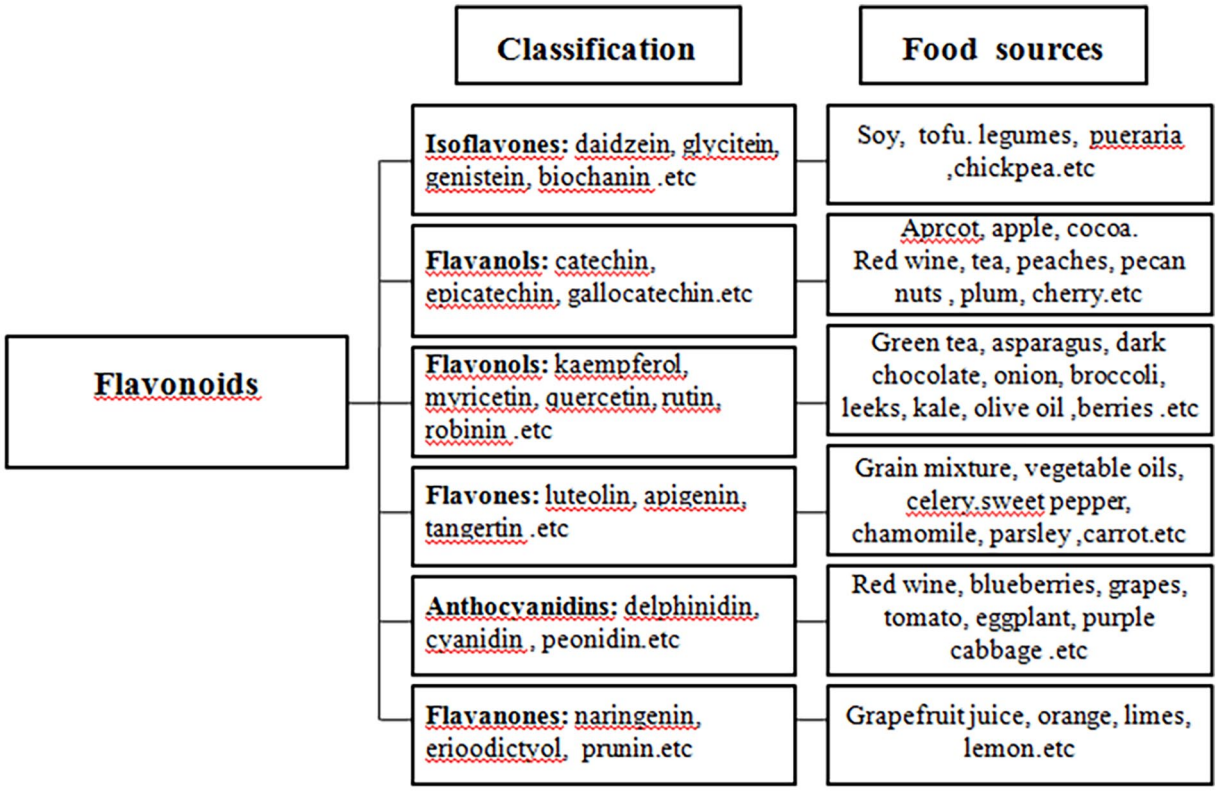

Figure 1. Flavonoid classification and food sources.

patients with cognitive dysfunction caused by thyroid disease, brain trauma, drug or alcohol intoxication, Parkinson's disease, etc.; (4) patients with a history of depression, anxiety, schizophrenia, or other mental disorders; (5) patients who have been using hypnotic or sedative drugs long-term; and (6) uncooperative participants or those with incomplete data. This study was performed according to the declaration of Helsinki and the good clinical practice guidelines and was approved by the Ethics Committee of Beijing Luhe Hospital, Capital Medical University , China (Ethics number: 2021-LHKY-036-01).

Demographic, lifestyle behaviors, and chronic disease assessment

A questionnaire survey was used to obtain information on the subjects' age, education level, lifestyle behaviors, and chronic disease status. (1) Age: The actual age of all survey participants was calculated by subtracting their date of birth from the survey date. (2) Education Level: Low education: No formal education or less than primary school education. Medium education: Junior high school, high school, or vocational education. High education: College or higher education. (3) Smoking: Defined as smoking at least 1 cigarette per day for more than 1 year. Individuals who met the smoking criteria but had not smoked for at least 1 year or never smoked during the survey were defined as non-smokers. (4) Drinking: Defined as drinking white wine at least once a week for more than 1 year. Individuals who had not drunk alcohol for at least 1 year or never drank during the survey were defined as non-drinkers. (5) Chronic Disease Status: Diagnosed with hypertension, diabetes, peripheral vascular disease, or a history of coronary heart disease by a formal medical institution.

Dietary assessment

Dietary data and intake levels of the subjects were obtained via a food frequency questionnaire. Initially, the questionnaire inquires whether the participant has consumed a particular food item. If affirmative, it proceeds to solicit information regarding the frequency of consumption and the quantity ingested daily. The daily intake for each food item is calculated as the product of the consumption frequency and the daily quantity reported. Participants were assisted by food imagery to ascertain the weight of the food items they consumed. Individual food consumption was calculated into quantitative flavonoid intakes based on the United States Department of Agriculture (USDA) database. This database provides the flavonoid values in foods and beverages.[4]

Laboratory measurements

Blood samples were obtained through venipuncture, centrifuged at a force of 2100 g for 15 minutes, and stored at −20°C for analysis. The concentration of serum S100β was determined using the Roche Diagnostics Cobas e411 instrument (Meyrun, France) and electrochemiluminescence immunoassay.

MCI diagnosis

Subjects suspected of having MCI based on scores from the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) were further evaluated. The primary symptom, as provided by the patient's family or informant, was a decline in memory that had persisted for over 6 months. However, the subjects maintained normal activities of daily living and did not meet the diagnostic criteria for dementia. Ultimately, a neurologist diagnosed them with MCI.

Statistical analysis

All data were processed and analyzed using SPSS 18.0 statistical software. If the quantitative data followed a normal distribution, they were presented as the mean ± standard deviation; otherwise, they were presented as the median and interquartile range. Categorical data were presented as frequency and proportion. Comparisons of quantitative data between 2 groups were performed using the *t*-test or the Mann–Whitney *U* test, while comparisons of categorical data were conducted using the chi-square test. Univariate logistic regression was used to assess the association between different types of flavonoids as categorical variables and the risk of MCI. Multivariate analysis was used to adjust for demographic and clinical characteristics. Pearson's correlation test was used to evaluate the correlation coefficient. A *P*-value of $<.05$ was considered statistically significant.

Results

This study included 270 patients with MCI (113 males and 157 females) and 270 control subjects with normal cognitive function (135 males and 135 females). The demographic and clinical characteristics of all subjects are summarized in Table 1. Significant differences were found between the 2 groups regarding education level ($P=.005$), Montreal Cognitive Assessment (MoCA) scores ($P<.01$), and Mini-Mental State Examination (MMSE) scores ($P<.01$).

Table 2 shows the dietary intake of flavonoid compounds. Compared to the control group, MCI patients had significantly lower intakes of total flavonoids, isoflavones, daidzein, glycitein, genistein, kaempferol, myricetin, flavonols, and anthocyanidins, while their intake of peonidin was significantly higher (all $P<.05$). No significant differences were observed in the intake of quercetin, flavones, luteolin, apigenin, cyanidin, and delphinidin between the 2 groups (all $P>.05$).

Table 3 indicates that univariate logistic regression analysis showed a negative correlation between the intake of total flavonoids, isoflavones, daidzein, glycitein, genistein, kaempferol, myricetin, and flavonols and the occurrence of MCI. Conversely, the intake of peonidin was positively correlated with MCI occurrence.

Table 4 demonstrates that even after adjusting for confounding factors, the significant associations between the intake of total flavonoids, isoflavones, daidzein, glycitein, genistein, myricetin, flavonols, and peonidin with MCI remained. Pearson correlation analysis revealed a significant negative correlation between the intake of myricetin and kaempferol and the levels of S100β in the blood, whereas other dietary flavonoids were not related to serum S100β levels (Figure 2).

Discussion

Flavonoids are a class of dietary polyphenols derived from plants that may influence multiple cellular targets in the brain.[14] Natural flavonoids are classified into 6 main subgroups, namely: flavones, flavanones, flavan-3-ols, flavanols, anthocyanidins, and isoflavones[14] (Figure 1). As antioxidants, previous studies have primarily focused on the direct action of flavonoids on neurons and glial cells through key signaling cascades, thereby exerting a protective effect on cognitive function. However, preclinical research also suggests that flavonoids may protect cognitive function by indirectly affecting the integrity of the BBB.[15] To date, no population-based studies have explored the impact of dietary flavonoid intake on cognitive function, particularly through its effects on BBB integrity.

Isoflavones are primarily accumulated in leguminous plants, with the main source being soybeans and their derivatives.14 The components of isoflavones include genistein, daidzein, and glycitein.[14] The impact of isoflavones on cognitive function is currently a subject of debate. A randomized, double-blind study by Gleason CE et al. found that daily intake of 100 milligrams of isoflavones significantly improved cognitive function in the elderly, including structured memory, visual spatial memory, verbal fluency, and rapid agility. They concluded that isoflavone intake has a beneficial effect on cognitive function.[16] However, other studies have reached opposite conclusions. A longitudinal study in Japan found a negative correlation between isoflavone intake and cognitive function decline in women but found no such association in men. Additionally, a 15-year follow-up study in Singapore found no correlation between dietary isoflavone intake and the risk of cognitive impairment.[17,18] The findings of this study indicate a negative correlation between total isoflavone intake and the risk of MCI, supporting the conclusions of Gleason et al but contradicting the results of the Japanese and Singaporean cohort studies. This discrepancy may be due to differences in the selected study populations. Estrogen receptor levels in the central nervous system may have beneficial effects on cognitive function, and isoflavones are natural estrogens. Therefore, postmenopausal women may benefit more from the intake of isoflavones in terms of improved cognitive function. Analysis of the Singapore study found that the cohort's dietary isoflavone intake was extremely high, making it difficult to determine the impact of a lack of dietary isoflavones on the risk of cognitive decline. There is also controversy regarding the impact of the isoflavone component genistein on cognitive function. A clinical randomized controlled study by José Viña et al. found that

Table 1. Distribution of demographic factors.

VARIABLE	CONTROL GROUP (270)	MCI GROUP (270)	*P*
Age, (y)	61.45 ± 2.746)	62.14 ± 2.794	.594[a]
Sex			
Male (%)	135 (50)	113 (41.9)	.07[b]
Female (%)	135 (50)	157 (58.1)	
Education			
Low level (%)	120 (44.4)	101 (37.4)	.005[b]
Medium level (%)	99 (36.7)	135 (50)	
High level (%)	51 (18.9)	34 (12.6)	
Alcohol drinking			
Drinker (%)	157 (58.1)	161 (59.6)	.793[b]
No-drinker (%)	113 (41.9)	109 (40.4)	
Smoking			
Smoker (%)	114 (42.2)	109 (40.4)	.727[b]
No-smoker (%)	156 (57.8)	161 (59.6)	
Family history			
Yes (%)	26 (9.6)	36 (13.3)	.224[b]
No (%)	244 (90.4)	234 (86.7)	
Chronic disease status			
Hypertension			
Yes (%)	54 (20)	64 (23.7)	.349[b]
No (%)	216 (80)	206 (76.3)	
Heart disease			
Yes (%)	26 (9.6)	30 (11.1)	.672[b]
No (%)	244 (90.4)	240 (88.9)	
Diabetes			
Yes (%)	21 (8.4)	26 (9.6)	.542[b]
No (%)	249 (91.6)	244 (90.4)	
MMSE score	27.68 ± 0.98	19.70 ± 3.35	<.001[a]
MOCA score	26.90 ± 0.84	18.52 ± 2.9	<.001[a]

[a]Data presented as means ± standard deviations were compared between 2 groups by using the Student t-test.
[b]Data presented as frequencies (percentages) were compared between 2 groups by using Chi-square test.

oral genistein tablets for 12 months effectively delayed cognitive decline in patients with AD.[19] However, a longitudinal study by Mei-Hua Huang et al on Chinese and Japanese women found no association between dietary genistein intake and cognitive function decline, which is not confirmatory to the findings of José Viña.[20] The results of our study found a negative correlation between the intake of the isoflavone component genistein and the risk of MCI. The intake of daidzein and glycitein also showed a negative correlation with the risk of MCI. This supports the views of José Viña et al but contradicts the findings of Mei-Hua Huang et al This may be related to the age differences of the study participants; Mei-Hua Huang selected participants aged between 42 and 52, where the cognitive protective effect of genistein may not be evident under normal estrogen levels. Pearson correlation analysis showed no correlation between the intake of total flavonoids, isoflavones,

Table 2. Dietary flavonoids compound intake.

VARIABLE MG/D	CONTROL GROUP	MCI GROUP	*P* VALUE
Total flavonoids	65.97 (10.94)	63.15 (11.86)	.004[a]
Isoflavones	4.10 (1.07)	3.83 (0.91)	.002[a]
Daidzein	1.79 (0.49)	1.56 (0.60)	<.001[a]
Genistein	2.21 (0.71)	2.01 (0.71)	.001[a]
Glycitein	0.43 (0.20)	0.37 (0.15)	<.001[a]
Flavonols	41.86 (8.30)	40.21 (10.08)	.038[a]
Quercetin	5.90 (2.00)	5.78 (1.93)	.476[a]
Myricetin	32.48 (10.67)	30.75 (9.66)	.050[a]
Kaempferol	3.34 (1.11)	3.09 (1.15)	.010[a]
Flavones	6.89 (1.31)	6.77 (1.31)	.272[a]
Luteolin	5.01 (1.17)	5.05 (1.21)	.661[a]
Apigenin	1.48 (0.50)	1.49 (0.47)	.791[a]
Anthocyanidins	12.03 (4.62)	11.34 (3.51)	.052[a]
Delphinidin	4.64 (0.99)	4.76 (0.97)	.158[a]
Cyanidin	6.76 (0.61)	6.89 (0.52)	.183[a]
Peonidin	0.69 (0.14)	0.65 (0.13)	<.001[a]

[a]Data presented as means ± standard deviations were compared between 2 groups by using the student's T test.

Table 3. Odds ratio of MCI for dietary flavonoids in univariate regression analysis.

VARIABLE	ODDS RATIO AND 95% CI		*P* VALUE
	LOW LEVEL	HIGH LEVEL	
Total flavonoids	Ref	0.980 (0.965-0.995)	.008
Isoflavones	Ref	0.752 (0.629-0.898)	.002
Daidzein	Ref	0.472 (0.340-0.656)	<.001
Genistein	Ref	0.682 (0.532-0.875)	.003
Glycitein	Ref	0.164 (0.061-0.443)	<.001
Flavonols	Ref	0.979 (0.961-0.998)	.028
Myricetin	Ref	0.981 (0.965-0.998)	.030
Kaempferol	Ref	1.226 (1.052-1.429)	.009
Peonidin	Ref	13.395 (3.671-48.876)	<.001

[a]The Dietary intake level of flavonoids were classified into high and low levels.

glycitein, genistein, and daidzein in the diet and the level of S100β in the blood, indicating that isoflavones and their components may protect cognitive function by directly acting on neurons and glial cells, but have no effect on the integrity of the BBB.

Flavonols are abundant in vegetables and fruits such as broccoli, onions, asparagus, and apples.[14] Key components of flavonols include myricetin, quercetin, and kaempferol.[14] The impact of flavonol intake on cognitive function has garnered significant interest. Thomas Monroe Holland and colleagues conducted 2 cohort studies on the effects of dietary flavonols on cognitive function. The first study examined the impact of dietary flavonols on cognitive decline in elderly individuals with normal cognitive function. It found a positive correlation

Table 4. Results of univariate and multivariate regression analysis for dietary flavonoids.

MODEL	ODDS RATIO AND 95% CONFIDENCE INTERVAL		*P* VALUE
	LOW LEVEL	HIGH LEVEL	
Total flavonoids			
Unadjusted	Ref	0.980 (0.965–0.995)	
Adjusted[a]	Ref	0.982 (0.965–1.000)	.035
Isoflavones			
Unadjusted	Ref	0.752 (0.629–0.898)	
Adjusted[a]	Ref	0.653 (0.527–0.810)	.001
Daidzein			
Unadjusted	Ref	0.472 (0.340–0.656)	
Adjusted[a]	Ref	0.428 (0.293–0.626)	.001
Glycitein			
Unadjusted	Ref	0.164 (0.061–0.443)	
Adjusted[a]	Ref	0.176 (0.056–0.551)	<.001
Genistein			
Unadjusted	Ref	0.682 (0.532–0.875)	
Adjusted[a]	Ref	0.657 (0.487–0.886)	.006
Flavonols			
Unadjusted	Ref	0.979 (0.961–0.998)	
Adjusted[a]	Ref	0.973 (0.950–0.995)	.019
Myricetin			
Unadjusted	Ref	0.981 (0.965–0.998)	.020
Adjusted[a]	Ref	0.976 (0.957–0.996)	
Kaempferol			
Unadjusted	Ref	1.226 (1.052–1.429)	
Adjusted[a]	Ref	1.126 (0.938–1.351)	.203
Peonidin			
Unadjusted	Ref	13.395 (3.671–48.876)	
Adjusted[a]	Ref	18.651 (4.012–86.694)	.001

[a]Adjusted for demographic and risk factors.

between total flavonol intake and a slower rate of decline in overall cognitive ability and multiple cognitive domains. Specifically, the intake of quercetin and kaempferol was associated with a slower rate of cognitive decline, while myricetin intake was not.[21] The second study investigated the impact of dietary flavonols on the incidence of AD, and found a positive correlation between flavonol intake and a reduced incidence of AD. In particular, myricetin and kaempferol intake were negatively correlated with AD incidence, while quercetin intake showed no significant association. In this study, we observed a significant negative correlation between total flavonol intake, kaempferol, and myricetin intake, and the risk of mild cognitive impairment (MCI).[22] However, no significant correlation was found between quercetin intake and the risk of MCI. Pearson correlation analysis revealed no correlation between dietary flavonol and quercetin intake and the level of S100β in the blood. Conversely, the intake of kaempferol and myricetin was negatively correlated with S100β levels, suggesting that kaempferol and myricetin may protect cognitive function by preserving the integrity of the BBB.

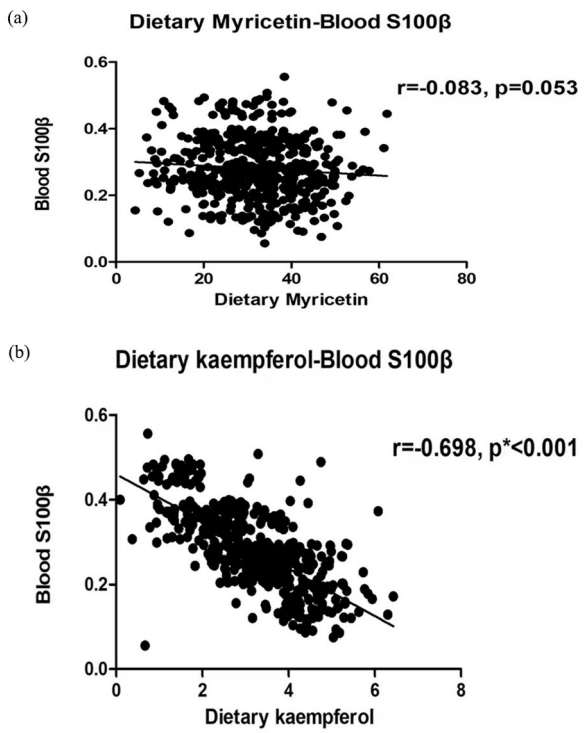

Figure 2. Correlations between blood level of S100β vs.: (a) Dietary Myricetin intake and (b) Dietary Kaempferol intake in cases and controls.

Flavones are found in celery, tea, red peppers, and oranges, with luteolin and apigenin being key components.[14] The impact of flavone intake on cognitive function is still debated. Esra Shishtar and colleagues conducted a longitudinal study and found no association between total flavone intake or individual flavones and cognitive decline.[23] Similarly, a longitudinal study in Northern Ireland followed 1126 female twins aged 18 to 89 for 10 years and found that higher total flavone intake was associated with an increase in age-related cognitive scores over the decade.[24] However, our study did not find a significant correlation between flavone intake and the risk of MCI, aligning with the findings of Esra Shishtar and colleagues. The differences in conclusions may be due to the Northern Ireland study's focus on females and a wide age range, as well as gender differences in flavonoid intake. Additionally, we did not find a correlation between flavones and their components and S100β blood levels.

Anthocyanidins are widely found in fruits and vegetables such as blueberries, grapes, red cabbage, tomatoes, purple potatoes, and eggplants. Their key components include delphinidin, cyanidin, and peonidin.[14] Limited randomized controlled research on the effects of anthocyanidins on cognitive function has produced controversial results. Krikorian and colleagues conducted a randomized controlled trial and reported no significant difference in performance on the California Verbal Learning Test (CVLT) after 16 weeks of grape juice supplementation.[25] In another study, they reported significant improvements in a verbal paired-associate learning task after 12 weeks of blueberry juice supplementation.[26] However, both studies had small sample sizes, with the grape juice intervention group consisting of only 10 participants (total of 39 participants) and the blueberry juice intervention group having 9 participants (total of 40 participants). In contrast, Kent and colleagues conducted a randomized controlled study on elderly individuals with mild to moderate dementia and found significant improvements in verbal fluency, short-term memory (RAVLT), and long-term memory after 12 weeks of cherry juice supplementation (138 mg daily).[27] Our study did not find a correlation between anthocyanidin intake and the risk of MCI. However, we did find that peonidin intake was positively correlated with the incidence of MCI. The controversy may stem from the different types of intervention juices used in randomized controlled trials, as different juices contain varying amounts of anthocyanidins. Additionally, no correlation was found between other anthocyanidin components and S100β blood levels. Peonidin may pose a risk factor for MCI due to its stimulating effects on the central nervous system.

Conclusions

The findings of this study suggest that a higher intake of isoflavones, daidzein, genistein, glycitein, and flavonols serves as a protective factor against MCI. Conversely, a higher intake of peonidin appears to be a risk factor for MCI. Importantly, these protective or adverse effects do not seem to be significantly associated with BBB impairment. The observed negative correlation between myricetin intake and serum S100β levels indicates that myricetin may help preserve cognitive function by maintaining BBB integrity. While kaempferol is not directly associated with the incidence of MCI, its negative correlation with BBB integrity suggests that it may support cognitive function when combined with other treatments.

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