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Systematic Review

Comprehensive Analysis of Phytoestrogens Intervention to Improve Cognitive Function in Menopausal Women: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Introduction: Dementia is marked by cognitive deficits which hinder daily functioning, with menopausal changes potentially impacting women's cognitive health and increasing dementia risk up to 70%. Studies suggest that hormone replacement therapy (HRT) can lower the risk of Alzheimer's disease in postmenopausal women, although the topic remains contentious. Phytoestrogens, which mimic estrogen, have shown promising outcome in some trials for improving cognitive function in postmenopausal women. Consequently, the aim of this systematic review is to explore the efficacy of phytoestrogens for treating dementia and cognitive impairment in menopausal women.

Material and Methods: The literature search was conducted in five databases. The outcome of interest measures the improvement of cognitive function in each included study. Different types of phytoestrogen interventions were utilized, such as isoflavone extracts with specified dosages, resveratrol, and either isolated soy protein (ISP) or soy-based products. The Cochrane Risk of Bias Tool 2 was used to assess the quality of the studies. The systematic review included a total of eight studies.

Results: This review included eight studies examining phytoestrogen interventions on cognitive function in 1,464 participants aged 45 to 92. While some studies showed no significant cognitive improvements, those using resveratrol and Ginkgo biloba reported notable enhancements, particularly in memory and executive function. Given that dementia and cognitive decline are common in postmenopausal women due to lower estrogen levels, phytoestrogens may offer potential benefits.

Conclusion: Phytoestrogens may improve cognitive function in menopausal women at risk of decline. However, further research is needed with more uniform populations, consistent interventions, and standardized assessments.

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INTRODUCTION

The World Health Organization (WHO) defines dementia as a collection of cognitive and functional impairments that arises due to something that is happening in the brain, which can be a disease or disorder [1]. It is marked by several cognitive impairments that result in a decline from the individual's previous level of functioning. Several higher cognitive abilities, including memory, reasoning, understanding, numerical skills, learning capacity, language, and decision-making or judgement, are impaired in dementia. These cognitive deficits are often accompanied by alterations in emotional state regulation, social behaviour, or motivation [2,3]. Globally, it is estimated that 55 million people are managing daily life with dementia, and approximately 7.7 million new cases are diagnosed annually. It is expected to reach around 78 million by 2030 and nearly double every 20 years until at least 2050, up to 139 million [4,5]. Dementia usually starts in the seventh or eighth decade of life, and the risk increases over time [6].

The majority of individuals affected by dementia are located in less economically developed countries, where there has been a rapid increase in the aging population [4].

From the Global Burden Disease Report in 2019, it is estimated that more women had dementia than men, and the same pattern is likely to continue until 2050 [7]. Former evidence showed that the reason for the pattern was due to sex differences in the biological mechanisms of Alzheimer's disease (AD) [8]. Growing evidence suggests that menopausal changes may affect women's intellectual abilities and could influence the future probability of developing dementia. Specifically, observational studies have linked decreased estrogen levels during menopause to a higher risk of dementia [9]. This connection has prompted multiple clinical trials to explore whether hormone replacement therapy in postmenopausal women might delay or prevent cognitive decline and the onset of dementia. However, the results of these trials have been inconsistent, with some showing beneficial effects, while others report no impact or even negative outcomes [10]. On the other hand, some studies suggest that there is a well-established link between the duration of the reproductive period, the timing of menopause, and the risk of neurodegenerative disorders, along with their various clinical symptoms [11,12].

According to the World Health Organization (WHO), menopause is the irreversible stoppage of the menstrual cycle due to the cessation of ovarian activity, not caused by any other pathological or physiological condition [13]. Menopause is confirmed after upon completion of 12 uninterrupted months without menstruation (amenorrhea), which is preceded by the perimenopause phase, like a change in menstrual flow or frequency [14]. A premature decline in estradiol (E2) increases the risk for various conditions in women, including heart disease, Parkinsonism, depression, bone loss (osteoporosis), high blood pressure, increased body weight, diabetes during midlife, cognitive impairments, and dementia [15]. Common complaints include memory issues, particularly difficulty remembering or recalling words and numbers, changes in sleep patterns, and changes in mood. Research indicates that cognitive impairment affects up to 70% of postmenopausal women [16–18].

Epidemiological studies show that hormone replacement therapy (HRT) can decrease the probability of developing AD by 50% in postmenopausal women [19]. Nevertheless, after the release of the Women's Health Initiative Study, the advantages and disadvantages of HRT have become a subject of debate. For women over 70 who used HRT for five years, there was an elevated risk of breast cancer, coronary heart disease, and cerebrovascular events, specifically stroke was observed [20]. Because of these side effects, many patients tried to stop treatment or seek other options for managing menopausal symptoms [3,21].

On the other hand, clinical studies indicate that administering estradiol (E2) can improve mood and cognitive function in postmenopausal women when started during early (peri) menopause instead of later [22]. This is due to estrogen's significant effect on brain function. Estrogen interacts with both α- and β-estrogen receptors present at the endothelium, facilitating vasodilation through the release of nitric oxide. Therefore, the decrease in estrogen in circulation after menopause negatively affects microcirculation, leading to increased arterial stiffness and decreased tissue perfusion. As a result, the cerebral blood flow and perfusion are limited. This reduction is linked to cognitive drop and the development of dementia, suggesting that estrogen is essential for maintaining neurovascular health and cognitive function [10]. High E2 levels have also been shown to have a positive impact in improving various cognitive domains, mainly enhancing memory by increasing α receptor levels in the hippocampus. Consequently, improving verbal memory and retrieval efficiency. The risk of early AD is increased fourfold in menopausal women who have low levels of E2 in comparison with those who have high levels of E2 [23].

Recent studies show that plant-based materials rich in bioactive phytochemicals—natural compounds found in plants that can interact with living tissues—have shown encouraging benefits for various bodily systems, particularly in terms of cardiovascular, metabolic, and endocrine health [24,25]. Phytoestrogens are plant-based compounds that are structurally identical to 17-estradiol. Nuts, seeds, fruits, and vegetables are rich in phytoestrogens. Examples of such food sources include soybeans, garlic, carrots, potatoes, rice, and fruits like apples and pomegranates, as well as coffee [26,27]. Phytoestrogens and estrogen have similar mechanisms that may improve neurocognitive performance, among which are boosting choline acetyltransferase and neurotrophic factor levels in the frontal cortex and hippocampus. Certain randomized trials investigating phytoestrogen supplements have demonstrated some kinds of improvements in cognitive abilities in improving cerebral perfusion, including improvements in memory performance and higher-order cognitive abilities in women after menopause aged 66 and below [28–31].

Recent systematic reviews have shown the benefit of phytoestrogens on dementia and cognitive function. However, the number of studies was limited, lacked standardized protocols, and relied on older literature [32,33]. Furthermore, only a few studies specialized in studying this topic in menopausal women [34]. Therefore, this systematic review utilized the latest

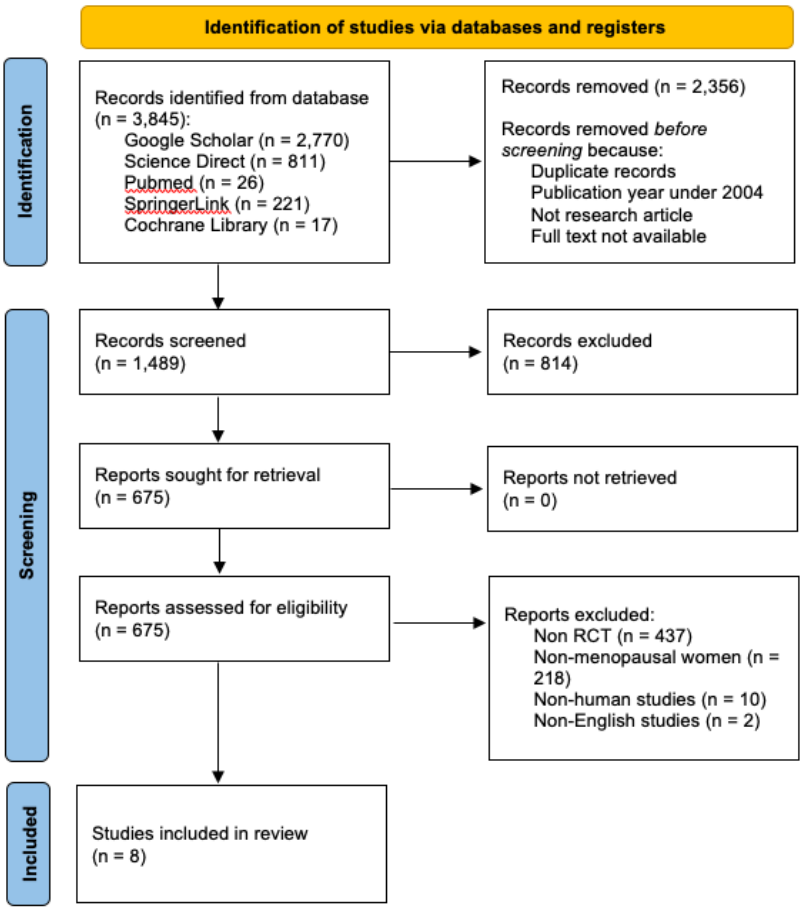


Fig.1 Prisma Flowchart for Study Selection

relevant RCTs to investigate the potential of phytoestrogens in improving cognitive function in menopausal women experiencing dementia or other kinds of cognitive disabilities.

MATERIAL AND METHODS

This review followed the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Eligibility Criteria

The Population - Intervention - Comparison - Outcome (PICO) framework was utilized to establish the criteria for study inclusion of 1) Population: menopausal women with cognitive impairment; 2) Intervention: phytoestrogens; 3) Comparison: placebo or no intervention; 4) Outcome: improvement of cognitive function. Study populations with cognitive impairment in this review included mild to severe cognitive impairment or had been diagnosed with dementia. All kinds of phytoestrogens, such as ginkgo biloba, ginseng, soy tablets, or other natural herb extract were included. The outcome of cognitive function was measured with all kinds of cognitive function's assessment, such as MMSE score, CGI, RAVLT, CVLT, TMT, WMS-R, WAIS-R, Digit Span, Boston Naming Test, Category Fluency, Letter Fluency, and Spatial Span Test. The studies incorporated in this review consisted of randomized controlled trials (RCT) published within twenty years (2004-2024). Exclusion criteria were adopted: 1) women who had taken supplementation or therapy affecting cognitive function or the brain structure; 2) women with other underlying diseases affecting the brain structure and function; 3) non-human trials and studies; 4) non-English studies; 5) grey literature.

Search Strategy

The literatures were from several databases, such as Google Scholar, PubMed, ScienceDirect, SpringerLink, and Cochrane Journal. The following keywords were used for literature searching, including ("Phytoestrogens") AND ("Dementia" OR "Cognitive

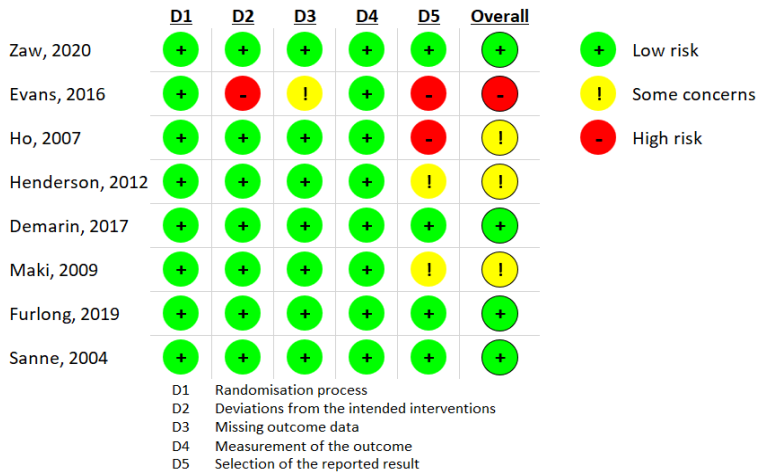


Fig.2. Risk of Bias Summary

Function") AND ("Menopause" OR "Menopausal Symptoms" OR "Menopausal Syndrome").

Data Extraction and Analysis

The selected studies were extracted into a Google Sheet, followed by assessment of their eligibility and accuracy. The analysis of each study was compiled in a table form, including author(s)'s name(s), year, country, number of subjects, age of subjects, type of intervention, duration of intervention, comparison group, and outcomes.

Risk of Bias Assessment

The risk of bias in the selected randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias Tool 2 (RoB 2), as outlined by Cochrane Reviews. The tool analysed the studies based on five areas of potential bias: the randomization process, deviations from planned interventions, outcome measurement, missing outcome data, and the selection of reported results. Based on the analysis from each domain, the qualities of the selected studies were categorized into three groups of classifications: low, unclear, and high risk of bias.

Intervention of Interest

Menopause signifies the transition from a woman's reproductive phase to the post-reproductive stage. During this time, there was a decline in estrogen. One of its functions was to improve brain perfusion and the low levels of estrogen in menopausal women could lead to cognitive impairment and dementia. Phytoestrogens might provide similar benefits and could become the alternative of HRT. Thus, the primary goal of this review is to discover the efficacy of phytoestrogens in various forms to improve cognitive function in menopausal women.

Outcome of Interest

This review had the objective of determining the effect of phytoestrogens in improving cognitive abilities in menopausal women compared to placebo. All forms of severity assessment of dementia were used in this review since there were various guidelines according to this matter, including MMSE score, CGI, RAVLT, CVLT, TMT, WMS-R, WAIS-R, Digit Span, Boston Naming Test, Category Fluency, Letter Fluency, and Spatial Span Test. The outcome of interest in this study was the improvement of the various assessment scales of cognitive function and dementia, which would allow for further investigation into the benefits of phytoestrogens for menopausal women with dementia or other cognitive impairment.

RESULTS

Study Selection and Identification

Upon completion of the literature analysis, 3,845 articles were released in the last ten years in five kinds of databases. Multiple articles were disqualified due to duplication of studies, publication year under 2004, not research articles, and unavailable in full text (n = 2,356). Due to ineligible data, 814 articles were excluded from the review; Among which are articles review and books, as well as articles that were restricted because of access limitations due to subscription. Furthermore, many journals fail to comply in line with the predetermined study design and inclusion criteria (n = 667). Fig.1 shows the PRISMA flowchart. Thus, 8 articles were incorporated into the systematic review.

Cognitive Function Analysis

Eight studies reported data on the average improvement in cognitive function from baseline to after the intervention. Ho et al found no notable enhancement in cognitive function was identified in the isoflavone group in comparison with the control group after six months of phytoestrogen intervention ($p>0.05$). After two years, a study by Maki et al. using red clover, black cohosh, and CEE/MPA for 12 months also found no notable enhancement in cognitive abilities in comparison with placebo ($p>0.05$). While this was ongoing, Henderson et al. used an isoflavone-rich soy protein supplement compared to a placebo group for 2.5 years to significantly improve cognitive function on the Letter-Number sequencing test ($p=0.033$) and Faces I, immediate recall ($p=0.024$). In 2015, Sanne et al. examined the effects of isoflavone-containing soy protein supplementation on cognitive abilities for 12 months, with nonsignificant results on all cognitive tests.

A year later, Evans et al. used resveratrol to significantly improve cognitive function for 14 weeks on the Rey Auditory Verbal Learning Test ($p=0.021$), and overall cognition ($p=0.018$). Meanwhile, Demarin et al. proved that giving Ginkgo biloba for 6 months can improve cognitive function through the Clinical Global Impression test ($p=0.038$). In 2019, Furlong et al. proved that there was no significant increase in cognitive function with the administration of soy drinks (Alpro®) compared to placebo ($p>0.05$). A year later, Zaw et al. studied that giving resveratrol for 12 months could significantly improve cognitive function through the forward spatial span test ($p=0.02$), dimensional change card sort test ($p=0.005$), and overall cognition ($p=0.005$).

DISCUSSION

Dementia and decrease of cognitive function are among the most frequently occurring symptoms found in postmenopausal women and affect the quality of life. Estrogen promotes nitric oxide-mediated vasodilation, improving blood flow. After menopause, lower estrogen levels lead to reduced microcirculation, arterial stiffness, and decreased cerebral blood flow. This reduction negatively impacts brain function and is linked to cognitive decline. Studies show that postmenopausal women have poorer cerebrovascular responsiveness (CVR) in comparison with premenopausal women, and lower CVR predicts worse cognitive performance. Hot flashes further reduce brain blood flow, increasing the risk of dementia, highlighting estrogen's role in maintaining brain and cognitive health [3,10].

The trend of using HRT in postmenopausal women is increasing due to its beneficial effects in reducing menopausal symptoms such as hot flushes yet there have been controversial research findings of the side effects of the treatment [35]. We analysed eight RCTs that assessed the use of various phytoestrogens to help prevent cognitive decline in postmenopausal women. This systematic review found that phytoestrogen intervention for at least 6 months, with both high and low doses of Ginkgo Biloba extract, low doses of resveratrol, or low doses of isoflavone-rich soy protein, may have a more neurovascular-protective effect in preventing the incidence of dementia. Numerous neuropsychological and cognitive function assessment tools were evaluated in this review, including the MMSE, CGI, RAVLT, CVLT, TMT, WMS-R, WAIS-R, Digit Span, Boston Naming Test, Category Fluency, Letter Fluency, and Spatial Span Test. These measurements are used to assess memory, attention, language, problem-solving, and other cognitive skills, which may decrease in individuals with cognitive impairment [36].

In this review, we found that the group with phytoestrogen intervention had improved overall cognition, especially those who received it in the form of Ginkgo Biloba, low-dose resveratrol, and low-dose isoflavone-rich soy protein [10]. The cognitive function is divided into six domains: memory and learning, language skills, higher-order thinking abilities, focused and sustained attention, social interactions, and sensory-motor functions. From the eight studies included in this review, memory domain, especially verbal memory, followed by executive function domain, showed the most significant test results. Verbal cognitive tests are clinically the most commonly used to evaluate memory and can be used to detect mild AD in elderly individuals [37]. Meanwhile, executive function is a broad term that defines basic cognitive functions, including concentration, self-regulation, working memory, cognitive flexibility, and advanced functions, such as planning, decision making, and problem solving. However, clinically, the available testing instruments are either limited to shortened versions or have limited ability to test executive function [38].

Isoflavone consumption appears to be safe, with the most common side effect being mild and occurring in the gastrointestinal tract [39]. According to the review's findings, there is some scientific evidence that isoflavones provide an advantageous improvements on cognitive function, thus potentially preventing and treating dementia The American Association of Clinical Endocrinologists advises women with an individual or family history of hormone-dependents cancers, cardiovascular disorders, or thromboembolic incidents to avoid using phytoestrogen. However, contrary to the mechanism of action, phytoestrogens have chemopreventive activity by inducing apoptosis and inhibiting intestinal epithelial cell proliferation, as well as anti-inflammatory activity by lowering IL-6 and TNF-α. As a result, additional research is required to ensure phytoestrogen safety [40].

CONCLUSION

The cognitive function of postmenopausal women who have consumed phytoestrogens in variable forms has statistically improved in general, more specifically, verbal memory, followed by executive function domain has been found to be intact. Menopausal women who are at risk of cognitive decline could benefit from phytoestrogen intervention. Due to the variations in sample size and characteristics, phytoestrogen regimens, and the various kinds of assessment in cognitive function, it is necessary to conduct further research using a more homogenous population, consistent phytoestrogen interventions, and fixed assessment of cognitive function, as well as dementia.

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CONFLICT OF INTEREST

In the interest of transparency, the authors disclaim any conflicts of interest pertaining to the publication of this work.

Availability of Data and Materials

All the data origins outlined in this research are channeled towards the author who corresponds.

Ethics Approval and Consent to Participate

This article does not involve human subjects, and therefore, obtaining informed consent is not applicable.

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Table 1. Summaries of Included Studies

Author, Year, Duration	Intervention	Characteristics						Outcomes
		Sample (n)	Sample Age	Domains	Cognitive Tests	Improvement	p-value	
Demarin, 2017 [21] 6 months	1. Ginkgo biloba 120 mg 2. Ginkgo biloba 60 mg 3. Placebo	59	67.1 ± 8.0	Neuropsychological	Sandoz Clinical Assessment Geriatric Scale / SCAG	No	0.676	No statistically significant difference between the G. biloba and placebo groups was found in MDRS, SCAG, and MMSE scores. However, there was a statistically significant difference between the G. biloba and placebo groups in CGI scores (P=0.038).
					Folstein Mini-Mental State Exam / MMSE	No	0.766	
					Mattis Dementia Rating Scale / MDRS	No	0.749	
					Clinical Global Impression / CGI	Yes	0.038	
Zaw, 2021 [10] 12 months	1. Resveratrol 75 mg twice daily 2. Placebo	125	45-85, 65 ± 7	Processing speed	Pattern Comparison Speed Test / PCT	No	0.485	Resveratrol supplementation significantly improved overall cognitive performance by 33% compared to placebo. It also enhanced the Dimensional Change Card Sort Test by 113% and the Forward Spatial Span Test by 208%. Subgroup analysis revealed that women over 65 experienced improved verbed a slight decline. These findings suggest resveratrol may be particularly beneficial for cognitive function in older women.
					Trail Making Task A / TMT	No	0.249	
				Language	Picture Vocabulary Test / PVT	No	0.212	
					Oral Reading Recognition Test / ORR	No	0.993	
				Working memory	List Sorting Working Memory Test / LSWM	No	0.691	
					Forward Spatial Span test	Yes	0.02	
				Episodic memory	Picture Sequence Memory Test / PSM	No	0.395	
				Verbal memory	Rey's Auditory Verbal Learning Test / RAVLT immediate recall	Yes	0.926	
					Rey's Auditory Verbal Learning Test / RAVLT 30-minute delayed recall	Yes	0.803	
					Dimensional Change Card Sort Test / DCCS	Yes	0.005	
					Flanker Inhibitory Control and Attention Test / FICA	No	0.293	
					Trail Making Task B / TMT	No	0.524	
				Overall cognition		Yes	0.005	
Evans, 2016 [3] 14 weeks	1. Resveratrol 75 mg twice daily 2. Placebo	80	45-85	Verbal memory	RAVLT	Yes	0.021	Improvement in overall performance 1.3% (P = 0.018), verbal memory 2.7% (P = 0.021)
				Semantic memory	Cambridge Semantic Memory Battery	No	>0,05	
					Category/letter fluency	No	>0,05	
					Category comprehension	No	>0,05	
					Naming	No	>0,05	
					Camel and cactus	No	>0,05	
				Visuospatial memory	Double span task	No	>0,05	
				Executive function	Trail making task	No	>0,05	
				Overall Cognition		Yes	0.018	

Author, Year, Duration	Intervention	Characteristics						Outcomes
		Sample (n)	Sample Age	Domains	Cognitive Tests	Improvement	p-value	
Maki, 2009 [24] RCT 12 months	1. Red clover (120 mg), 2. black cohosh (128 mg), 3. Hormone therapy 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (CEE/MPA) 4. Placebo	66	44-62, 53	Verbal memory	California Verbal Learning Test / CVLT modified	No	0.057	Neither of the herbal treatments had an impact on any cognitive measure.
					Logical memory subtest of the Wechsler Memory Scale-Revised	No	>0,05	
				Short-term figure memory	Benton Visual Retention Test	No	>0,05	
				Visuospatial ability	Modified Card Rotations test	No	>0,05	
				Verbal fluency	Letter Fluency	No	>0,05	
				Attention and working memory	Digit Span Forward	No	>0,05	
					Digit Span Backward	No	>0,05	
				Auditory attention	Brief Test of Attention-Modified	No	>0,05	
				Visuoperceptual speed	Finding As test	No	>0,05	
				Everyday memory abilities	Memory Functioning Questionnaire / MFQ	No	>0,05	
				Positive and negative mood states	Positive and Negative Affect Scale / PANAS	No	>0,05	
Ho, 2007 [26] 6 months	1. Daily oral intake of 80 mg soy-derived isoflavones Placebo (Starch)	168	55-76	Memory	Hong Kong List Learning Test / HKLT	No	0.23	The neuropsychological test results indicated no significant differences between the two groups in any of the objective tests at baseline.
				Visual reproduction	Rey-Osterrieth Complex Figure Test and Wechsler Memory Scale-Revised / WMS-R	No	0.48	
				Executive function	Color Trail	No	0.71	
				Attention	Verbal Fluency	No	0.33	
				Attention	Digit Symbol / WAIS-R	No	0.34	
				Motor	Finger Tapping	No	0.33	
				Language	Boston Naming Test	No	0.8	
				Global Cognitive Level	MMSE	No	0.85	
Henderson, 2012 [27] 2,5 years	1. Isoflavone-rich soy protein 25 mg (consists of 91 mg of aglycone, 52 mg of genistein, 36 mg of daidzein, and 3 mg glycitein) daily 2. Placebo (milk protein)	313	45-92 years	Overall cognition	Cognitive composite score	No	0.36	There was no significant between-group difference in change from baseline in global cognition
				Executive/expressive /visuospatial factor	Symbol Digit Modalities Test	No	0.68	
					Trail Making Test, Part B	No	0.41	
					Shipley Abstraction	No	0.84	
					Letter-Number Sequencing	Yes	0.033	
					Block Design	No	0.79	
					Category Fluency	No	0.92	
					Boston Naming Test	No	0.41	
				Verbal episodic memory (list learning) factor	California Verbal Learning Test, immediate recall	No	0.66	
					California Verbal Learning Test, delayed	No	0.61	

Author, Year, Duration	Intervention	Characteristics						Outcomes
		Sample (n)	Sample Age	Domains	Cognitive Tests	Improvement	p-value	
					recall			
				Verbal episodic memory (logical memory) factor	East Boston Memory Test, immediate recall	No	0.49	
					East Boston Memory Test, delayed recall	No	0.77	
				Verbal episodic memory factor	Faces I, immediate recall	Yes	0.024	
					Faces II, delayed recall	No	0.15	
Sanne Kreijkamp-Kaspers, 2015 [29] 12 months	1. 25.6 g of soy protein containing 99 mg of isoflavones (52 mg genistein, 41 mg daidzein, and 6 mg glycetein or total milk protein as a powder) 2. Placebo	202	44-63	Memory	RAVLT immediate recall, maximum score 75	No	0,36	This double-blind randomized trial does not support the hypothesis that the use of soy protein supplement containing isoflavones improves cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women when started at the age of 60 years or later.
					RAVLT delayed recall, maximum score 15	No	0,68	
					RAVLT recognition recall, maximum score 30	No	0,53	
					Forward Digit span, maximum score 8	No	0,27	
					Reversed Digit span, maximum score 7	No	0,32	
					Door test, maximum score 24	No	0,84	
				Complex attention	A1 Trail Making test	No	0,76	
					A2 Trail Making test	No	0,82	
					B Trail Making test	No	0,14	
					Digit symbol substitution	No	0,38	
				Verbal task, score number of nouns named	Fluency N	No	0,85	
					Fluency A	No	0,60	
					Fluency animals	No	0,27	
					Fluency occupations	No	0,59	
					Boston naming task, maximum score 30	No	0,93	
				Cognitive	Mini-mental state examination, maximum score 30	No	0,47	
Furlong, 2019 [30] 12 weeks	1. Soy drinks (Alpro®) low (10 mg), 2. Soy drinks (Alpro®) medium (35 mg), 3. Soy drinks (Alpro®) high (60 mg) dose	101	44-63	Cognitive function	5-choice reaction time (RTI)	No	0.764	No significant differences between the groups for any of the cognitive function outcomes measured.
					Spatial span (SSP)	No	0.735	
					Spatial working memory (SWM)	No	0.245	
					Pattern recognition memory (PRM)	No	0.453	
					Match to sample visual search (MTS)	No	0.234	