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Effect of phosphatidylserine on cognitive function in the elderly: A systematic review and meta-analysis

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Abstract Phosphatidylserine (PS) is an essential component of the cerebral cortex and is associated with cognitive function. In this systematic review, the effects of PS on cognitive function in the elderly population are examined. The literature search included PubMed, EMBASE, Cochrane, and Web of Science databases. Subsequently, nine studies, including five randomized controlled trials and four pre-post studies, were selected. There were 961 participants in the selected studies; PS dosage varied from 100 to 300 mg/d, and the experimental period ranged from 6 weeks to 6 months. Five out of the nine selected studies were assessed to have a 'low' risk of bias, whereas the other four studies were assessed to have 'some concerns' regarding the risk of bias. The results of the meta-analysis concluded that PS had a positive effect on the memory of older adults with cognitive decline. Thus, PS appears to improve age-associated cognitive decline, especially memory, with no adverse effects.

Keywords: phosphatidylserine, cognitive decline, meta-analysis, systematic review

Introduction

Age-related cognitive decline is becoming a critical health problem as the world population is rapidly aging. Each year, approximately 10 million patients are diagnosed with dementia worldwide (World Health Organization, Dementia, 2021). If this alarming trend continues, there will be approximately 150 million patients with cognitive decline by 2050 (Alzheimer's disease international, 2021). There are several types of dementia such as Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, and Parkinson's disease dementia (WebMD, 2020). AD accounts for the majority (60%-80%) of dementia cases and is divided into three stages: early (mild), middle (moderate), and late (severe) depending on the degree of disease progression. Disease-mediated aberrations in cognitive ability negatively influence language, learning, memory, attention, planning, and problem-solving (Murman, 2015). Remarkably, dementia is a deadly condition to which no suitable treatment has been discovered so far. The US Food and Drug Administration (FDA) has approved a limited range of medications for the treatment of cognitive impairment, such as cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and glutamate regulators (memantine) (NIH, 2021). Recently, an intravenous anti-amyloid antibody (aducanumab) was approved for therapy (NIH, 2021). However, these drugs have common side effects, such as headache, nausea, vomiting, diarrhea, muscle cramps, fatigue, and indigestion (NIH, 2021). Nonetheless, research on discovering pharmaceuticals or nutraceuticals to prevent cognitive decline, which compensates for these shortcomings, continues to expand, including exploration and research on nutritional interventions (Toita et al., 2018; Kang et al., 2021).

Phosphatidylserine (PS) is the most abundant acidic phospholipid found in cell membranes, mainly in the cytoplasmic membrane, accounting for 13-15% of phospholipids in the human cerebral cortex (Svennerholm, 1968). It regulates various signaling molecules, including Akt, protein kinase C (PKC), and Raf-1, which stimulate neuronal survival, growth, and synaptogenesis (Kim et al., 2014). In addition, PS hosts Ca^{2+}-dependent membrane fusion between presynaptic vesicles and the plasma membrane of the targeted synapse to regulate exocytosis (Tucker et al., 2004). Furthermore, PS regulates amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptors that mediate synaptic transmission in the central nervous system and alter the microtubule-associated protein tau in the brain (Baudry et al., 1991). In conclusion, PS can activate neurotransmitter signaling pathways and regulate neurotransmitter ligand-receptor binding, and its effect on neuropathophysiology has been investigated for years.

PS is found in animals (derived from the bovine brain cortex), plants (derived from the soybean and sunflower), and marine life (derived from fish and krill) (Vance, 2018), but there are distinct differences in their fatty acid composition. The fatty acids in PS extracted from the bovine cortex (BC-PS) exhibit docosahexaenoic acid (C22:6 ω-3; DHA); on the other hand, soybean-derived PS (SB-PS) contains high linoleic acid (C18:2 ω-6) content (Kim et al., 2010). Marine-derived PS (MS-PS) has the highest proportion

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of eicosapentaenoic acid (C20:5 ω-3; EPA) and DHA (Burri et al., 2012). PS has been shown to confer significant improvement in cognitive impairment in animal experiments and clinical trials, especially in Alzheimer's patients (Crook et al., 1992). However, due to the concern of bovine spongiform encephalopathy-causing prion transmission, the applications of BC-PS are remarkably diminished. As such, competent SB-PS has entered the spotlight as an alternative (Vakhapova et al., 2011).

Although several experiments have shown that PS improves cognitive function, systematic reviews and meta-analyses evaluating the efficiency of PS in the elderly have hardly been established. Therefore, this systematic review summarizes the clinical studies associated with the efficacy of PS supplementation in the elderly.

Materials and Methods

Search strategy

The literature search included PubMed, EMBASE, Cochrane, and Web of Science on February 23, 2021. The search term 'Phosphatidylserine' was used as a keyword. The literature was screened by identifying the titles, abstracts, and full texts that did not meet the eligibility criteria. This systematic review was carried out independently by two researchers. Disagreements were resolved by discussing with another researcher.

Criteria for eligibility

The literature was screened for eligibility based on the following inclusion criteria: (1) clinical study regarding humans, (2) elderly participants (age ≥65 yrs) (Singh et al., 2014), (3) indication of PS content, and (4) oral intake of PS. In addition, we excluded the literature that did not evaluate cognitive function or involved combined intervention along with PS administration.

Bias risk assessment

Individual randomized controlled trials (RCTs) were assessed for the risk of bias using the Cochrane Risk of Bias 2 (ROB2) tool. There are three levels of risk of bias: low, some concerns, and high. The following domains were evaluated: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result.

Pre-post studies were assessed using the Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) assessment tool. There are five judgment levels regarding the risk of bias: low, moderate, serious, critical, and no information. The following domains were evaluated: confounds, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, outcomes measurement, and selection of reported results.

Quality of evidence assessment

The Grading of Recommendations Assessment Development and Evaluation (GRADE) tool was used to assess the quality of the evidence for each outcome (Balshem et al., 2011). There are four evidence quality levels: 'high,' 'moderate,' 'low,' and 'very low'. The evidence quality is initially assumed to be 'high' in RCTs and 'low' in observational studies. It may be downgraded due to an improper judgment regarding the risk of bias, inconsistency or imprecision of results, indirectness in evidence, or publication bias. Evidence quality was upgraded considering the magnitude of effect, plausible confounding, and evidence of a gradient dose-response.

Meta-analysis

The Review Manager (RevMan) software (version 5.4) from Cochrane Collaboration was used for the meta-analysis to assess the effectiveness of the PS supplement on memory in patients with cognitive decline. The outcomes from each study were statistically combined via the fixed effects model. Regarding continuous data aggregated using the different measurements, a standard mean difference (SMD) and 95% confidence interval (CI) were calculated using the mean variances from baseline, the variance of standard deviation, and the number of participants. I-squared statistics (I^2) were performed to evaluate the heterogeneity in study outcomes. A p-value <0.05 was considered significant for all analyses.

Results and Discussion

Study Selection

The literature selection process is shown in the flow diagram (Fig. 1). The literature search included articles from reputable electronic databases (15,398 from PubMed, 2,601 from EMBASE, 210 from Cochrane, and 15,432 from Web of Science). After removing duplicates, the collected literature included 21,501 citations. Nine studies met the inclusion criteria, 5 RCTs and 4 pre-post studies. Afterward, 5 RCT studies were analyzed in the meta-analysis.

Data Abstraction

Study characteristics are summarized in terms of design, intervention, participants, and outcomes (Tables 1 and 2). The pooled total number of participants was 961. The supplemented PS dosage varied from 100-300 mg/d. Three studies combined PS treatment with DHA and EPA. The PS source was either bovine brain cortex, soybean, or marine, and the duration of intervention ranged from 6 weeks to 6 months. Three studies were conducted on participants diagnosed with dementia, and the other six studies were conducted on non-demented participants with memory impairment. In RCT, PS intervention was compared against the control, which used placebo capsules of the same appearance, such as corn oil and cellulose. In pre-post studies, before and after intervention data were compared, as before intervention data was used as control data.

Risk of Bias Assessment

Using the Cochrane ROB2 and ROBINS-I tools, 5 RCTs and 4 pre-post studies were assessed individually (Figs. 2A and 2B). Out of 5 RCT studies, 1 study was evaluated to 'low' risk of bias, and 4 studies had 'some concerns' regarding the risk of bias. The RCT studies with 'some concerns' randomly assigned participants into

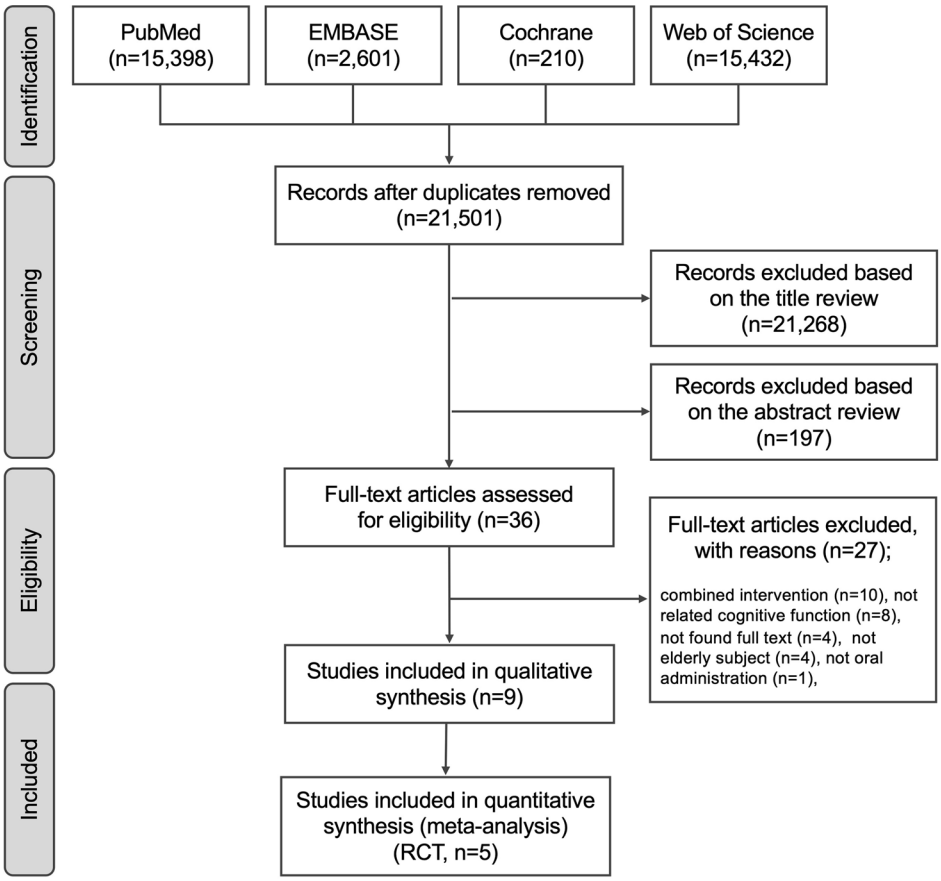


Fig. 1. Flow diagram of the systematic review and meta-analysis process.

study groups but did not report computerized randomization methods. Two of them did not report considerations of intention-to-treat or per-protocol analysis. All four pre-post studies were evaluated as having a 'low' risk of bias.

Meta-analysis

The meta-analysis included 5 RCTs that investigated PS intervention versus placebo in terms of memory and daily living activities (Fig. 3). The 'Buschke selective reminding test (BSRT),' 'circle crossing test,' 'modified Benton test,' 'Rey auditory verbal learning tests (Rey-AVLT),' and 'semantic memory test' were the memory-related evaluation items synthesized for this meta-analysis. I^2, an indicator of heterogeneity, was shown to be 22%, showing consistency in the meta-analysis results. The effect of PS on cognitive function, especially for memory, was statistically significant (SMD=0.22, 95% CI: 0.06 to 0.38, p<0.01). The daily living activity-related evaluation items synthesized for meta-analysis were 'activities of daily living' and the 'Crichton rating scale.' I^2 was 46%, which means the results are conflicting. Large I^2 values indicate that it is difficult to determine whether results are due to chance. Applying GRADE criteria, the outcomes of memory-related studies were of moderate quality (data not shown). The moderate certainty of the evidence means the true effect is likely to be close to the estimated effect; however, there is a possibility that they could be substantially different. Taken together, PS supplementation had beneficial effects on memory but did not affect the ability to perform daily living activities.

The Efficacy of PS

All 9 studies were comprehensively reviewed according to the source of origin since RCTs, and pre-post studies were incompatible during the meta-analysis. The PS used in the included studies originated from the bovine brain cortex, soybeans, and marine sources. In 8 studies, the dosage of PS was 300 mg/d, and one study evaluated a PS dosage of 100 mg/d. Further, 300 mg/d of BC-PS was administered to participants with moderate-to-severe cognitive decline for 6 months. A significant improvement was found in the 'BSRT' regarding total recall, long-term storage, long-term retrieval, and consistent long-term retrieval (Cenacchi et al., 1993). In another study using BC-PS, the 'clinical global impression (GCI)' assessment improved significantly in those with primary degenerative dementia; however, the 'Gottfries, Brane, and Steen (GBS) dementia rating scale' and 'psychometric test scores' showed no significant improvements (Engel et al., 1992). Moreover, BC-PS did not improve the 'Crichton rating scale' of cognitive function tests in mild to moderate dementia patients (Delwaide et al., 1986). Thus, the intervention effects of BC-PS depended on the severity or progress of dementia. Treatment with both BC-PS and SB-PS conferred improvement in memory test vocabulary/picture matching scores for Alzheimer's disease patients.

Table 1. Characteristics of the included randomized controlled trials

Author, year	Study design	Intervention (source, dose, duration)	Condition	Participants (sample size,[a] gender, mean age)		Outcome of interest [1)]
				Experimental	Control	
Cenacchi, 1993	RCT, parallel	Brain cortex-derived PS 300 mg/d 6 mo	Moderate-severe cognitive decline	*n*=215/241 (29% men) 77.8±5.6 yr	*n*=210/253 (32% men) 77.3±6.3 yr	BSRT (TR, LTS, LTR, LTRc) and GRS (ADL, WA, ADB)
Delwaide, 1986	RCT, parallel	Brain cortex-derived PS 300 mg/d 6 wk	Mild-moderate dementia	*n*=17/20 NI 83.5 yr	*n*=18/22 NI 81.2 yr	Circle crossing test, Crichton rating scale, and Peri scale
Zhang, 2015	RCT, parallel	Brain cortex- and soybean-derived PS 300 mg/d 20 wk	AD	*n*=32 (50% men) 74.9±18.2 yr	*n*=25 (48% men) 75.3±11.8 yr	Semantic memory test (vocabulary matching score and picture matching score)
Vakhapova, 2010	RCT, parallel	Marine source-derived PS 300 mg/d PS plus 79 mg/d DHA+EPA 15 wk	Non-demented elderly with memory complaint	*n*=60/79 (48% men) 72.9±8.2 yr	*n*=62/78 (53% men) 73.0±8.3 yr	RAVLT, RCFT, Clinical Global Impression of Change, and Computerized neuropsychological assessment tool
Engel, 1992	RCT, crossover	Brain cortex-derived PS 300 mg/d (wash 4 wk) - PS/placebo 8 wk - (wash 8 wk) - placebo/PS 8 wk	Primary degenerative dementia	*n*=18/NI (39% men) 69.1±7.0 yr	*n*=15/NI (40% men) 67.1±7.9 yr	CGI, GBS, and psychometric tests (modified Benton test, associate learning, logical memory, trail making test, digit symbol substitution test, similarities, mental arithmetic, color word interference, and word fluency)

[1)]BSRT, Buschke Selective Reminding Test; TR, Total Recall; LTS, Long Term Storage; LTR, Long Term Retrieval; LTRc, Consistent Long-Term Retrieval; GRS, Plutchik Geriatric Rating Scale; ADL, Activities of Daily Living; WA, Withdrawal-Apathy; ADB, Antisocial Disruptive Behavior; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test; CGI, Clinical Global Impression; GBS, the dementia rating scale of Gottfries, Brane and Steen.
[a]Compliance/baseline proportion.

Table 2. Characteristics of the included pre-post studies

Author, year	Study design	Intervention (exposure, dose, duration)	Condition	Participants (sample size,[a] gender, mean age)	Outcome of interest[1)]
Schreiber, 2000	Pre-post	Soybean-derived PS 300 mg/d 12 wk	age-associated memory impairment	*n*=15/18 NI 71.3±3.6 yr	Memory and learning battery (immediate memory, visual and auditory, visual and verbal recall, learning, and memory tasks of everyday life)
Vakhapova, 2014	Pre-post, Open-label extension	Marine source-derived PS 100 mg/d PS plus 26 mg/d DHA+EPA 15 wk	non-demented elderly with memory complaints	*n*=121/122 (50% men) 72.2 yr	Computerized neuropsychological assessment tool and CGI-C
Richter, 2010	Pre-post	Soybean-derived PS 300 mg/d PS plus 37.5 mg/d DHA+EPA 6 wk	subjective memory complaints	*n*=8 (38% men) 69.3±3.2 yr	CDR battery (individual tasks and cognitive factors)
Richter, 2013	Pre-post	Soybean-derived PS 300 mg/d 12 wk	subjective memory complaints	*n*=26/30 (27% men) 74.6±1.7 yr	Computerized test battery and Rey-AVLT

[1)]CGI-C, Clinical Global Impression of Change; CDR, Cognitive Drug Research; Rey-AVLT, Rey Auditory Verbal Learning Test.
[a]Compliance/baseline proportion.

The included reported that, when treated with 300 mg/d SB-PS, participants with age-associated memory impairment improved 'memory and learning test' performance, such as immediate acquisition of 'learning rate fuld', 'name-face' immediate acquisition, 'name-face' recall, and 'facial recognition' (Schreiber et al., 2000). Another study included in the meta-analysis reported improvements in 'cognitive drug research (CDR)' evaluations, such as digit vigilance reaction time, delayed word recall, and decay immediately to delayed word recall, following treatment with SB-PS containing omega-3 fatty acids in volunteers with subjective memory complaints (Richter et al., 2010). Similarly, subjects with memory complaints positively responded to SB-PS supplementation

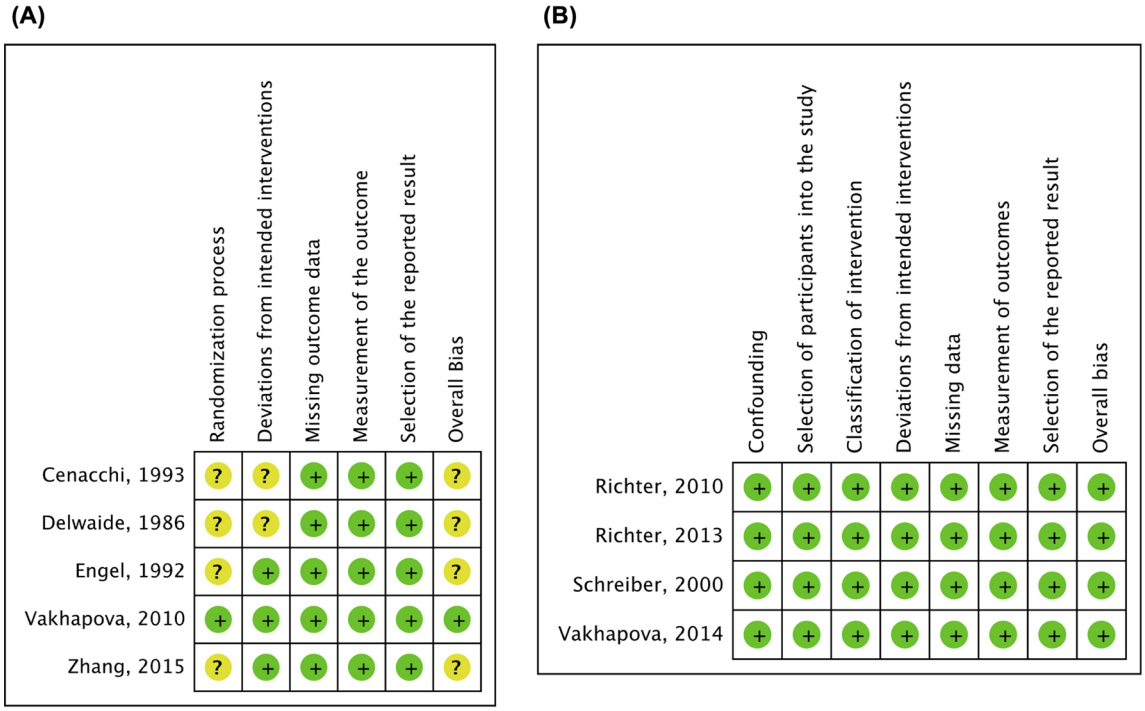
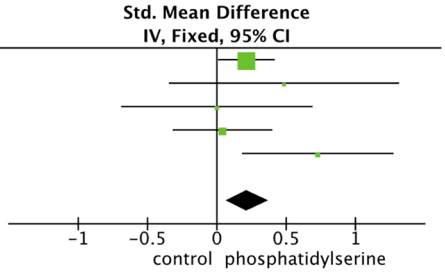


Fig. 2. Risk of bias assessment in a systematic review of phosphatidylserine supplementation on cognitive function. (A) Randomized controlled trials and (B) pre-post studies.

(A)

Study or Subgroup	Phosphatidylserine Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cenacchi, 1993 (1)	3.55	8.22	191	1.8	8.169	197	62.7%	0.21 [0.01, 0.41]
Delwaide, 1986 (2)	2.5	7.767	10	-3.21	13.314	14	3.7%	0.48 [-0.34, 1.31]
Engel, 1992 (3)	-0.1	8.626	18	-0.1	9.795	15	5.3%	0.00 [-0.69, 0.69]
Vakhapova, 2010 (4)	0.93	3.573	60	0.79	3.307	62	19.8%	0.04 [-0.31, 0.40]
Zhang, 2015 (5)	1	0.5	32	0.5	0.854	25	8.5%	0.73 [0.19, 1.27]
Total (95% CI)			**311**			**313**	**100.0%**	**0.22 [0.06, 0.38]**

Heterogeneity: Chi² = 5.16, df = 4 (P = 0.27); I² = 22%
Test for overall effect: Z = 2.75 (P = 0.006)

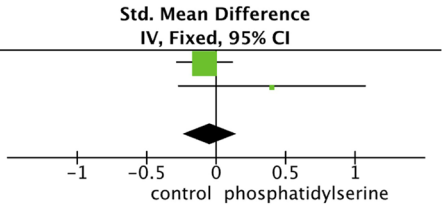


Footnotes
(1) BSRT, Total recall
(2) Circle crossing test
(3) Modified Benton test
(4) RAVLT, delayed recall
(5) Semantic memory test, Vocabulary matching score

(B)

Study or Subgroup	Phosphatidylserine Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cenacchi, 1993 (1)	-0.13	1.875	191	0.03	1.961	197	91.9%	-0.08 [-0.28, 0.12]
Delwaide, 1986 (2)	2.12	4.604	17	0	5.631	18	8.1%	0.40 [-0.27, 1.07]
Total (95% CI)			**208**			**215**	**100.0%**	**-0.04 [-0.23, 0.15]**

Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 0.45 (P = 0.65)



Footnotes
(1) Activities Daily Living
(2) Crichton Rating Scale

Fig. 3. Forest plot and meta-analysis of studies evaluating phosphatidylserine on cognitive function of memory and activities of daily living. (A) Comparison of PS versus control for memory and (B) Comparison of PS versus control for activities of daily living.

in terms of the 'computerized cognitive tool' assessment regarding memory recognition, memory recall, executive function, mental flexibility, and 'Rey-AVLT,' such as immediate recall and total learning (Richter et al., 2013). Overall, SB-PS supplementation improved cognitive function regarding memory and learning in elderly, non-demented individuals with age-associated cognitive decline. The 15-week RCT study showed that 300 mg/d of MS-PS combined with DHA and EPA treatment improved immediate verbal memory in non-demented elderly individuals with memory impairment (Vakhapova et al., 2010). Furthermore, according to an open-label extension study after completion of the RCT study, 100 mg/d MS-PS improved or maintained 'CGI-C' and neurological computerized cognitive assessment items, especially sustained attention, memory recognition, and final score (Vakhapova et al., 2014). In addition to the included studies, a previous study showed that 200 mg SB-PS supplementation for 2 months significantly improved short-term auditory memory and attention in children with attention-deficit hyperactivity disorder (ADHD) (Hirayama et al., 2014). Also, a nutritional supplement containing PS with omega-3 fatty acids, L-α-glycerophosphocholine, etc., improved recall, recognition, and spatial short-term memory in an open-label study (Richter et al., 2011). Taken as a whole, BC-PS, SB-PS, and MS-PS supplementation enhanced memory- and learning-related cognitive functions in the elderly.

In the current study, the dosage of PS was 100 and 300 mg/d with or without omega-3 fatty acids. Several participants dropped out due to flatulence, gastrointestinal discomfort, severe psychomotor agitation, nausea, itching, vomiting, and dizziness; however, it could not be determined whether the symptoms were side effects of the intervention. There were no major adverse effects in the included studies, and intervention was generally well-tolerated. Considering that adverse effects were reported in previous studies that investigated 800 mg/d PS in healthy adults (Monteleone et al., 1992; Hellhammer et al., 2004), PS is considered safe. Interestingly, the studies related to BC-PS were primarily conducted in the 1980s-1990s. Despite the advantageous effects on cognitive function, the possibility of cross-contamination with prions causing bovine brain encephalopathy raised serious concerns regarding the safety of BC-PS. Since then, SB-PS has been alternatively studied since the 2000s. According to an *in vivo* study, SB-PS has similar cognition-improving effects regarding 'two-way active avoidance' and 'behavioral tests for cognitive performance' compared with BC-PS (Blokland et al., 1999). More recently, MS-PS, also high in DHA, improved cognitive function (FDA, 2009; Kang et al., 2021). In sum, soy-lecithin and marine resources swiftly replaced bovine cortices as PS sources since the 1990s due to the mad cow disease outbreak. Homogeneity regarding cognitive function and safety continues to be established between alternative PS sources.

Conclusion

In conclusion, this review investigated the effects of PS on age-associated cognitive function in the elderly. As a result, 5 RCTs and 4 pre-post studies were finally included for further analysis. The ROB2 assessment of the 9 studies indicated that 5 studies had a 'low' risk of bias, and the other 4 studies had 'some concern' regarding the risk of bias. According to the meta-analysis, PS supplementation did not modify the ability to perform tasks of daily living included in the Crichton rating scale (I^2=46%). The memory domain, however, was improved by PS supplementation (I^2=22%). In conclusion, PS supplementation (especially 300 mg/d) has the potential to improve cognitive function, especially within the memory domain, without adverse events. Throughout the mad cow disease outbreak, soy-lecithin and marine resources have become the main sources of PS.

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