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Astaxanthin and improvement of dementia: A systematic review of current clinical trials

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ABSTRACT

Worldwide, the incidence of neurodegenerative diseases especially dementia is steadily increasing due to the aging population. Abundant research emerges on the probability of combating or preventing the degeneration process, with the most established one being to tackle the existence of oxidative stress and free radicals production due to their nature of aggravating dementia. Astaxanthin, a marine carotenoid, was proven to be a protective agent of cerebral ischemia through many animal model clinical trials. This review summarizes the evidence of Astaxanthin's benefits for cognitive function across clinical trials done in older age. The results are of interest as its supplementation does not exhibit unwanted issues on the consumer based on physical and laboratory examinations. Despite not being supported statistically, however, subjective and objective cognitive amelioration were reported according to the majority of this review's trial subjects. Although there is no clear and direct mechanism for cognitive improvement by Astaxanthin activity in the body systems, the encouragement of Astaxanthin supplementation should be considered as the elderly with dementia may highly benefit from the improved cognitive function.

Introduction

Due to inevitable degenerative processes, older adults are prone to functional decline including dementia [1]. Dementia as a neurodegenerative disease encompasses Alzheimer, Lewy body dementia, frontotemporal lobar degeneration, and vascular dementia [2–4] in which cognitive decline could be manifested as early as 1 month prior to a stroke event [5] and the risks increase attributable to demographic status [6–10], vascular risks [11–15], inflammation biomarker, lifestyle [3,16,17], radiographic lesion [18–21], and comorbidities prior to the disease [22]. Deterioration of memory, orientation, language, attention, and executive function are among the most prevalent symptoms [5,23]. Although the exact mechanism is still indistinct, cognitive impairment and other neurodegenerative processes are postulated to be rooted in molecular homeostasis disturbances, mitochondrial dysfunction, oxidative stress, and neuroinflammation process [24]. Various pharmaceutical compounds and supplements have been studied for their anti-oxidant and anti-inflammatory properties in neuron damage [25,26], due to the highly sensitive cerebral tissue to free radicals causing impairment in cognitive domain function previously mentioned [27].

As the body's anti-oxidant regulation ability declines with aging [28], supplementation of antioxidants is deemed important. Astaxanthin (ASX), a carotenoid abundantly in crustaceans and red-fishes, has recently been studied to contain anti-tumor, cardio-protective, and neuroprotective properties [29] due to its antioxidant activity potentially higher than other carotenoids such as lutein, lycopene, alpha-carotene, and beta-carotene due to its unique structure [30], comparing their physical and chemical interaction between each carotenoid and cell membranes [31]. Said antioxidant properties lower oxidative stress as it suppress inflammatory mediators and reactive oxygen species (ROS). ASX is also proposed to have anti-hypertensive activity, lower VLDL (very low-density lipoprotein), lower triglyceride,

Abbreviations: AB, Amyloid-beta; AD, Alzheimer's Disease; ASX, Astaxanthin; BDNF, Brain-derived Neurotrophic Factor; BMI, Body mass index; CNVS, Central Nervous System Sign; LUCCAO, Left Unilateral Common Carotid Arteries Occlusion; PI3K/AKT, Phosphatidylinositol 3-kinase/protein kinase B; RCT, Randomized Controlled Trial; VAD, Vascular Dementia; VBM, Verbal Memory.

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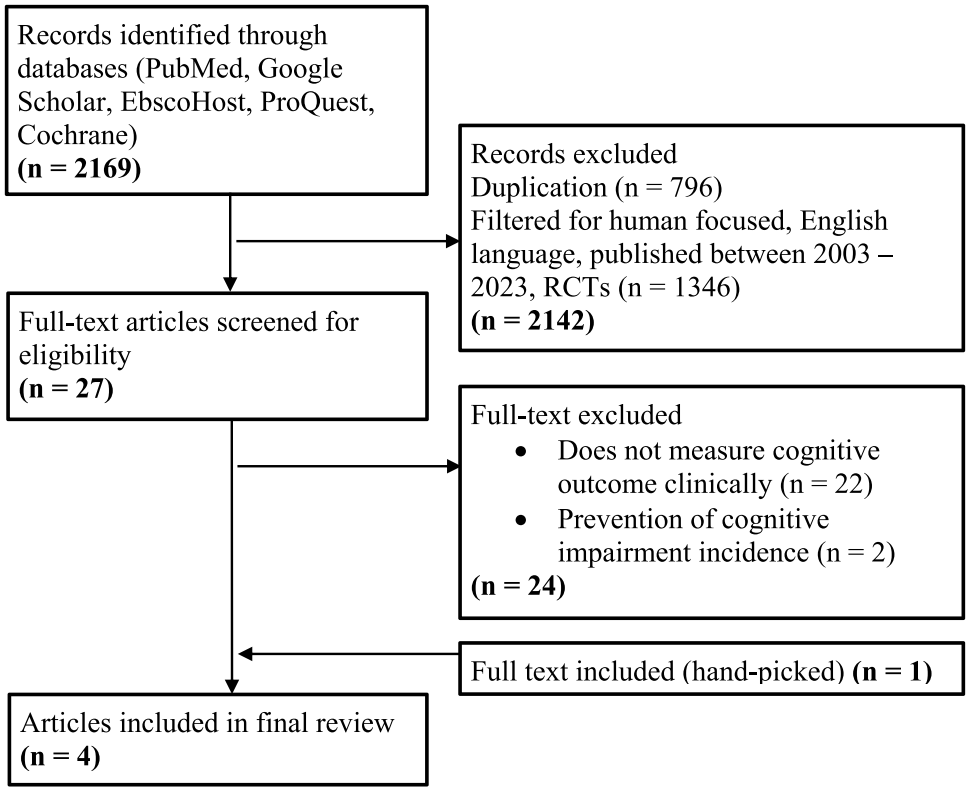

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicting the systematic study selection process.

and lower blood sugar [32]. Prior studies denote the role of ASX in preventing the progression of vascular dementia (VAD) and Alzheimer's disease (AD) in rat model of VAD and AD [33,34], but none are done in humans, especially in older population. Hence, this literature systematically reviews the role of ASX supplementation in improving the symptoms of dementia.

Material and methods

In order to obtain an initial list of manuscripts of interest, a PubMed, Google Scholar, ProQuest, EBSCOHost, and Cochrane systematic literature search was conducted and mapped according to the guideline of PRISMA (*Preferred Reporting Items for Systematic Review and Meta-Analyses*) [35] (Fig. 1) with the term '*Astaxanthin*' or '*Carotenoid*' and '*cognitive impairment*' or '*dementia*'. The search was filtered to include only human-focused studies published in the English language available in full text, between 2003 and 2023. All titles and abstracts identified were screened for the inclusion of possibly eligible studies and the exclusion of irrelevant studies. Two authors (NPU and PKL) conducted this screening and review independently, and inconsistencies were solved through a consensus. For studies with relevant titles and/or abstracts or studies that did not have enough information in the abstracts to make a decision, full-text articles were obtained. The full-text articles were evaluated for inclusion or exclusion. Detailed study characteristics such as the authors, interventions (such as Astaxanthin dosage, duration of exposure), presence of cognitive impairment, instruments used, and any adverse effects both clinically and laboratory were extracted by KRD. The priori inclusion criteria were randomized controlled trials addressing the effects of Astaxanthin consumption to prevent the progression of cognitive impairment or dementia symptoms regardless of its etiology, measured subjectively or objectively with instruments and compared to preexisting baseline cognitive status or study control. Exclusion criteria eliminated studies that focus on Astaxanthin supplementation in animals. The findings were summarized in a narrative

Table 1
Astaxanthin studies on cognitive improvement.

Year, Author	Subjects	Study Period	Intervention	Outcome
2012, Katagiri et al. [39]	96 subjects aged 45 – 64 years	12 weeks	ASX supplementation (6 or 12 mg/ day)	Memory function measured with CogHealth battery and GMLT improved compared with baseline but not statistically significant
2018, Hayashi et al. [38]	54 subjects aged 45 - 64 years	8 weeks	ASX supplementation (8 mg/ day)	Medium-term memory function measured with 5 min + cued test, verbal fluency, and Stroop test improved, but not specific in >55 years old
2018, Ito et al. [37]	21 subjects aged 30 - 60 years	12 weeks	Supplementation of *Haematococcus pluvialis* Astaxanthin derivatives, (6 mg/ day), *Sesamum indicum* Sesamin derivatives (10 mg/ day)	Improvement in processing and psychomotor speed measure with ADAS-Cog compared with controls, improvement compared to baseline measured with CNSVS (Cognitrax)
2020, Sekikawa et al. [36]	36 subjects aged 40–70 years	12 weeks	ASX supplementation (9 mg/ day) and Tocotrienol (50 mg/ day)	Memory function improved compared with controls measured with CNSVS (Cognitrax)

Abbreviation: ADAS-Cog: Alzheimer Disease Assessment Scale-Cognitive subscale; CDT: Clock Drawing Test; CNSVS: Central Nervous System Vital Signs; GMLT: Groton Maze Learning Test; RCT: Randomized Control Trial.

review.

Results

Cognitive functions

Out of 4 studies, two studies measured cognitive function using CNSVS (Cognitrax). Sekikawa et al. [36] demonstrated notable changes in social acuity domain, as the score of the ASX group was significantly higher than that of the placebo group at baseline (ASX group, 97.4 ± 13.6 points; placebo group, 69.2 ± 55.3 points; $p = 0.043$). At 12 weeks after supplementation, in terms of psychomotor speed and processing speed, ASX-treated individuals performed statistically significant increase in processing speed ($p = 0.018$) compared with individuals in the placebo group [37]. There were no significant intergroup differences regarding the amount of change after administration for any of the items in word memory test, verbal fluency test, and Stroop test [38]. CogHealth test yielded significantly improved performance after 12 weeks of high dose ASX consumption for 'choice reaction', 'delayed recall', 'divided attention', and 'working memory' [39]. In the same study, the Groton Maze Learning Test (GMLT) evaluated short-term spatial working memory, concluding that improved performance was supported by ingestion of a low dose of ASX for 8 weeks [39]. Table 1 addresses detailed study results on cognitive functions.

Hematological and urinalysis tests

Blood elements related to oxidative stress and brain-derived neurotrophic factor (BDNF) levels were also evaluated, resulting in no significant difference in both groups [36,37]. One study reported proteinuria and finding of occult blood in the ASX-treated group [37], however, the same side effects were more prevalent in the placebo group at any time point[36]. One study [39] concluded no confirmed adverse effects in hematological parameters, somatometry, and urinary tests, also related to its safety outcome.

Subjective symptoms

There was only 1 study [36] evaluated subjective complaints, assessed with questionaries, and reported on a scale of 1 (strongly disagree) to 6 (strongly agree). At the 12th week of intervention, the results of the question "During the last week, have you had trouble remembering people's names or the names of things?" were median 3.0 and 4.0 in the ASX treated group and placebo group respectively ($p = 0.036$).

Safety assessment

One study [38] reported 2 "unrelated" adverse effects post supplementation, including contact dermatitis subsequent to the subject's activity and mild acne vulgaris which did not reappear after the 48th day after administration. Ito et al. [37] reported minor adverse effects including cold, diarrhea, and dizziness in the ASX-supplemented group. Various symptoms such as cold, feeling of smothering, malaise, tonsilitis, and lassitude were reported in the placebo group. In addition, 2 cases of low back pain were reported in both intervention groups. No concern regarding side effects of ASX ingestion was observed in 2 studies [36, 39].

Discussion

A systematic review was conducted in June – July 2022. Four RCTs-1 done in Italy, 3 done in Japan- involving 207 subjects in middle and older age. ASX supplementations are done via the oral route in all 4 studies. The primary outcome of all studies is the improvement of cognitive function post-intervention in comparison to controls or baseline cognitive function measured at the beginning of the study. To the best of our knowledge, over the past 10 years, we were only able to identify 4 positive RCTs.

Cerebral tissue is vulnerable to the effects of oxidative stress considering its high oxygen demand [40]. Chronic and progressive loss of anatomical or physiological neuronal function seen in Alzheimer's and other types of dementia as a result of not only aging but also cumulative oxidative stress [29] is associated with growing research targets in antioxidant therapy. ASX is carotenoid *xanthophyll* believed to have a vital role in anti oxidative and anti-aging processes, due to its molecular structure and its arrangement in the plasma membrane, factors that favor the neutralization of reactive oxygen and nitrogen species. The key advantage of ASX is that the compound can penetrate the blood brain barrier with its unique chemical structure, providing an even more neuroprotective effect on the central nervous system [36,41].

Astaxanthin has the molecular formula C40H52O4, with 596.84 g/mol molar mass. Astaxanthin consists of two terminal rings joined by a polyene chain. This molecule has two asymmetric carbons located at the 3, 3′ positions of the β-ionone ring with hydroxyl group (-OH) on either end of the molecule. In case one, hydroxyl group reacts with a fatty acid then it forms a mono-ester, whereas when both hydroxyl groups are reacted with fatty acids the result is termed a di-ester. Astaxanthin neutralises free radicals or other oxidants by accepting or releasing electrons without being destroyed or becoming pro-oxidants [31].

A trial by Katagiri et al. in individuals aged 50–69 years old complaining cognitive complaints such as memory loss, although not statistically significant compared to the control group due to its limited subject size, displayed a benefit of 12 weeks high dose (12 mg) ASX supplementation by faster response time in CogHealth test [39].

Hayashi et al. conducted a trial to study the effect of ASX supplementation in individuals aged 45–64 years old in a period of 8 weeks, unveiling the superiority of ASX supplementation in the group of subjects under 55 (44 – 55) years old compared to the placebo group in the "words recalled after 5 min" test. Surprisingly, there was no improvement in cognitive function in the ≥ 55-year-old age group. It is suspected due to significantly higher body weight, BMI, also systolic and diastolic blood pressure in this age group resulting in different and already pronounced risk factors of dementia in the older groups. Nonetheless, ASX supplements may be effective in preventing cognitive decline if consumed from a young age [38]. Another study measured the effect of ASX derived from *H. pluvialis* combined with tocotrienols on cognitive function in healthy adults with mild memory decline. ASX administered 9 mg per day for 12 weeks revealed significant score changes in the combined memory domains in the Cognitrax instrument as well as verbal memory (VBM) scores and subjective symptoms [36]. In an RCT, the outcome of ingested ASX and Sesamin combined for 12 weeks measured by the Central Nervous System Sign (CNVS) test showed significant improvements in psychomotor and processing speed in the ASX group compared to placebo, exhibiting that daily supplementation of ASX can also improve cognitive function related to comprehensive capabilities and perform complex tasks with accuracy [37]. The BLAtwelve Study showed additional supplementation of ASX was proven to be beneficial not only in reducing executive function deterioration but also in the prevention of cognitive decline [42].

The role of ASX in studies that have been carried out shows its capacity to counteract oxidative damage by several mechanisms such as elimination of reactive oxygen and free radicals that cause excessive stress, inhibiting peroxidation of fats, and regulation of gene expression related to oxidative stress. Its anti-apoptotic properties are also demonstrated through Phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways [36].

PI3K/AKT signaling pathway transduces cell surviving signal, inhibiting cell apoptosis, and cytokines expression [43] thus maintaining cell integrity [44,45]. Inflammation plays a vital role in central nervous system dysfunction both in acute and chronic processes [32]. The vascular dementia mice model was established by left unilateral

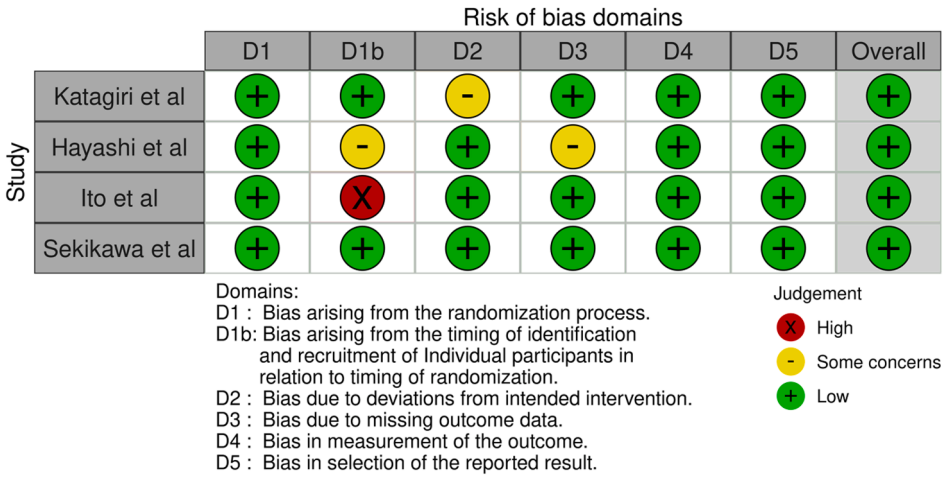

Fig. 2. Critical Appraisal with ROB-2 Tool for Randomized Controlled Trial Studies.

common carotid arteries occlusion (LUCCAO) [33]. ASX administration decreases IL-1β pro-inflammatory cytokine and increases IL-4 expression at the hippocampal and prefrontal cortex, supporting the theory that vascular dementia might be caused by excessive expression and the response of pro-inflammatory mediators [33]. ASX supplementation as a 2 weeks preemptive traumatic brain injury was proven to increase cerebral tissue resiliency to trauma shown with an improvement of neuromotor and cognitive function post traumatic brain injury [46], positively correlates with its ability to cross the Blood brain barrier and modify brain's response to stress which further upregulate Neurotropic Brain Derived Factor (BDNF) and cAMP response element-binding protein [47]. Moreover, the presence of excessive Phospholipid hydroperoxides in human erythrocytes-which was previously linked to a higher risk of cognitive decline-could be diminished by the administration of ASX [48]. Fig. 3 describes a detailed neurodegeneration process.

In AD, damage caused by oxidative stress will lead to the accumulation of amyloid-beta (AB) in the hippocampal area. With increasing age, the elimination of AB by neprilysin enzymes and phagocytic cells decreases [36]. Furthermore, it is postulated that said AB accumulation is estimated to have occurred about 20 years before the onset of Alzheimer's showing the important role of potent antioxidants at a young age to prevent cognitive decline [49]. In addition to the neuroprotective properties previously mentioned, ASX was also found to reduce phospholipid peroxide levels in red blood cells, which benefits the demented individual that was shown previously to have an increase in erythrocyte phospholipid peroxide [50] expected to improve the oxygen and blood

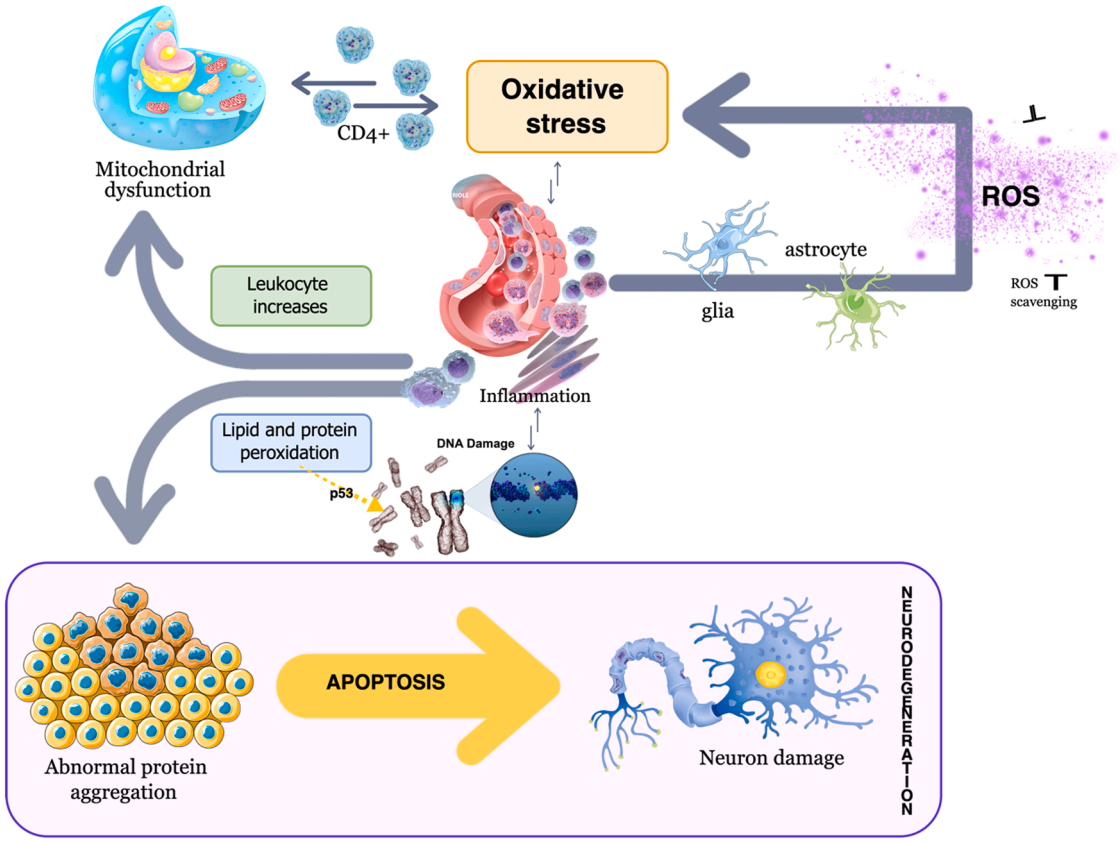

Fig. 3. Neurodegeneration pathway.

supply to the brain in VAD [38]. Previous studies testify that ASX supplementation can also improve visual and verbal memory, coincides with proving its uniqueness and possible superiority as opposed to other supplements such as Ginkgo Biloba, where improvements in psychomotor speed in ASX supplementation can prevent vehicle accidents in the elderly by increasing speed and accuracy in receiving information. In addition, not only can ASX reduce the damage caused by oxidative stress, but several studies in mice have shown that ASX also enhances the activity of endogenous antioxidants [37].

Food intake and blood carotenoid concentrations vary greatly among populations, depending on various factors, for example, the availability of food sources, and individual factors such as race, age, health status, gender, and genetic factors. Carotenoid intake in European countries has an average of 1.2 – 2 mol/L per individual and 1.2 – 2.5 mol/L per individual in the United States [51]. Studies conducted in developing countries are not yet available. Synthetic-produced ASX has lower antioxidant activity in contrast to the natural source (*H. pluvialis*). Yet, naturally concentrated ASX poses a relatively higher price, emerging strategies to help increase productivity and reduce costs through an effective downstream process [41].

On the basis of the parameters tested, administration of ASX supplement was not associated with any problems related to safety, especially in several studies involving the age group above 50 years [36,37,39,52], demonstrating the safety of ASX for consumption as daily supplementation as an adjunct for the prevention of cognitive decline in certain chronic diseases. Dermatitis and acne vulgaris were found in 2 subjects but were later inclined to the cause of the subject's own individual activity [38]. Limitations of this study include limited studies due to the limited number of RCTs. In addition, there is no other method of ASX ingestion other than oral, hence no comparable measurement. Although ASX has been known for its potential as an antioxidant that can directly penetrate the blood brain barrier that affects the central nervous system [36,41], further studies are needed regarding the exact and safe dose needed, especially for the elderly (Fig. 2).

Conclusions

To conclude, ASX acts as an antioxidant compound with neuroprotective properties in conditions of excessive oxidative stress expression in the process of neuronal damage. The functions of anti-inflammatory, anti-oxidant, anti-apoptotic, and protection from mitochondrial damage have been reviewed and tested clinically in some studies denoting the role of ASX in the prevention and improvement of chronic neurodegenerative diseases. Further clinical trials related to ASX with cognitive function in a larger number of subjects with more varied doses and observation of possible side effects are paramount to examine the synergistic and independent functions of ASX in the improvement of cognitive dysfunction especially in the elderly.

CRediT authorship contribution statement

Nunki Puspita Utomo: Methodology, Data curation. **Rizaldy Taslim Pinzon:** Supervision, Methodology, Conceptualization. **Patrick Kurniawan Latumahina:** Writing – original draft, Validation, Methodology, Data curation. **Kadex Reisya Sita Damayanti:** Writing – review & editing, Writing – original draft, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] E. Margioti, M.H. Kosmidis, M. Yannakoulia, et al., Exploring the association between subjective cognitive decline and frailty: the Hellenic Longitudinal Investigation of Aging and Diet Study (HELIAD), Aging. Ment. Heal. 24 (1) (2020) 137–147, https://doi.org/10.1080/13607863.2018.1525604.

[2] A. Lau, I. Beheshti, M. Modirrousta, T.A. Kolesar, A.L. Goertzen, J.H. Ko, Alzheimer's disease-related metabolic pattern in diverse forms of neurodegenerative diseases, Diagnostics 11 (11) (2021), https://doi.org/10.3390/DIAGNOSTICS11112023.

[3] R.T. Pinzon, R.D.L. Sanyasi, S. Totting, The prevalence and determinant factors of post-stroke cognitive impairment, Asia. Pacif. J. Heal. Sci. 5 (1) (2018) 78–83, https://doi.org/10.21276/apjhs.2018.5.1.17.

[4] Seshadri S., Economos A., Wright C. *Vascular Dementia and Cognitive Impairment.* Vol 01. Sixth Edit.; 2015. doi:10.1016/B978-0-323-29544-4.00017-7.

[5] Z. Mohamed Fuad, H. Mahadzir, S.Z. Syed Zakaria, N. Mohamed Ibrahim, Frequency of cognitive impairment among malaysian elderly patients following first ischaemic stroke—a case control study, Front. Public Heal. 8 (November) (2020) 2–8, https://doi.org/10.3389/fpubh.2020.577940.

[6] O.J. Gannon, L.S. Robison, A.J. Custozzo, K.L. Zuloaga, Sex differences in risk factors for vascular contributions to cognitive impairment & dementia, Neurochem. Int. 127 (2019) 38–55, https://doi.org/10.1016/j.neuint.2018.11.014.

[7] E.Y.H. Tang, O. Amiesimaka, S.L. Harrison, et al., Longitudinal effect of stroke on cognition: a systematic review, J. Am. Heart. Assoc. 7 (2) (2018), https://doi.org/10.1161/JAHA.117.006443.

[8] J.H. Sun, L. Tan, J.T. Yu, Post-stroke cognitive impairment: epidemiology, mechanisms and management, Ann. Transl. Med. 2 (8) (2014), https://doi.org/10.3978/j.issn.2305-5839.2014.08.05.

[9] W. Srithumsuk, M. Kabayama, Y. Gondo, et al., The importance of stroke as a risk factor of cognitive decline in community dwelling older and oldest peoples: the SONIC study, BMC. Geriatr. 20 (1) (2020) 1–10, https://doi.org/10.1186/s12877-020-1423-5.

[10] J.M. Farfel, R. Nitrini, C.K. Suemoto, et al., Very low levels of education and cognitive reserve: a clinicopathologic study, Neurology 81 (7) (2013) 650–657, https://doi.org/10.1212/WNL.0b013e3182a08f1b.

[11] F. Tumiwa, R.T. Pinzon, S. Adisaputro, Hubungan hipertensi dengan gangguan fungsi kognitif pada pasien post-stroke iskemik Di Rs Bethesda Association Between Hypertension with cognitive impairment on post-stroke ischemic patient in Bethesda Hospital, J. Keokteran. Yars. 25 (3) (2017) 135–144.

[12] W.S. Aronow, Hypertension and cognitive impairment, Ann. Transl. Med. 5 (12) (2017) 259, https://doi.org/10.21037/atm.2017.03.99.

[13] E.Y.H. Tang, C.I. Price, L. Robinson, et al., Assessing the predictive validity of simple dementia risk models in harmonized stroke cohorts, Stroke. (July) (2020) 2095–2102, https://doi.org/10.1161/STROKEAHA.120.027473.

[14] P. van Vliet, Cholesterol and late-life cognitive decline, J. Alzheimer. Dis. 30 (Suppl 2) (2012) S147–S162, https://doi.org/10.3233/JAD-2011-111028.

[15] F.I. Fitri, A.S. Rambe, Correlation between hypertension and cognitive function in elderly, IOP. Conf. Ser. Earth. Environ. Sci. 125 (1) (2018), https://doi.org/10.1088/1755-1315/125/1/012177.

[16] M.K. Scullin, D.L. Bliwise, Sleep, cognition, and normal aging: integrating a half century of multidisciplinary research, Perspect. Psychol. Sci. 10 (1) (2015) 97–137, https://doi.org/10.1177/1745691614556680.

[17] M. Danovska, D. Peychinska, Post-stroke cognitive impairment – phenomenology and prognostic factors, J. IMAB. -. Annu. Proceed. (Scientif. Pap.) 18 (3) (2012) 290–297, https://doi.org/10.5272/jimab.2012183.290, 2012.

[18] C. Laredo, Y. Zhao, S. Rudilosso, et al., Prognostic significance of infarct size and location: the case of insular stroke, Sci. Rep. 8 (1) (2018) 1–10, https://doi.org/10.1038/s41598-018-27883-3.

[19] T.S. Chaudhari, R. Verma, R.K. Garg, M.K. Singh, H.S. Malhotra, P.K. Sharma, Clinico-radiological predictors of vascular cognitive impairment (VCI) in patients with stroke: a prospective observational study, J. Neurol. Sci. 340 (1–2) (2014) 150–158, https://doi.org/10.1016/j.jns.2014.03.018.

[20] R.O. Boletimi, M.A.H.N. Kembuan, J.M. Pertiwi, Gambaran Fungsi Kognitif Pasien Pasca Stroke, Med. Scope. J. 2 (2) (2021) 66–72.

[21] N.P. Utomo, R.T. Pinzon, Risk Factors of Cognitive Impairment Post Ischemic Stroke, Egypt. J. Neurol. Psychiatry. Neurosurg. (2023) 59, https://doi.org/10.1186/s41983-023-00654-2.

[22] P.M. Rist, J. Chalmers, H. Arima, et al., Baseline cognitive function, recurrent stroke, and risk of dementia in patients with stroke, Stroke 44 (7) (2013) 1790–1795, https://doi.org/10.1161/STROKEAHA.111.680728.

[23] S. Duong, T. Patel, F. Chang, Dementia: what pharmacists need to know, Can. Pharm. J. (Ott) 150 (2) (2017) 118–129, https://doi.org/10.1177/1715163517690745.

[24] B. Grimmig, S.H. Kim, K. Nash, P.C. Bickford, R. Douglas Shytle, Neuroprotective mechanisms of astaxanthin: a potential therapeutic role in preserving cognitive function in age and neurodegeneration, GeroScience 39 (1) (2017) 19–32, https://doi.org/10.1007/s11357-017-9958-x.

[25] S. Davinelli, S. Ali, V. Solfrizzi, G. Scapagnini, G. Corbi, Carotenoids and cognitive outcomes: a meta-analysis of randomized intervention trials, Antioxidants. 10 (2) (2021) 1–13, https://doi.org/10.3390/antiox10020223.
[26] E.E. Devore, J.H. Kang, M.J. Stampfer, F. Grodstein, The association of antioxidants and cognition in the Nurses' Health Study, Am. J. Epidemiol. 177 (1) (2013) 33–41, https://doi.org/10.1093/aje/kws202.
[27] B.L. Tan, M.E. Norhaizan, W.P.P. Liew, H.S. Rahman, Antioxidant and oxidative stress: a mutual interplay in age-related diseases, Front. Pharmacol. 9 (OCT) (2018) 1–28, https://doi.org/10.3389/fphar.2018.01162.
[28] P. Maurya, P. Kumar, S. Nagotu, S. Chand, D.P. Chandra, Multi-target detection of oxidative stress biomarkers in quercetin and myricetin treated human red blood cells, RSC Adv. 6 (2016) 53195–53202, https://doi.org/10.1039/C6RA05121A.
[29] A. Donoso, J. González-Durán, A.A. Muñoz, P.A. González, C. Agurto-Muñoz, Therapeutic uses of natural astaxanthin: an evidence-based review focused on human clinical trials, Pharmacol. Res. 166 (January) (2021), https://doi.org/10.1016/j.phrs.2021.105479.
[30] S.H. Kim, H. Kim, Inhibitory effect of astaxanthin on oxidative stress-induced mitochondrial dysfunction-a mini-review, Nutrients 10 (9) (2018), https://doi.org/10.3390/nu10091137.
[31] R.R. Ambati, S.M. Phang, S. Ravi, R.G. Aswathanarayana, Astaxanthin: sources, extraction, stability, biological activities and its commercial applications–a review, Mar. Drug. 12 (1) (2014) 128–152, https://doi.org/10.3390/md12010128.
[32] H. Wu, H. Niu, A. Shao, et al., Astaxanthin as a potential neuroprotective agent for neurological diseases, Mar. Drug. 13 (9) (2015) 5750–5766, https://doi.org/10.3390/md13095750.
[33] N. Zhu, X. Liang, M. Zhang, et al., Astaxanthin protects cognitive function of vascular dementia, Behav. Brain. Funct. 16 (1) (2020) 1–10, https://doi.org/10.1186/s12993-020-00172-8.
[34] V. Balendra, S.K. Singh, Therapeutic potential of astaxanthin and superoxide dismutase in Alzheimer's disease, Open Biol. 11 (6) (2021) 1–11, https://doi.org/10.1098/rsob.210013.
[35] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (n71) (2021), https://doi.org/10.1136/bmj.n71.
[36] T. Sekikawa, Y. Kizawa, Y. Li, T. Takara, Cognitive function improvement with astaxanthin and tocotrienol intake: a randomized, double-blind, placebo-controlled study, J. Clin. Biochem. Nutr. 67 (3) (2020) 307–316, https://doi.org/10.3164/jcbn.19-116.
[37] N. Ito, H. Saito, S. Seki, F. Ueda, T. Asada, Effects of composite supplement containing astaxanthin and sesamin on cognitive functions in people with mild cognitive impairment: a randomized, double-blind, placebo-controlled trial, J. Alzheimer Dis. 62 (4) (2018) 1767–1775, https://doi.org/10.3233/JAD-170969.
[38] M. Hayashi, T. Ishibashi, T. Maoka, Effect of astaxanthin-rich extract derived from Paracoccus carotinifaciens on cognitive function in middle-aged and older individuals, J. Clin. Biochem. Nutr. 62 (2) (2018) 195–205, https://doi.org/10.3164/jcbn.17-100.
[39] M. Katagiri, A. Satoh, S. Tsuji, T. Shirasawa, Effects of astaxanthin-rich Haematococcus pluvialis extract on cognitive function: a randomised, double-blind, placebo-controlled study, J. Clin. Biochem. Nutr. 51 (2) (2012) 102–107, https://doi.org/10.3164/jcbn.D-11-00017.
[40] S. Salim, Oxidative Stress and the Central Nervous System, J. Pharmacol. Exp. Ther. 360 (1) (2017) 201–205, https://doi.org/10.1124/jpet.116.237503.
[41] Z. Jafari, A. Bigham, S. Sadeghi, et al., Nanotechnology-Abetted Astaxanthin formulations in multimodel therapeutic and biomedical applications, J. Med. Chem. 65 (1) (2022) 2–36, https://doi.org/10.1021/acs.jmedchem.1c01144.
[42] F. Crosta, A. Stefani, F. Melani, et al., Improvement of executive function after short-term administration of an antioxidants mix containing bacopa, lycopene, astaxanthin and vitamin B12: the BLAtwelve study, Nutrients 13 (1) (2021) 1–16, https://doi.org/10.3390/nu13010056.
[43] S. Matsuda, Y. Ikeda, M. Murakami, Y. Nakagawa, A. Tsuji, Y. Kitagishi, Roles of PI3K/AKT/GSK3 pathway involved in psychiatric illnesses, Diseases 7 (1) (2019), https://doi.org/10.3390/diseases7010022.
[44] J.-Y. Lin, W.-W. Kuo, R. Baskaran, et al., Swimming exercise stimulates IGF1/PI3K/Akt and AMPK/SIRT1/PGC1α survival signaling to suppress apoptosis and inflammation in aging hippocampus, Aging (Albany NY) 12 (8) (2020) 6852.
[45] X.-S. Zhang, X. Zhang, Q. Wu, et al., Astaxanthin alleviates early brain injury following subarachnoid hemorrhage in rats: possible involvement of Akt/bad signaling, Mar. Drug. 12 (8) (2014) 4291–4310, https://doi.org/10.3390/md12084291.
[46] Fleischmann C., Shohami E., Trembovler V., Heled Y., Horowitz M. Cognitive effects of astaxanthin pretreatment on recovery from traumatic brain injury. Front. Neurol.. 2020;11(October). doi:10.3389/fneur.2020.00999.
[47] S. Fakhri, L. Dargahi, F. Abbaszadeh, M. Jorjani, Astaxanthin attenuates neuroinflammation contributed to the neuropathic pain and motor dysfunction following compression spinal cord injury, Brain. Res. Bull. 143 (2018) 217–224, https://doi.org/10.1016/j.brainresbull.2018.09.011.
[48] K. Nakagawa, T. Kiko, T. Miyazawa, et al., Antioxidant effect of astaxanthin on phospholipid peroxidation in human erythrocytes, Br. J. Nutr. 105 (11) (2011) 1563–1571, https://doi.org/10.1017/S0007114510005398.
[49] L. Arwin, J.N. Pratiwi, Peran Neuroprotektor Astaxanthin Dalam Pencegahan the Role of Neuroprotector Astaxanthin Against Alzheimer Disease, J. Ilmu. Keperawatan. Jiwa. 3 (1) (2020) 47–52.
[50] T. Miyazawa, K. Nakagawa, H. Takekoshi, et al., Ingestion of Chlorella reduced the oxidation of erythrocyte membrane lipids in senior Japanese subjects, J. Oleo. Sci. 62 (11) (2013) 873–881, https://doi.org/10.5650/jos.62.873.
[51] Böhm V., Lietz G., Na Olmedilla-Alonso B., et al. From carotenoid intake to carotenoid blood and tissue concentrations-implications for dietary intake recommendations. doi:10.1093/nutrit/nuaa008.
[52] M. Yoshida, T. Hayashi, K. Fujii, H. Ishiura, S. Tsuji, Y. Sakurai, Selective impairment of On-reading (Chinese-style pronunciation) in alexia with agraphia for kanji due to subcortical hemorrhage in the left posterior middle temporal gyrus, Neurocase (2020) 220–226, https://doi.org/10.1080/13554794.2020.1788608.