Effects of Astaxanthin on Cognitive Function in Humans

Subjects: Others

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Astaxanthin is a potent antioxidant, which has been outlined to be beneficial for cognitive function both in vitro and in vivo. Astaxanthin has been researched in relation to various facets of cognitive function in humans, including episodic memory (visual and verbal stimuli), working memory/short-term memory, processing speed, response inhibition, cognitive shifting, and attention.

Keywords: nutrition ; supplement ; antioxidant ; cognition

1. Introduction

Dietary antioxidants are substances which are present in food or supplements that decrease the adverse effects associated with both reactive nitrogen species (RNS) and reactive oxygen species (ROS) to a significant degree in relation to normal physiological functions [1]. The negative effects of RNS and ROS are thought to contribute significantly to oxidative stress, which is a key factor underpinning cognitive decline and impaired cognitive functions [2]. As a result, nutritional interventions which utilise antioxidants have been of interest when considering methods to reduce cognitive function decline and improve cognitive performance [3]. Common dietary antioxidants include ascorbic acid (vitamin C), α-tocopherol (vitamin E), polyphenols, selenium, and carotenoids [4][5]. There are a wide variety of dietary sources of antioxidants, such as plants, fruits, and vegetables. They can either be ingested as part of a balanced diet or be taken as a supplement. The latter has been of particular interest due to the role supplements have in both the improvement and maintenance of overall health and well-being, especially in individuals where sufficient intake through ordinary diet is challenging. This has been evidenced by the rising prevalence of supplement use in the wider population [6]. Many types of antioxidants have received extensive research attention, particularly ascorbic acid [7][8] and α-tocopherol [9][10]. The carotenoids, which are the antioxidants responsible for producing the bright colours associated with plants, algae, vegetables, and fruits, have received some research attention, which, when considered holistically, covers a wide variety of applications [11][12][13]. A key contributing factor towards the depth of this research base is accessibility, as carotenoids are typically obtained from readily available fruits, vegetables, and supplements. They can also protect cells from oxidative processes mediated by either singlet oxygen, free radicals, or light [14]. Due to the absence of accessibility issues surrounding ingestion and the outlined advantageous properties, carotenoids have been investigated as a beneficial area of exploration [15][16].

One of the most potent carotenoids is natural astaxanthin (AST) [17], which has been shown to offer a superior radical absorbance capability when compared to antioxidants of a similar chemical nature, such as α-tocopherol [18]. It has been suggested to have the greatest oxygen radical absorbance capability, bettering other antioxidants, such as vitamin E [17][19]. Astaxanthin is found across a range of sources, especially in crustacean and salmonid aquaculture. It is also often acknowledged for generating the unique pink colour associated with salmon, shrimp, krill, and lobster. This colour is thought to stem from 11 conjugated double bonds and how they are expressed [20]. Notable key natural sources of astaxanthin include red yeast, *Phaffia rhodozyma*, shrimp, salmon, crustacean by-products, and some forms of green algae [21].

The specific properties of AST allow it to maintain the structure and subsequent integrity of cell membranes, facilitating both improvement in gene expression and immune system functioning, respectively [22]. The previously established effects are achieved by managing lipid peroxidation (LPO), neutralising ROS, and scavenging free radicals [23]. The primary benefit of AST is, however, its capability for mitigating oxidative stress (OS), both in vitro and in vivo [24]. The OS reduction effect is thought to stem from AST's interaction with the phosphoinositide 3-kinase/protein kinase B pathway (**Figure 1**). This interaction has been outlined to facilitate OS reduction due to its role in aiding the process of dissociating NRf2 from KEAP1 [25].

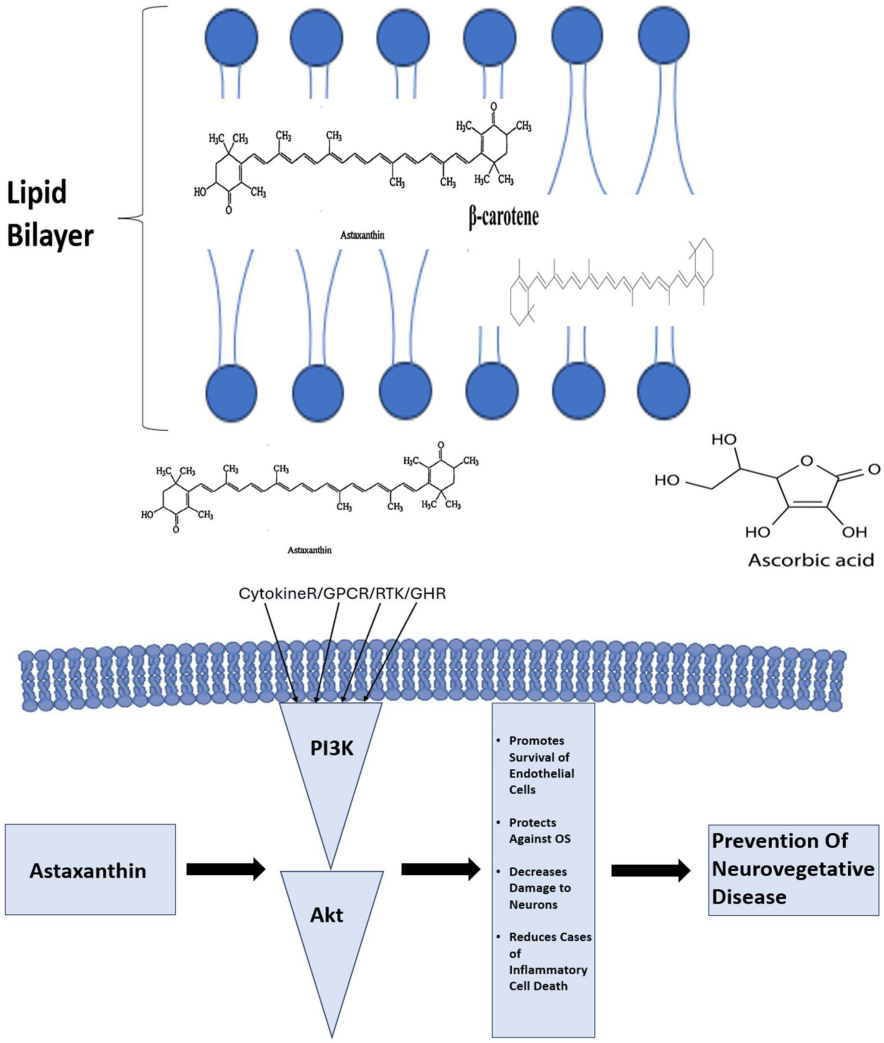

Figure 1. A graphic outlining the breakdown of AST's actions compared with other carotenoids alongside an illustration of the P13K/Akt pathway and its interactions with subsequent downstream consequences.

When distinguishing the efficacy of AST from other carotenoids, it is also important to consider the transportation mechanisms adopted by different subgroups. Polar carotenoids, such as zeaxanthin and lutein, are transported using different densities of lipoproteins (high and low). In contrast, non-polar carotenoids, for example, lycopene and β-carotene, are transported by lipoproteins of low and very low density. Astaxanthin has been shown to use all the lipoprotein densities, with low density (29%), very low density (36–64%), and high density (24%) all being outlined as methods of transportation [26]. This range of transportation routes, along with AST's ability to cross the blood–brain barrier [27] and act both inside and on the surface of the double layer cell membrane [28], as depicted in **Figure 1**, are thought to contribute highly to its efficacy. This ability offers a clear advantage when contrasted against vitamin C and β-carotene, which individually only act solely either outside or inside of the double layer cell membrane [28].

2. Proposed Benefits of Astaxanthin

The benefits of astaxanthin, particularly in human samples and human tissue, have only been explored more thoroughly in recent years [17][29]. This could be suggested to stem from the current focus on dietary supplementation for the general populous as opposed to only athletes [30]. The outlined viewpoint in addition to its economic implications [31] offers a justification to expand on the finding that humans cannot synthesise astaxanthin naturally, meaning it cannot be utilised without being consumed as part of a person's diet [32]. Astaxanthin supplementation has been used as an intervention in both animal- and human-based studies [17][33][34]. The proposed benefits have been suggested to include, but are not limited to, decreases in inflammation, the combatting of neurodegenerative disease, improvements to cognitive function, anti-cancer properties, better recovery, and improved cellular, eye, skin, and heart health [28][35][36][37].

As more research is being published, the exploration of astaxanthin has progressed away from animal studies and towards human populations. Whilst other proposed benefits of AST, for example, skin health [29], have been reviewed utilising solely human-based research, at present, there has been no critical review outlining the effects of astaxanthin on cognitive function and neurodegeneration holistically in human samples. This offers a rationale for research in the area. The following critical review aims to explore this gap in the wider literature base and therefore aid in furthering overall

understanding of the effects of astaxanthin in humans. To explore the effects of AST in relation to cognition and neurodegeneration in its entirety, the effects of astaxanthin as part of a compound, as well as the literature outlining its impact on indirect factors related to cognition, such as mental and physical fatigue, will also be reviewed.

3. The Effects of Astaxanthin on Cognitive Function in Humans

Astaxanthin has been researched in relation to various facets of cognitive function in humans, including episodic memory (visual and verbal stimuli), working memory/short-term memory, processing speed, response inhibition, cognitive shifting, and attention [38][39][40]. Research has also been conducted which focusses on the effects of AST in relation to neurological protection and the prevention of neurological degeneration/neurological disease [27][41]. Finally, AST's effects on cognition as part of a compound, for example, its effects when ingested alongside tocotrienol or sesamin, have also been explored. This area encompasses the effects of AST on indirectly associated factors, such as mental and physical fatigue [42][43]. Whilst AST has been suggested to be beneficial, it is important to review the research critically, as the finalised claims could have implications in the treatment of cognitive impairment/neurodegeneration as well as the enhancement of cognitive function. Furthermore, the outlined implications could contribute significantly to both quality and length of life [44][45]. This is especially the case for cognition due to the established link between oxidative stress and the areas of neurodegeneration, cognitive ageing, cognitive decline, and cognitive longevity [46]. As a result, it is important that research in this area, which has the potential to be used as a basis for change, is both dependable and of a high calibre.

A study examining differences in cognitive function utilised AST supplementation versus a placebo over an 8-week period in a dose of 8 mg·day^{-1} [38]. The research method allowed for different facets of cognition to be assessed. This was achieved using a word memory test, Stroop test (multiple steps), and verbal fluency test. No tests showed any inter-group differences between the placebo and AST groups. However, a further analysis splitting the sample by age (<55 vs. ≥55) revealed significant intra-group findings. The results of the word memory test, which were specifically looking at "words recalled after five minutes", showed a significant improvement (p = 0.027) following AST supplementation in the <55 years subgroup; this indicates that this demographic may experience positive changes to cognitive function following a course of AST supplementation.

Closer scrutiny of the research in this area suggests it is important to consider the role of age, blood pressure (BP), and body mass index (BMI). With age, the prevalence and severity of cognitive performance decline across different areas has been suggested to increase [47]. This decline is thought to stem from a decrease in executive function [48], processing speed [49], or a combination of both [50]. The above relationship in addition to the association between high BP, high BMI, and cognitive decline risk [51] could impact findings in older and unhealthy middle-aged populations. It is also beneficial to acknowledge the potential of the research, as, whilst there were no inter group differences, the AST group showed improvement from their respective baseline measurements on more individual items across the tests when compared to the placebo group. This implies that under different study parameters, which also incorporate a stronger control of extraneous variables, such as age, BMI, and BP, a significant finding could be elicited. More research is therefore needed in this area to substantiate any claims supporting or refuting the efficacy of the supplement. Until such work is conducted, it can be argued that whilst AST does not support these facets of cognition across all age and health demographics, it can offer beneficial effects for cognitive function.

Alternative findings partially support the notion that these results are method- and population-dependent. Elderly subjects (n = 96) were given 12 weeks of AST supplementation over the course of a double-blind placebo control trial [39]. Cognition was assessed using both CogHealth, which is a selection of card games completed on a computer that are designed to assess different facets of cognition, and the Groton Maze Learning Test (GMLT—a computer-generated maze requiring individuals to move from one area on the screen to another). Results were compared across two supplementation conditions and a placebo control. The GMLT scores improved across both high- and low-dose conditions (6 and 12 mg·day^{-1}), whereas CogHealth scores only improved in the 12 mg·day^{-1} group. It is, however, important to note that these findings, whilst evidenced, were not shown to be statistically significant; therefore, similar research with larger sample sizes, or more robust research designs, would be required to substantiate the results. Further insight can also be gained from a breakdown of the testing methods. Only one of the measures for episodic memory assessed by the CogHealth test improved. The results showed an improvement in working memory; however, no acknowledgeable changes in response time (the second outcome measure associated with visual stimuli), implying that AST only has a partial effect on outcomes of visual episodic memory under given dose-dependent parameters.

There is evidence within the literature to substantiate the claim that AST supplementation can improve working memory. Research by Satoh [52] reported a mean percent accuracy increase from 90.46 to 96.30% (p < 0.05 vs. baseline) in a measure of working memory. The findings of the outlined research also provide support for an alternative viewpoint

regarding AST and response time. Decreased response time from baseline ($p < 0.05$ vs. baseline) on simple reaction (341.68 to 281.76 ms), choice reaction (504.53 to 463.63 ms), divided attention (494.13 to 412.07 ms), delayed recall (1008.19 to 916.77 ms), and working memory tasks (762.94 to 654.83 ms) was shown following supplementation, suggesting the effects of AST on response time to be task- and population-dependent. Measures of event-related potential (P300) taken during the same study indicated a significant increase ($p < 0.1$ vs. baseline) in amplitude (mean µV: 7.6 to 10.54) despite not showing an increase in latency (mean: 359.40 to 363.10 ms) following 12 weeks of AST supplementation, implying an effect on cognition, memory, attention, and information processing due to the established use of response time as a measure of psychomotor speed [53]. When considering the findings of this research, it is useful to acknowledge the demographic, as the sample did have age-related forgetfulness. Further research substantiating the claim in a completely healthy, or younger, demographic would therefore be advantageous for population-wide generalisability.

The findings of previously outlined research pertaining to the effects of AST suggest that supplementation has no significant effects on measures of response inhibition or cognitive shifting capabilities assessed through semantic and phonemic fluency. The Stroop test has also been used under different parameters to assess changes in response inhibition following AST supplementation [38]. During this study, two outcomes were measured by analysing step two (a reverse Stroop interference task) and step four (the Stroop interference task) of the Stroop test. No significant differences were found in this study ($n = 54$, age = 45–64) within or between groups following 8 weeks astaxanthin supplementation (8 $mg \cdot day^{-1}$).

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