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Super Nutritive Marine Astaxanthin, an Effectual Dietary Carotenoid for Neurodegenerative Diseases

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ABSTRACT

The red-pigmented astaxanthin (3,-3'-dihydroxy-β,β-carotene-4,4'-dione) were commonly found in marine algae and aquatic animals such as shrimp, lobster, and trout. These pigments are produced as secondary metabolites which fall in arytenoids under class xanthophylls. Synthetic astaxanthin has a wide range of commercial applications such as color additives, usage in cosmetics and immune-boosters. In aquaculture, supplementing synthetic astaxanthin as feed, enhances skin pigmentation which possesses commercial importance. However, synthetic astaxanthin is not highly efficient compared to naturally derived counter forms. On the other hand, humans should only depend on microbial and aquatic sources for their dietary intake of natural astaxanthin. Being a powerful antioxidant, natural astaxanthin is called as king of antioxidants which has scavenging activity 6000 times stronger than vitamin C and 50 times more powerful than vitamin E in protecting cell membranes. It also has a single oxygen quenching activity up to 800 times stronger than coenzyme Q, 550 times more powerful than green tea catechins, 4.9 times stronger than beta-carotene and three times stronger than lute in. Furthermore, researchers revealed that this carotenoid has the capacity to alleviate tumor activity, protecting against lipid per oxidation, free radicals, oxidative damage to LDL-cholesterol and UV light affects on cell membranes and tissues. Also, it is mainly recommended for curing the macular degeneration of cataracts. Anti-aging properties of astaxanthin improve skin health by reducing wrinkles and repairs the UV-induced DNA damage in human cells. Interestingly, the ability of astaxanthin in crossing the blood-brain barrier has brought this compound to limelight as a potential target in treating neurodegenerative diseases including Parkinson's and Alzheimer's disease. Hence, in this review, we are mainly focusing on the therapeutic usage of astaxanthin in neurodegenerative diseases.

Keywords: Astaxanthin, carotenoid, neurodegenerative, anti-aging.

1. INTRODUCTION

Exciting evolution behind astaxanthin: Among secondary metabolites, carotenoid family constitutes of more than 750pigments that are greatly distributed in plant and animal kingdom. However, these pigments were synthesized *denovo* only in higher plants and protists [10]. Among arytenoids, astaxanthin is exclusively found in green algae (*Haematococcus pluvialis*), red

yeast(*Phaffia rhodozyma*),marine bacterium (*Agro bacterium aurantiacum*)and crustacean (as byproducts). Under stress conditions like increased salinity, lack of nutrients, and excessive sunshine, microalgae produces astaxanthin using counter-defense mechanism [16]. Being ubiquitous in marine environment, astaxanthin is the main reason for the intensified colour pigmentation of aquatic animals such as shrimp, crayfish, salmon, trout, red sea bream, krill, and lobster. Besides, it is also found in some birds like flamingos, quails, and other species paving uncountable health benefits. Behavioural ecologists unveiled that consumption of astaxanthin-rich microalgae by aquatic animals resulted in higher accumulation of astaxanthin in their flesh which transfers through food chain from lower to higher organisms. On top of that, astaxanthin is produced in large scale and is used as a commercial strategy for colourful and healthier aqua farming [18].

Metabolite description: Astaxanthin is a lipophilic terpene xanthophylls carotenoid, chemically identified as 3,3'-dihydroxy-β,β'-carotene-4,4'-dionehaving molecular formula $C_{40}H_{52}O_4$ with a molar mass of 596.84 g/mol.It has two carbonyl groups, two hydroxyl groups and eleven conjugated double bonds. It also exhibits different stereo isomeric (3R, 3'R-3R,3S-3S,3S), esterifies and non-esterifies forms in which proportion varies between organisms. The stereoisomer's (3R-3R') and (3S-3'S) were abundant in nature. *Haematococcus* biosynthesizes the (3*S*, 3′*S*)-isomer whereas yeast *Xanthophyllomyces dendrorhous* produces (3*R*, 3′*R*)-isomer (Hussain *et al*.,2006). Wild salmon contains the 3S, 3'S form of ASX almost exclusively [41].

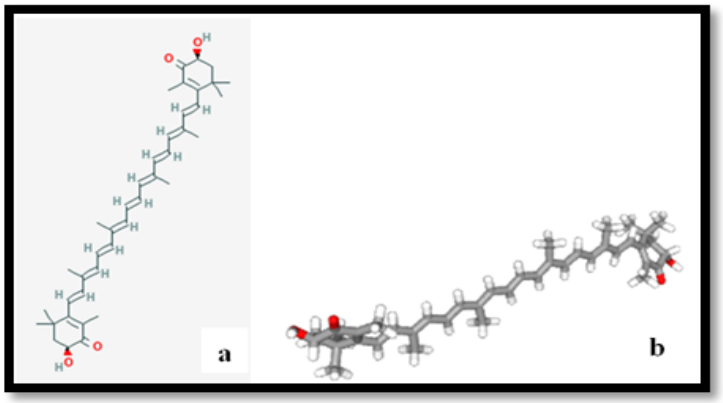

Fig 1.Configuration of astaxanthin (a)Two dimensional (b)Three dimensional structure (Source:Pubchem)

Esterifies forms have higher polarity and antioxidant activity which enables them to terminate free radical reaction in many living organisms. In addition to that, astaxanthin in nature is either esterifies with one or two fatty acids to form monoester and dieter forms or conjugated with proteins producing an array of colours in different organisms. It is the main compound for the chromospheres of blue, green, and yellow pigments of lobster [26].

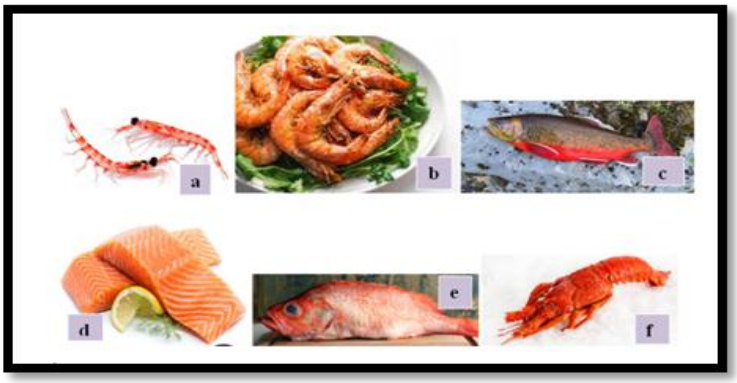

Fig 2. Marine animal sources for astaxanthin(a)Krill (b)Shrimp (c)Trout (d)Salmon flesh(e)Red seabream fish (f)Crayfish(Source: Google images)

It has the ability to be dissolved in the lipid fraction of complex molecules such as lipoproteins, fatty acids to form esters. Reddening of some snow algae and *Haematococcus* is the result of such esters accumulating in cytoplasm lipid droplets [33].

Safety and Bioavailability of astaxanthin: In Europe, Japan, and USA, astaxanthin produced from *H.pluvialis* is highly intake as a dietary supplement and are approved as salmon feed. Food and Drug Administration (FDA) has approved astaxanthin from *H. pluvialis* for direct human consumption dosages up to 12 mg per day and up to 24 mg per day for no more than 30 days. The European Food Safety Authority (EFSA) on Additives and Products or Substances used in Animal Feed (FEEDAP) advised an acceptable daily intake (ADI) of 0.034 mg/kg bw of astaxanthin (2.38 mg per day in a 70-kg human). Studies revealed that humans supplemented with more than 4 mg of astaxanthin remained healthy without adverse effects [41][37]. Immune-tolerance was observed with participants taken around 40 mg with only mild events reported in 48hr post intake [26].

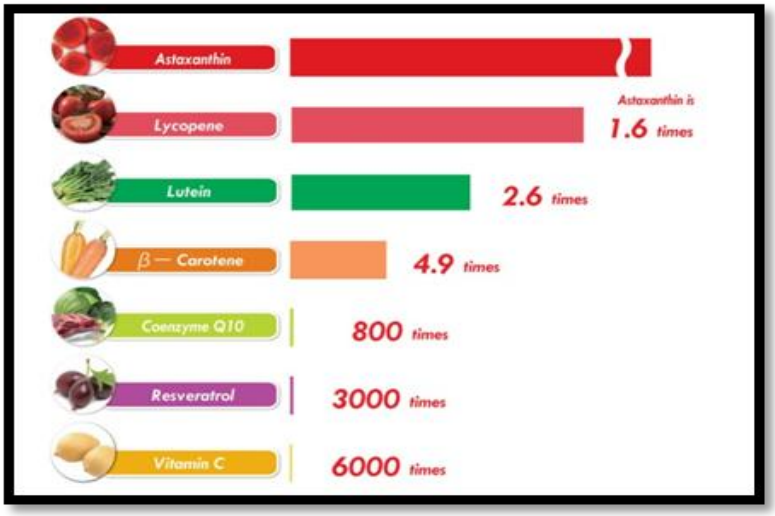

Fig 3. Efficiency of astaxanthin over other nutrient compounds (Source: Astareal Inc. Revised from Nishida Y et al., 2007, sci.11:16-20).

Literature evidence shows improvements in astaxanthin bioavailability but enhancement of astaxanthin bioavailability has not gained significant attention. Moreover, further investigation is needed in terms of novel delivery strategies that include nanoparticles, topical application cream, and defined phospholipids complexes, thereby enhancing the bioavailability [4].

Pharmacokinetics: Carotenoids are absorbed into the body like lipids and transported via the lymphatic system into the liver. Higher absorption of carotenoids is achieved with high cholesterol diet. Astaxanthin mixes with bile acid after ingestion and produces micelles in the intestine tenue. The intestinal mucosal cells absorbs astaxanthin partially which allows the entry of astaxanthin into chylomicrons. In chylomicrons, astaxanthin is digested by lipase and released into the lymph thereby reaches the liver. Any chylomicron remnants are rapidly removed by the liver and other tissues. Astaxanthin is assimilated with lipoproteins and transported into the tissues. Among many naturally occurring carotenoids, astaxanthin is considered as one of the best carotenoids being able to protect cells, lipids and membrane lipoproteins against oxidative damage [30].

Effect of astaxanthin in nervous system: Presence of unsaturated fats and iron in nervous system with intense metabolic activity makes it more susceptible to oxidative damage [9].This oxidative stress is responsible or least ancillary factor in major neurodegenerative diseases which includes Alzheimer's, Huntington's, Parkinson's and amyotrophic lateral sclerosis (ALS).Rich diet of antioxidants can prevent the risk of neurodegenerative diseases. Recent studies revealed that astaxanthin can cross the blood brain barrier in mammals exhibiting antioxidant benefits.

Previous reports showed that astaxanthin can inhibit 6-hydroxy dopamine induced neuronal apoptosis, mitochondrial anomalies and intracellular ROS in SH-SY5Y cells [14]. Due to the potential antioxidant properties of astaxanthin, they can enhance the cell and mitochondrial membrane stability by that having defensive reaction on neurodegenerative disease. It might be a useful neuroprotective tonic agent to cure oxidative stress-related neurodegeneration [3]. In addition to that, astaxanthin lowers ischemia induced apoptosis, free radical damage neurodegeneration and cerebral infarction in brain tissue through the inhibition of oxidative stress, anti-apoptosis and reduction of glutamate release. Besides, astaxanthin modulates synaptic plasticity and cognitive function in young and aged mice [12].

IVError! No bookmark name given. PARKINSON'S DISEASE

About 0.1-0.2% of global population has been significantly affected by Parkinson's disease which is a second most multisystem neurodegenerative disorder [48].The progression of PD is mainly due to the CNS inflammation caused by oxidative stress leading to degeneration of non-dopaminergic neurons that alters physical posture and balance [39].Woefully, only few treatments are available for delaying or preventing this stage. rimming *etal*., 2018 [11] stated that mice fed with astaxanthin opted from *H.pluvialis* for four weeks prevented neurotoxicity in PD induced mice and found that carotenoid can be used as a adjuvant in adverse cases. In addition to that, they demonstrated that astaxanthin has anti-inflammatory effects, attenuating microglia activation in substantial nigra and striatum.SH-SY5Y which is a human neuroblastoma cell line is checked for dose dependent manner that activated the ROS-mediated apoptosis indicating astaxanthin as a powerful antioxidant and neuroprotective [24].Besides, astaxanthin is likely to suppress apoptosis, inhibit mitochondrial abnormalities and the creation of intracellular ROS [14].

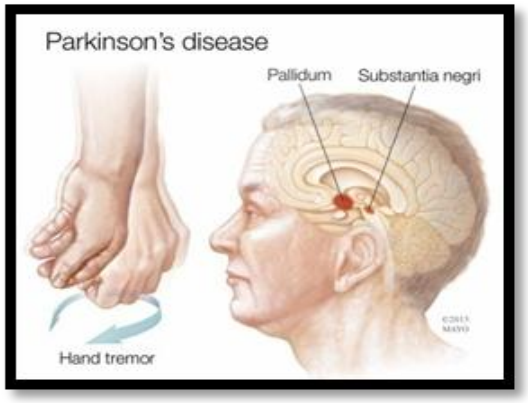

Fig 4. Pathophysiology of Parkinson's disease

(Source: https://newsnetwork.mayoclinic.org)

II. ALZHEIMER'S DISEASE

Alzheimer's disease (AD) discovered by Alois Alzheimer in 1906, is one of the most serious chronic neurodegenerative disorders, distinguished by cognitive dysfunction and memory detriment. It is caused by neuronal destruction especially inthe brain areas of hippocampus and neocortex. In last 10 years, there is a massive increase in the occurrence of Alzheimer's disease affecting every one out of five persons aged 65 and upto 40% of people over age of 85 all over the world [20].There is no clear evidence for the physiopathology of AD, yet some studies ensures that AD is triggered with a sign of abnormal aggregation of amyloid beta plaques in brain. This aggregation may happened due to the disproportion in production and dispersing amyloid beta [50]. Tau protein tangling is also observed with AD affected persons, thereby blocking the neural

signals passage [18]. But molecular mechanism behind the tau protein tangling and amyloid beta plaques aggregation is needed to be studied. Furthermore, few studies have interpreted that the existence of impaired mitochondria in the neurons of AD patients could be possibly due to alteration in mitochondrial DNA and oxidative stress induced at mitochondrial site[38][27].Since astaxanthin having singlet quenching strong antioxidant activity along with anti-inflammatory properties, mitochondrial oxidative stress can be dripped down at a considerable rateby repressing the neurodegeneration. The astonishing mechanism behind is astaxanthin exhibits the inhibition of lipid per oxidation and regulates oxidative stress associated genes [4]. Astaxanthin is proved to be a strong suppressor of inflammatory mediators like TNF-α, and IL-1, thereby jamming the nitric oxide synthesis and NF-B-dependent signalling pathway [28][47][40]. Also, it decreases the inflammatory mediators like MAPK, IL-6,by regulating the NF-B cascade in microglial BV-2 cell line [22].These studies certified that alternative use of astaxanthin as adjuvant in AD treatment diminished the microglia activation responsible for pro-inflammatory cytokines liberation having beneficial fallout in neural health of affected patients [38].Age related reduced activity of endogenous antioxidant enzymes can be overcome by astaxanthin supplementation, thus enhancing and supporting the SOD enzyme [35].When mice were treated with astaxanthin supplementation for 30 days (2mg/kg of mice),decreased advanced protein oxidation product (APOP),glutathione, malondialdehyde (MDA) levels and lipid peroxidation levels with increased SOD and catalase activity in specific brain areas of cerebellum, frontal cortex, striatum and hippocampus were observed [1].In PC12 Neuronal cells, beta-amyloid (30μM) induced neurodegeneration overcome by astaxanthin(0.1μM) via deactivating TNF-α, IL-1β, Caspase-3. It represses the reactive oxygen species activity [3]. Furthermore, studies unveiled that in the same cellline induced with n-methyl-4-phenylpyridinium iodide (MPP+), astaxanthin has a beneficial effect in hippocampus calcium dysfunction lowering cell death rate [51]. Significant escalation in plasticity and neurogenesis in aged people by astaxanthin prescription was achieved and also had a positive effect in treatment of reduced cognitive functions [52].In clinical trials, evidence in enhancement of behavioural execution in tasks related to hippocampus region is attained by astaxanthin given in diet which has a additive curable effect in neurodegeneration [12].Dose dependent astaxanthin treatment in neural stem cells proved that it can induce neural colony followed by ameliorating proliferation rates.When exposed to oxidative agents, astaxanthin leads to the proliferation thereby upregulating CDK2 and inhibiting apoptosis in neural progenitor cells [22].

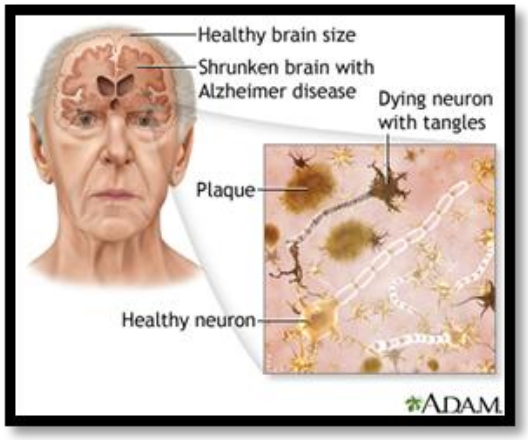

Fig 5. Pathophysiology of Alzeimer's disease(Source: https://www.mountsinai.org)

III.AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis (ALS) commonly called as "Lou Gehrigs disease" is a fatal neurological disorder catagorized by arapid loss of motor neurons located at the bulbar or spinal

levels. It mainly affects the voluntary movements that are linked to motor neurons. At last, it results in the restless muscle movement followed by weakness and the affected individual cannot control their voluntary movements. Two forms of disease exists, one is sporadic which is a sudden onset of disease and another is familiar type, genetically inherited one. Both types occurs at varying rate in which first type occurs between 50-65 years spontaneously and second type happens at a lesser rate of 5-10% worldwide. In reality, the affected rate of few geographical areas like Japan and South west new guinea is quite higher which is 50-100 times than all over the world [52]. Many studies revealed that ALS is caused by unsystematic immune response, protein trafficking, high levels of glutamate discrepancy. The foremost reason is gene mutation of cu/zn superoxide dismutase 1 (SOD1) which is a cytosolic enzyme ubiquitous that effectuate ROS homeostasis[5].Misfiling of SOD1 makes structural uncertainty caused by more than 110 mutation in the SOD1 gene suggesting neural toxicity and depleting counter-ant oxidative mechanism in this diseased condition [48].Free radical mediated oxidative damage can be compensated by natural nutrient derived enzymes and components such as vitamin E, astaxanthin and vitamin C.Among all other antioxidants, astaxanthin rescue thediethyldithiocarbamate (DDC) induced defected neurons in rat spinal neurons which showed inhibited neurite growth caused by high level of oxidative stress. On the other hand, very less concentration of astaxanthin (100nM) than other antioxidants (1mM) is sufficient for the effectual and specific treatment for endogenous oxidative stress induced motor neural degeneration. Dose efficacy at lower amounts makes astaxanthin more unique in breaking the lethal disease bond in ALS affected patients [16].

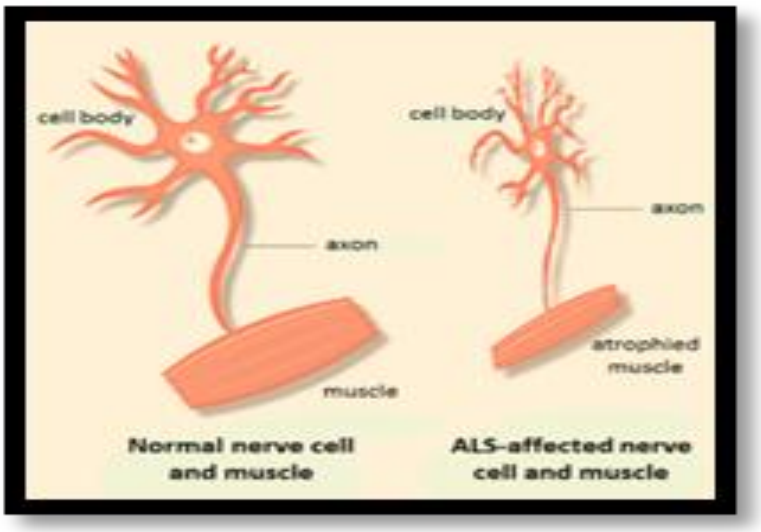

Fig 6. Path physiology of amyotrophic lateral sclerosis (ALS) (Source:https://www.universiteitleiden.nl)

CONCLUSION

Beyond marine mysteries, astaxanthin with its uncountable beneficial effects, is one of the nature's evolutionary boon in response to the micro-algal stress conditions. Furthermore, it has a remarkable health benefits against UV-induced DNA damage in skin, cardiovascular disease, obesity, hypertension, gastrointestinal & liver diseases, macular degeneration in glaucoma and cataracts as well as having anti-diabetic potential, anti-aging in human health[3][5][13].Excluding health benefits, it is also used as a natural colour additive in food industry. In addition to that, it plays a pivotal role in aqua farming. Especially in salmon farming, astaxanthin is the proven nutrient key ingredient in animal feed for effective pigmentation as well as disease free fishes. Both natural and synthetic forms of astaxanthin has high demand in last decades paving way for genetic engineering to meet the global commercial need of worldwide customers and natural product industries. The global market of carotenoid is 1.20 billion USD which is expected to

attain 1.53 billion by 2021 with CAGR of 3.78% in-between 2016-2021 [14].Treatment of neurological disease is quite challenging due to the blood-brain barrier which hinders the entry of bioactive compounds with higher molecular weight (larger molecules).This condition needs an effectual compound that can pass through this barrier even with smaller molecular weight. In addition to that, this entry can only be achieved when the compound is more potent and efficient even in smaller concentration as well as having less molecular weight, mostly failed by many antioxidants. Being a strongest antioxidant among all other arytenoids, astaxanthin is more suitable to compete with these challenges. Promising action in reversing neurodegeneration of astaxanthin makes this compound as a multitargeted powerful drug for age related neurological diseases such as Parkinson's, Alzheimer's, even lethal ALS.Bioavailability and safety doses of astaxanthin is overwhelming due to abundant marine sources as well as the extraordinary efficacy even in nano doses. Both *in vivo* and *invitro*neurologicalstudies confirms that the results are much more encouraging in which natural marine astaxanthin can be suggested as a super brain nutrient in diet that fights neuronal apoptosis, oxidative stress and brain aging. Thus, marine based super nutritive astaxanthin is the best remedy to unfold the neuro-pathophysiological riddles.

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Conflict of Interest

None of the authors have any conflicts of interest to declare.