



(REVIEW ARTICLE)



The role of astaxanthin in oxidative stress derived diseases

Madhurima Mahanti *

Department of Home Science, University of Calcutta, West Bengal, India.

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Abstract

Astaxanthin, a microalgal carotenoid is basically beneficial because of its multi-beneficiary effect on health. Nowadays, due to environmental pollution, sedentary lifestyle, unhealthy food habits etc are influencing the production of ROS in the body, which are reaching at their peak and harm different organs, resulting in different dreaded and degenerative diseases. Astaxanthin being a powerful antioxidant than other carotenoids act as a safe-guard to different organs that are affected by oxidative stress. In this review, detailed insight of the preventive role of Astaxanthin in various diseases is to be discussed.

Keywords: Microalgal; Carotenoid; ROS; Antioxidant; Degenerative diseases; Sedentary lifestyle

1. Introduction

Over the years there have been significant updates and breakthroughs in the world of Nutrition. Carotenoid Astaxanthin is one of the examples of these new breakthroughs. Carotenoid is not an unknown term in the world of Nutrition but the application of Astaxanthin has drawn the attention of people recently.

The application of Astaxanthin is not only bound to the cosmetic industry, food industry but also applicable in the pharmaceutical and nutraceutical industry. Besides the natural sources, the beneficial use of Astaxanthin biomass and extracted powder as a new innovative nutritional supplement which has a free radical scavenging property has drawn the attention [1]. Besides being effective to oxidative stress derived diseases, the other main focus is on Astaxanthin's potential as an anti-cancer and anti-tumour agent which opens a broad area for cancer research and chemotherapy.

2. What is astaxanthin??

3,3'-dihydroxy- β , β -carotene-4,4'-dione is popularly known by its common name as Astaxanthin. It is one of the xanthophylls, carotenoids that are Oxygenated-derivatives of carotenoids that include β -cryptoxanthin, Lutein and Zeaxanthin [2]. Astaxanthin is basically a reddish orange pigment with some other characteristics like it is soluble in lipid and keto-carotenoid in nature because of the presence of carbonyl or ketone groups in its structure [3][4]. Astaxanthin was first observed by Kuhn and Sorensen from a marine crustacean lobster [5].

Shrimps and crabs contain Astaxanthin that is surrounded by crustacyanin protein. When there is application of heat, there is destruction of crustacyanin protein and Astaxanthin is released.

* Corresponding author: Madhurima Mahanti

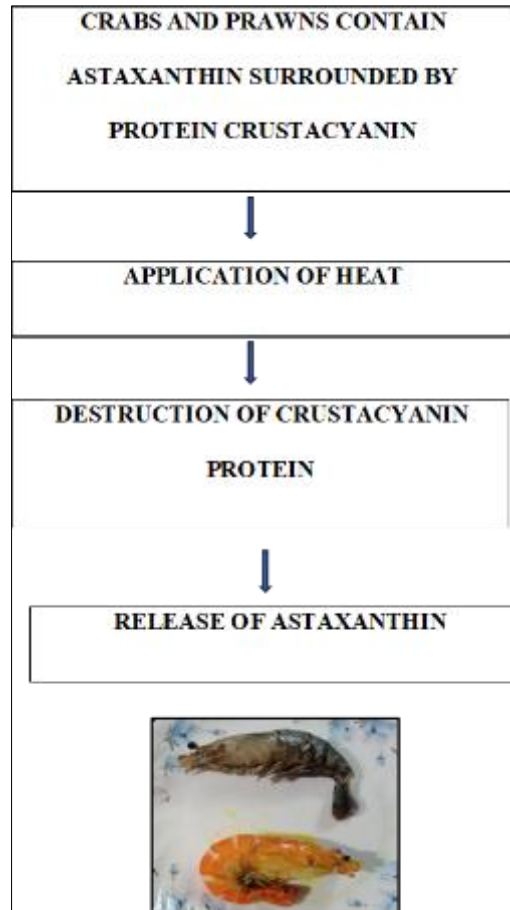


Figure 1 Conversion of colour in the prawns due to astaxanthin

2.1. Chemical structure of astaxanthin

Astaxanthin is called oxygenated products of carotenoids because of the presence of oxygen containing functional groups. Astaxanthin is composed of two terminal rings that contain one hydroxyl group and one carbonyl group in each. The two rings are joined by polyene chain [2] [5]. Polyene chain is responsible to reduce reactive oxidative stress molecules [6].

2.2. Isomers of astaxanthin

Isomers are molecules with distinct structures but identical molecular properties. Astaxanthin has two types of main isomers one is geometric isomers and other one is optical isomers. Geometric isomers include all-trans, 9-cis, 13-cis and 15-cis isomers. In optical isomers (which are the mirror images of each other) there are three forms that include a pair of enantiomers and a meso form [2] [7].

2.3. Sources of astaxanthin

Astaxanthin may be a new name but the sources of Astaxanthin are quite known. It can be found in both animal and plant kingdom. Astaxanthin can easily be found in marine environment [8]. It is present in different aquatic animals such as shrimp, lobster, trout fish, salmon, crab and asteroidean [9]. Astaxanthin is responsible for the formation of reddish colour or hue to the flesh of salmons, crabs, lobsters because of being a reddish orange pigment [10]. It has been proved that wild-caught salmon is a good source of Astaxanthin [5]. The by-products of these aquatic animals are also a good source of Astaxanthin. Specifically, the heads and the shells of the shrimps are said to be the excellent source of Astaxanthin [11].

There are different types of microalgae like *Chlorella* spp, *Dunaliella* spp, *Spirulina* spp and *Haematococcus* spp [12]. The most important and high yielding source of Astaxanthin is microalgae specifically *Haematococcus pluvialis* [13]. It is served as a food source to different marine animals. Through the food chain or transfer of nutrient, marine animals such as shrimp, lobster and crab can store or accumulate Astaxanthin.

Microalgae or Microphytes are unicellular, autotrophic-photosynthetic algal microorganisms. They can be either prokaryotic or eukaryotic [14]. Microalgae can be found in internal environment as well as in the external environment [15]. There is a growing interest to supply Astaxanthin in the form of biomass of microalgae. Biomass means dried cell of microorganisms. Microalgal biomass is a new alternative to nutritional supplements. It is generally recognised as safe and get acceptance by people. Application of Astaxanthin is common in the form of soft gels, biomass and granulated powder besides natural dietary sources. Astaxanthin biomass can be incorporated into different foods like smoothies, puddings in the form of *Haematococcus pluvialis* extract powder [16].

For the production of biomass from *Haematococcus*, a two-step process is required. In different types of stressful condition many green algae such as *Haematococcus* can produce Astaxanthin and canthaxanthin [17]. The green microalgal *Haematococcus* strains are placed in photo bioreactors where green vegetative cells are produced. The vegetative green cells turn into red colour in open system under stress condition (high temperature, salinity) from where Astaxanthin (up to 5% of dry weight) can be collected [18].

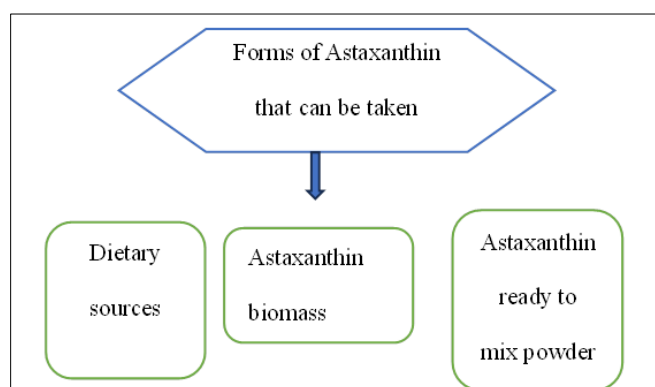


Figure 2 Forms of astaxanthin that can be taken

2.4. Absorption and doses of astaxanthin

It is important to evaluate the Astaxanthin level for human consumption. Numerous recommendations from various regulatory authorities are evaluating the maximum safe daily intake of Astaxanthin in the form of supplements. After clinical trial it is concluded that the recommended or approved doses varied in different countries and ranged between 2 to 24mg [19]. The absorption of carotenoid is directly connected to nutrients. Being a lipid soluble carotenoid, the absorption of Astaxanthin increases with the consumption of dietary oils, (which is a kind of fat) and the absorption rate is slower with the consumption of low-fat diet [5]. From a study on the rat called rat single pass intestinal perfusion study, it is observed that jejunum is the main area for the absorption of Astaxanthin [20].

3. What is oxidative stress and the role of astaxanthin in spectrum of diseases that are connected to oxidative stress??

Our body contains both free radicals and antioxidants. To maintain the body function there must be an established relationship between free radicals and antioxidants [21]. Free radicals are produced as a part of normal cell metabolism. For example, we continuously receive oxygen for maintenance of respiratory system. Molecular oxygen itself a free radical. On the other hand, some antioxidants are naturally present in the body and some antioxidants are supplied to the body by the consumption of plant-based foods. Free radicals contain unpaired electron which can easily donate or accept electrons and becomes more reactive.

Oxidative stress is defined as excess production of ROS due to imbalance between free radicals and antioxidant in the body. This can be the cause of damage to different organs and results in various diseases. Reactive oxygen species are formed as a result of poor eating habits, excessive pollution, or diseases [22].

Astaxanthin is protective against oxidative stress which is the key cause of different types of diseases in human body because oxygen free radicals attack on different components of biological properties in human body just like lipid component of cell membrane and DNA [22]. We know oxidative stress is interconnected to different types of chronic and sometimes non-communicable diseases just like ocular diseases, cardiovascular diseases, central nervous system related disorders etc. Astaxanthin arouses transcription factor Nrf2 (nuclear factor erythroid 2 related factor 2) which is proved to regulate antioxidant responses [9].

3.1. Review on different beneficiary effects of astaxanthin against oxidative stress affected organs

The background of this paper is actually based on thorough review of original studies all over the world by several researchers and scientists well given immense insight to complete the following reviews in brief.

Astaxanthin is effective towards health because of its antioxidant, antitumor, anti-inflammatory, neuron-protective, optic-protective properties [2]. Natural Astaxanthin is way more potential than the synthetic Astaxanthin. Synthetic Astaxanthin has economical and financial values but Astaxanthin found naturally is more effective towards human health perspective [23]. People are familiar with some known antioxidants like Beta-carotene, Ascorbic acid and Tocopherol. But these known antioxidants have low free radical scavenging property than the unknown Astaxanthin. The antioxidant property of Astaxanthin is 54, 14, 65 times more than the Beta carotene, Vitamin E and Vitamin C respectively [24].

3.1.1. Brain health

Nervous system contains both peripheral nervous system and central nervous system. Brain and spinal cord, these two are the main components of central nervous system whereas the peripheral nervous system is composed of somatic and autonomic nervous system. The central nervous system is highly affected by reactive oxygen species because there are different types of glial cells in the CNS that can cause neuro-inflammation by increasing the ROS and cytokines which are responsible for brain damage. Besides this, CNS has not the ability to make more neuronal cells. Astaxanthin increases the formation of neuronal cells by improving the gene expression of different cytoskeletal protein such as MAP-2, BDNF, GAP-43. MAP-2(Microtubule Associated Protein 2) [10].

Astaxanthin is also effective towards Alzheimer’s disease. Alzheimer is the result of high accumulation of Beta-amyloid protein. This protein generally stored in the hippocampus in the temporal lobe and cerebral cortex .This protein specifically increases reactive oxygen species and reactive nitrogen species [25]. CNS and peripheral nervous system are separated from each other by blood brain barrier. Blood brain barrier prevent the circulation of different toxic products. Astaxanthin can cross the blood brain barrier because of its lipid solubility and it is stored in the hippocampus situated in the temporal lobe and cerebral cortex and helps to reduce the proper functioning of the reactive oxygen species and nitrogen species by its free radical scavenging property.

The other positive effects of Astaxanthin are to reduce the other harmful substances like oxidation product MDA (malondialdehyde) which are associated with destruction of neuronal cells and Astaxanthin also disrupts acetylcholine esterase which breaks down the acetylcholine neurotransmitter, is associated with the transport of signals from brain to muscles [26] [27].

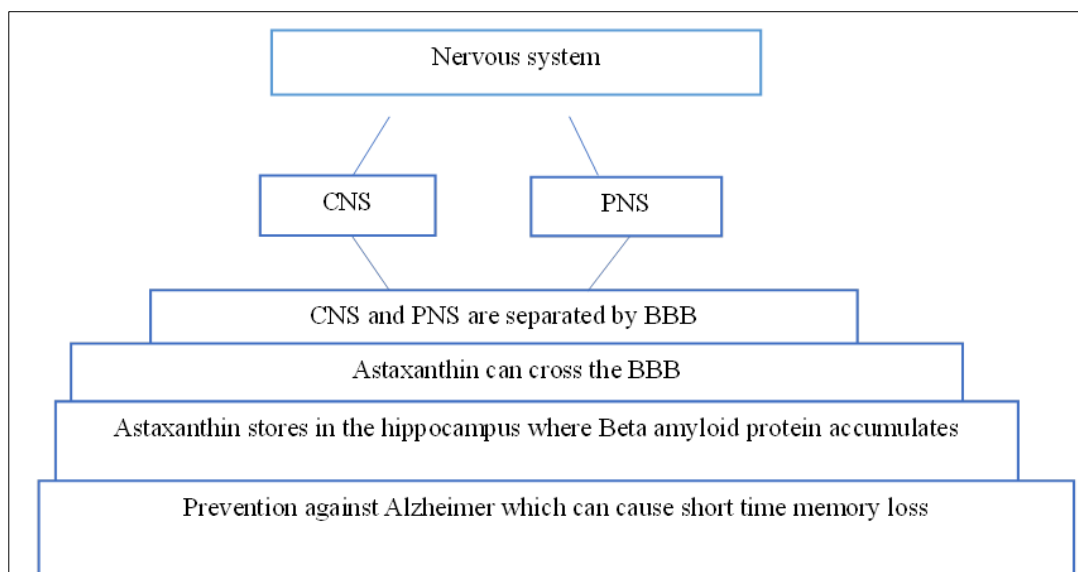


Figure 3 The relationship between astaxanthin and Alzheimer

3.1.2. Optic health

Eye health is very important to maintain daily lifestyle. Oxidative stress can occur internally and externally. Continuous exposure to sunlight, ultra violet rays and pollution as well as different biological mechanism can cause the formation of ROS that affects the eyes [28].

Retina and macula both contain photoreceptors and the main function of the photoreceptors is to detect light and need high oxygen. Both of these conditions lead to the formation of oxidative stress and can cause different eye related disorders like glaucoma, optic neuropathies and age-related macular disorders that can cause vision loss [8].

Inflammation in the middle eye layer can cause Uveitis. Vision loss and eye pain are common symptoms of Uveitis. Cellular infiltration, an increase in protein permeability and the up regulation of inflammatory cytokines and chemokines like MCP-1, MIP-1 in the aqueous humour and uveal regions all contribute to the breakdown of blood aqueous barrier in Uveitis. Up regulation of inflammatory cytokines and chemokines increase the production of ROS [8]. Astaxanthin being a pro antioxidant prevents the breakdown of blood aqueous barrier.

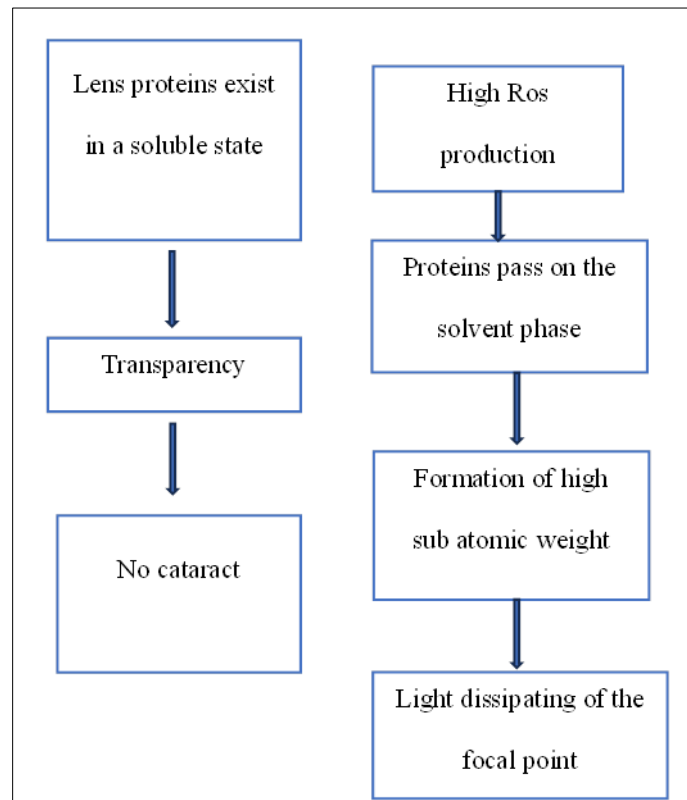


Figure 4 Cataract/no cataract formation (In the presence /absence of ROS)

3.1.3. Skin health

Besides our terraneous world there is much more insight in the marine world that is truly beneficial to human health. Astaxanthin is one of them. UV rays are constantly coming in contact in our daily life because of the presence of sun. UV radiations are of two types UV-A, UV-B. UV-B is stronger than UV-A because of its short wavelength. UV radiation specifically UV-B can damage different molecular structures such as DNA by the production of cyclobutane pyrimidine dimers. On the other hand, UV-A arrives at the most significant skin tissues [29]. It supports oxidative damage by interacting with intracellular components like chromophore riboflavin or membrane bound enzymes, but it does not directly cause DNA damage. Reactive oxygen species can alter and destroy DNA thus can lead to skin aging by the production of matrix metalloproteinases that destroy the collagen and elastin in the dermal skin layer [30].

Astaxanthin is proved to be effective against atopic dermatitis by inhibiting the gene expression of interleukin-6 and tumour necrosis factor. Astaxanthin helps to improve the water and glycerol transport by improving the activity of water channel aquaporin-3 activity [31].

3.1.4. Cardiovascular health

Cardiovascular-disease involves heart and blood vessels related disorder. Cardiovascular diseases involve Atherosclerosis, ischemia etc. These disorders are result of excessive production of oxidative stress related products such as ROS and RNS [32]. Astaxanthin supplementation improves endothelial function that involves maintaining blood flow and thus reduces a cluster of risk factors that are likely to develop heart related disorders [33].

Several studies with rabbit showed that Astaxanthin consumption declines the formation of lipid peroxidation products. In a study with myocardial ischemia reperfusion model that involves rat showed that a combination of Astaxanthin, zeaxanthin and lutein in safflower oil is proved to be effective to maintain heart function.

Hypertension is one of the major complications in cardiovascular diseases. In a study with spontaneous hypertensive rats, it is found that Astaxanthin is helpful to reduce the blood pressure in those hypertensive rats [34]. Astaxanthin helps to reduce the low-density lipoprotein and increases the level of high-density lipoprotein that is beneficial to reduce the formation of plaques in the arteries. Thus, Astaxanthin is effective to prevent hyperlipidemia, a condition characterized by high levels of cholesterol and triglycerides in the blood [35].

3.1.5. Gut health

Helicobacter pylori causes peptic ulcer. In peptic ulcer the lining of the stomach or the duodenum are destroyed. Lesion in the stomach and duodenum can produce ROS that can lead to inflammation. *Helicobacter pylori*, the reason of gastric inflammation affects the stomach by increasing the activity of IL -8 expression level and NF- κ B. Interleukin 8 can activate neutrophils that can deteriorate tissue injury and thus increases the production of ROS. Astaxanthin reduces the activity of IL-8 by the production of PPAR- γ and catalase in the gastric epithelial cells that are infected by *Helicobacter pylori* [36].

3.1.6. Muscle Health

Exercise is essential to build muscular flexibility and muscular endurance. But sometimes heavy or prolonged exercises can lead to the formation of reactive oxygen species and reactive nitrogen species. The more prolonged or heavy the exercise is, the greater the production of ROS and RONS [37]. Astaxanthin being an effective antioxidant prevents the formation of these molecules as well as has a beneficial effect on muscles by improving exercise performance. Oxidative stress destroys different organs including the muscles. Oxidative stress specifically causes damage to the muscle tissue that can lead to muscle tissue damage commonly known as Sarcopenia. Sarcopenia is the major cause of osteoporosis, physical disability etc.

Not only overuse of muscles is harmful but also prolonged no use of muscles can lead to muscle atrophy [38]. Inactivity induced oxidative stress has a direct negative effect on the formation of muscle contractile proteins such as actin and myosin. Astaxanthin is effective to reduce the activity of oxidative stress that is involved with degradation of these muscle contractile proteins [39]. Aoi et al proved the efficient effect of Astaxanthin on skeletal muscle through the in vivo studies with 8-week-old ICR mice. Aoi et al also took three forms of Astaxanthin, one is esterified form of Astaxanthin from *Haematococcus pluvialis*, second one is non-esterified form of Astaxanthin basically from synthetic Astaxanthin, third one is non-esterified form of Astaxanthin from *Phaffia rhodozyma*. Mice that were taken for examination, subjected to exercises given three forms of Astaxanthin (dose of 0.02% each) for five weeks. In the examination it is proved that Astaxanthin which is derived from *Haematococcus pluvialis* was more effective towards skeletal muscle health [38].

3.1.7. Reproductive health

New prospect of Astaxanthin is that it has beneficial effect on reproductive health of male. Astaxanthin improves various functions that are related to reproductive system. Astaxanthin improves the overall functionality of sperms to fertilize the ovum. The spermatozoa deposited at the mouth of uterus then cervix and then the body of uterus and facilitates the fertilization process. Astaxanthin also improves the release of enzymes which help to soften the zona pellucida [40]. It also helps to form different sex organs. In old age prostate problem is common. Astaxanthin helps to comfort this problem.

Cancer, a dreaded disease affects different organs. For the treatment of cancer, chemotherapy is much needed. In chemotherapy different agents are used, Methotrexate is one of them. Methotrexate can affect the reproductive organs in males by reducing the quantity and quality of sperms and also by reducing the level of superoxide- dismutase which has the ability to reduce the ROS [41]. Astaxanthin helps to maintain the production of superoxide dismutase which has antioxidant responses.

Ovaries composed of follicles are the main organs in the female reproductive system. Granulosa and theca cells are the parts of follicles. These two components of follicles are the main cause of secretion of estrogen and progesterone. ROS affect the ovaries by affecting the development process of follicles. In a study with 3- nitropropionic acid affected ovary, it is found that Astaxanthin suppresses the level of sialic acid which is the result of 3- nitropropionic acid accumulation in the ovary that can decrease the antioxidant responses [42].

3.1.8. Breast cancer and Glioblastoma

Melanoma cells are metastatic and highly invasive tumours that frequently exhibit molecular modifications that contribute to multidrug resistance. Ordinary treatment is not at all effective for longer duration, requiring a through quest for new options. Due to the safety, acceptability, tolerability, carotenoids derived from microalgae such as Astaxanthin has recently been investigated as an antimelanoma agent [43]. Astaxanthin has an emerging prospect against breast cancer. In cancer including breast cancer, the cells are migrating from one cell to another. Thus, the cancer is spread to all over the body if not treated in earlier stage. Astaxanthin not only blocks or reduces this migration of breast cancer cells but also reduces hyperplasia of breast cancer cells [44].

Glioblastoma, one of the types of brain tumour in central nervous system. Glioblastoma basically occurs in the glial cells in CNS. CNS and peripheral nervous systems are divided by BBB. Astaxanthin has the ability to cross BBB and shows its antitumor activity by protecting the blood vessels and by reducing the movement of three types of Glioblastoma cells [45].

To examine the antitumor activity BALB/c mice are taken and fed with Astaxanthin three weeks before and one weeks before introducing methylcholanthrene-induced fibrosarcoma (Meth-a tumour cell) in their bodies. Three weeks after introducing tumour cells, it is observed that tumour size and weight are relatively low in the mice that are fed with Astaxanthin respectively than the mouse which is not fed with Astaxanthin before [46]. Besides this, it also inhibits the production of tumour cells by stopping the formation of exact copy of tumour cells and also by destructing the production of tissue melting proteins from where tumour can be produced [6].

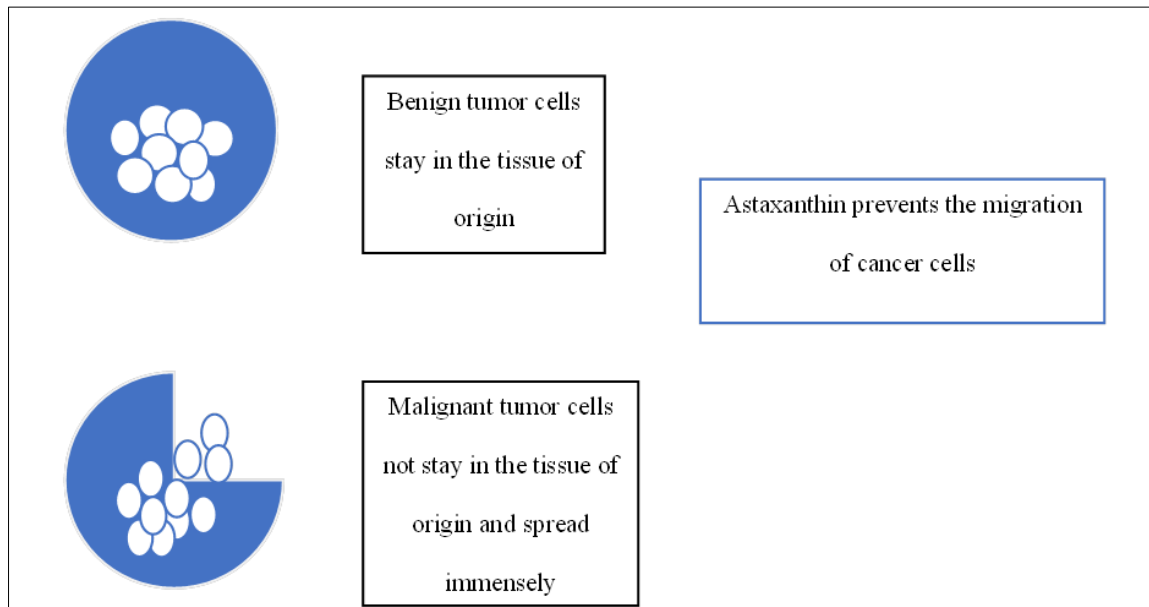


Figure 5 Benign tumor vs Malignant tumor

3.1.9. Covid -19

There is a close relationship between oxidative stress and corona virus. COVID- 19 is the result of increased level of pro inflammatory cytokines. Different respiratory disorders like pneumonia, bronchitis are associated with COVID-19. The inflammatory cytokines cause disproportion between repair mechanism and immune system that weaken the body. COVID -19 shows its adverse effects on the weakened body [47]. Corona Virus specially affects the lungs by increasing the production of NADP oxidase and NO oxidase. SARS-CoV-2(2019-nCoV) affects the whole world by expressing its dreaded effect on Human health. In COVID-19, different agents that cause inflammations were elevated like interleukin-6, tumour necrosis factor, IL7, IL 8 etc [48]. These pro inflammatory agents can cause ARDS (acute respiratory distress

syndrome). Astaxanthin is highly effective to boost the immune system by declining the formation of different inflammatory agents.

4. Conclusion

Through the detailed discussion and critical evaluation, we came across several positive effects of Astaxanthin. Oxidative stress combating property makes Astaxanthin an effective carotenoid. Astaxanthin by the depletion of different inflammatory cytokines and chemokines boosts up the immune system. So, the implementation of Astaxanthin in the diet is required either in the form of natural sources or in the form of supplements. Being beneficial to the alimentary system and neuron system, it also has immense beneficial prospect on reproductive systems and cardiovascular system. The role of Astaxanthin to suppress the migration of malignant cancer cells has drawn special attention on the future studies. The effectiveness of Astaxanthin is higher than other carotenoids. This property makes Astaxanthin more potential carotenoid. Besides dietary sources emphasis should be given on the production of supplementary and nutraceuticals forms of Astaxanthin in the market.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest.

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