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Role of Antioxidants in the Prevention of Cancer: A Comprehensive Review

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Abstract:

Cancer is a complex and pernicious disease that continues to be a significant global health concern. Preventive strategies, including dietary interventions, have gained attention in recent years due to their potential to reduce cancer risk. Oxidative stress, arising from an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defense mechanisms, has been implicated in cancer initiation and progression. Antioxidants, naturally occurring compounds found in various foods and supplements, have emerged as promising agents in cancer prevention. They play a significant role in neutralizing reactive oxygen species (ROS) and protect cells from oxidative damage. A well-balanced diet rich in fruits, vegetables, whole grains, nuts and seeds are the reliable source of antioxidants. Specific antioxidants, such as carotenoids, flavonoids, and polyphenols, are abundantly present in these dietary sources.Observational studies have consistently demonstrated an inverse relationship between antioxidant intake and the risk of various cancer types, including lung, breast, prostate, and colorectal cancer. Moreover, randomized controlled trials have shown promising results in reducing cancer incidence, although conflicting findings exist.This comprehensive review aims to provide a detailed analysis of the role of antioxidants in cancer prevention, elucidating their mechanisms of action, dietary sources, and potential limitations.It will also serve as a valuable resource for researchers and clinicians in understanding the role of antioxidants in cancer prevention and developing preventive measures to minimize the risk of cancer.

Keywords:

Antioxidants, astaxanthin, beta- carotene,cancer, catechins, flavonoids,oxidative stress, polyphenols,reactive oxygen species (ROS), zeaxanthin.

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1. Introduction:

Cancer is a complex and multifactorial disease characterized by the uncontrolled growth and spread of abnormal cells. Oxidative stress, caused by an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms, has been implicated in the development and progression of cancer. Antioxidants play a critical role in neutralizing (ROS) and protecting cells from oxidative damage, making them potential candidates for cancer prevention [1]. In recent years, there has been increasing interest in the role of antioxidants in cancer prevention. Understanding the mechanisms and potential benefits of antioxidants in cancer prevention is of great importance [2]. According to the World Health Organization (WHO), cancer is one of the leading causes of death globally, and the number of new cancer cases is projected to increase by about 70% over the next two decades [3].This review discusses the role of oxidative stress and oxidative damage in carcinogenesis. It highlights the involvement of reactive oxygen species (ROS) in DNA damage, mutagenesis, and the development of cancer.

2. Role of Oxidative Stress and Oxidative Damage in Carcinogenesis

Reactive oxygen species, including superoxide anion (O_2•-), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH), are generated as byproducts of normal cellular metabolism. However, excessive production of (ROS) can cause oxidative damage to cellular components, leading to DNA mutations, activation of oncogenes, inactivation of tumor suppressor genes, and dysregulation of cellular processes involved in cancer development [4].

3. Oxidative DNA Damage and Carcinogenesis:

Oxidative stress-induced DNA damage is a crucial event in carcinogenesis. ROS can directly attack DNA, leading to the formation of DNA adducts, strand breaks, and base modifications. These DNA lesions can result in mutations and chromosomal aberrations, contributing to the initiation and progression of cancer [5].

4. Antioxidant Defense System and Carcinogenesis:

The antioxidant defense system, comprising of enzymatic and non-enzymatic antioxidants, acts as counterbalance (ROS) and protect cells from oxidative damage. Dysregulation of the antioxidant defense system can lead to increased oxidative stress and contribute to carcinogenesis. Genetic variations in antioxidant enzymes and decreased antioxidant capacity have been associated with an elevated risk of cancer [2].

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5. Role of Antioxidants in the prevention of Cancer

5.1.1 Catechins

Catechin, derived from the catechu extract of *Acaciacatechu* L.,3, 3', 4', 5, 7- is a pentahydroxyflavone compound with two stereo- isomeric forms, namely (+)-catechin and its enantiomer. It serves as the chemical family name for compounds derived from catechin, collectively known as tea polyphenols. These tea polyphenols possess antioxidant properties due to their ability to effectively neutralize free radicals. Among the tea polyphenols, epicatechin gallate (ECG) exhibits the highest potency as a radical scavenger, followed by epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin (EC), and catechins[6].Please refer to the figure no 1 (biochemical structure of catechin).

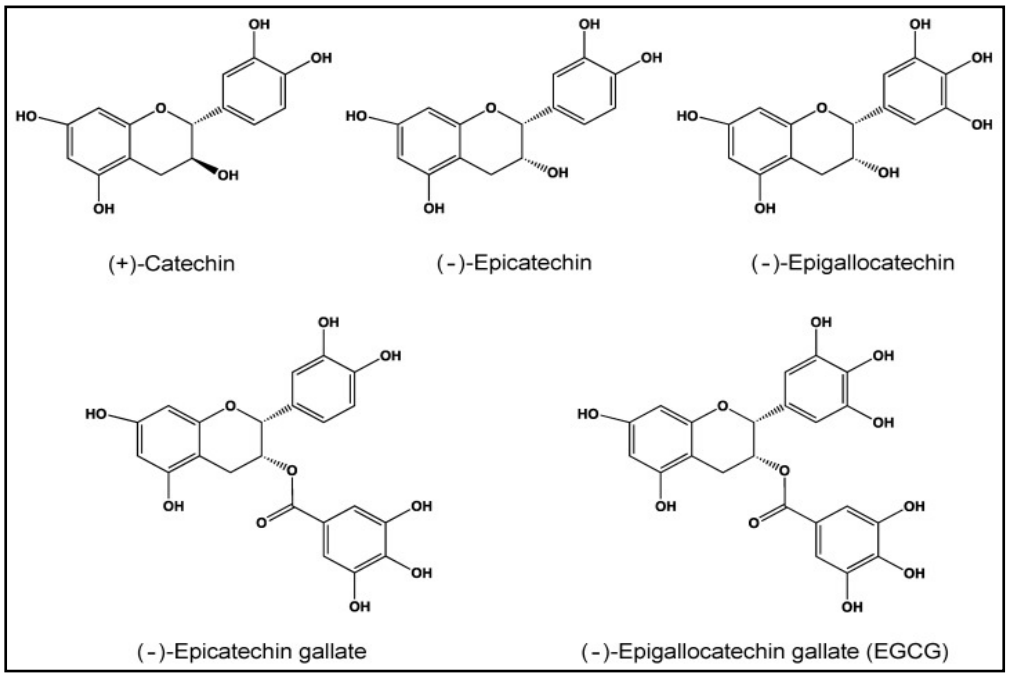

Figure 1: Biochemical structure of Catechin [Isemura, M. (2019), [6]

5.1.2 Food Sources of Catechins

Tea, derived from the leaves and buds of *Camelliasinensis*, is a prominent source of catechins. The major catechin found in tea is (−) epigallocatechin-3-gallate (EGCG). EGCG offers numerous health benefits, including its potential as an anticancer, anti-obesity, antidiabetic, anti-cardiovascular, anti-infectious, hepatoprotective, and neuroprotective agent. Other food sources that contain catechins include apples, pears, persimmons, apricots, broad beans, wines, cacaos, grapes, and berries [6]. Please refer the figure no 2 food sources of catechins.

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Food	Catechins (mg/100g)	Catechins (mg/serving)
Apple	10-43	20-86
Apricot	10-25	20-50
Beans	35-55	70-110
Black tea	6-50	12-100
Blackberry	9-11	9-11
Cherry	5-22	10-44
Chocolate	46-61	23-30
Cider	4	8
Grape	3-17.5	6-35
Green tea	**10-80**	**20-160**
Peach	5-14	10-28
Red raspberry	2-48	2-48
Red wine	8-30	8-30
Strawberry	2-50	2-50

Figure 2: Sources of Catechins widely distributed in Foods [Sari, L. M. (2019), [7]

5.1.3 Mechanism of Action

Numerous human epidemiological and clinical studies have investigated the potential anticancer effects of tea, supported by cell-based and animal experiments. However, conflicting results have also been reported. Detailed molecular mechanisms have been proposed to explain how EGCG and other catechins exert their effects. One particularly intriguing mechanism involves the role of reactive oxygen species (ROS). EGCG is believed to have dual actions on ROS, acting both as an antioxidant and a pro-oxidant. Evidence suggests that EGCG can eliminate ROS by scavenging while also enhancing ROS production. The pro-oxidant activity is thought to be associated with the catechin-quinone redox system. Catechins demonstrate antioxidant efficacy through various mechanisms, including scavenging ROS, chelating metal ions, inducing antioxidant enzymes, inhibiting pro-oxidant enzymes, and promoting the production of phase II detoxification enzymes and antioxidant enzymes [7].

5.1.4 Role of Catechins in Cancer Prevention & Treatment

The role of catechins in cancer prevention and treatment has been extensively studied, with various mechanisms of action being explored. These mechanisms include anti-inflammatory and antioxidative effects, the induction of drug-metabolizing and detoxifying enzymes, promotion of DNA repair, and modulation of tumor suppressor genes. Among the catechins, particularly EGCG, have been extensively investigated and shown to exhibit diverse anticancer effects. These effects include the induction of apoptosis (programmed cell death) and cell-cycle arrest, inhibition of NF-jB (a transcription factor involved in inflammation), suppression of overexpression of cyclooxygenase-

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2 (COX-2), and inhibition of the activation of different types of receptor tyrosine kinases (RTKs). The regulation of apoptosis is a crucial step in both the prevention and treatment of cancer, as it helps eliminate precancerous and cancer cells and serves as a protective mechanism against cancer. Experimental studies conducted on cells have demonstrated that EGCG has the ability to inhibit the growth of various types of mouse and human cancer cells by inducing apoptosis [7, 8]. Please refer to the figure 3 for modulation of cell signaling pathways by catechins.

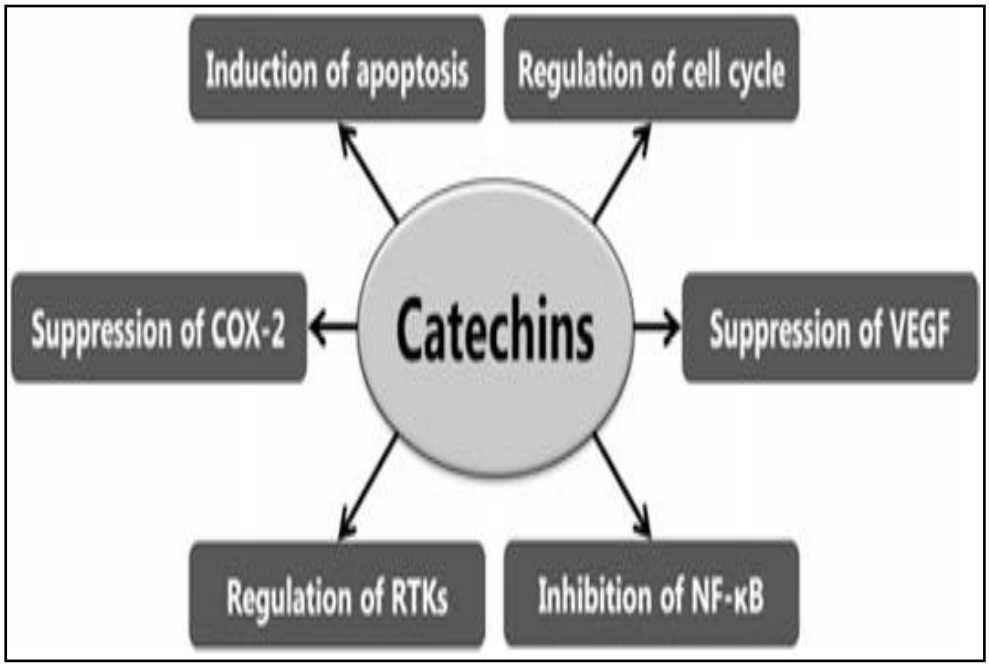

Figure 3: Modulation of cell signaling pathways by Catechins [Shirakami, Y., (2016), [8]

5.2.1 Beta-carotene

Carotenoids are naturally occurring pigments found in various fruits and vegetables, responsible for their vibrant colors [9]. Among the numerous carotenoids present in our diet, many exhibit antioxidant properties. One extensively studied carotenoid is beta-carotene, which is abundant in most fruits and vegetables in many countries. It serves as a precursor to retinol (vitamin A) and has shown potential in preventing cancer and inhibiting its growth.As an antioxidant, beta-carotene plays a crucial role in protecting DNA from damage caused by free radicals [10]. Moreover, it demonstrates the ability to induce cell differentiation and apoptosis, particularly in the early stages of tumor formation, thereby hindering cancer development. Additionally, beta-carotene enhances the activity of the immune system by promoting the release of natural killer cells, lymphocytes, and monocytes, which further aids in combating cancerous cells.Structurally, beta-carotene is a cyclic carotene derived from the dimerization of all-trans-retinol [11]. Its unique properties and mechanisms of action make it a promising candidate for potential use in cancer prevention and therapy, making it a subject of significant scientific interest and investigation in the field of

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oncology.

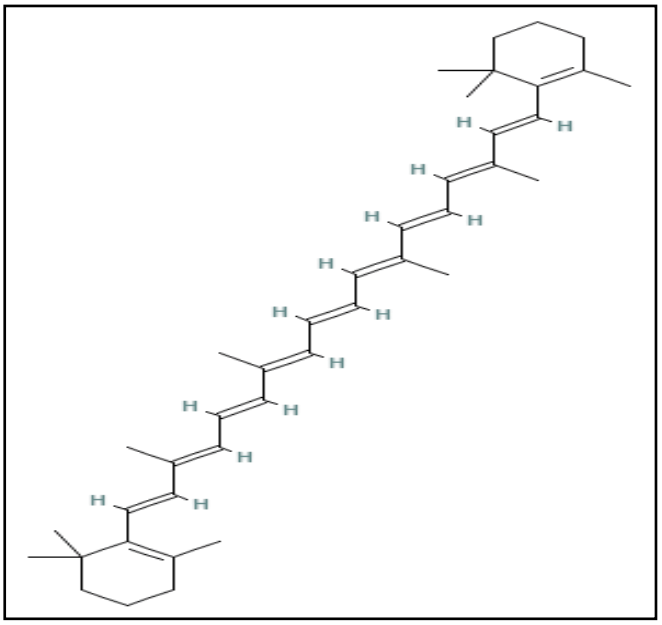

Figure 3: Biochemical Structure of Beta-carotene [National Center for Biotechnology Information. (2023), [10]

5.2.2 Sources

The major food sources of beta-carotene include yellow, red, and green (leafy) vegetables such as spinach, carrots, sweet potatoes, and red peppers. Fruits like mangoes, papayas, and apricots are also rich sources of beta-carotene.

5.2.3 Mechanism of Action

Beta-carotene plays a significant role in cancer prevention, which can be attributed to its conversion into Vitamin A and retinoids. Several epidemiological studies have shown a decreased cancer risk with higher intake of beta-carotene, whereas the same associations were not observed with preformed Vitamin A intake. This suggests that beta-carotene may have unique cancer-preventive properties beyond its conversion to Vitamin A.One of the mechanisms through which beta-carotene exerts its cancer preventive effects is its potential as an antioxidant, effectively scavenging free radicals. By protecting cells from oxidative damage, beta-carotene helps prevent DNA damage, a crucial step in the development of cancer. This underscores the importance of non-enzymatic and enzymatic antioxidants, including beta-carotene, in safeguarding cellular integrity.Additionally, beta-carotene is known to enhance immune function, contributing to its cancer preventive action. Furthermore, it impacts cellular communication mediated by gap junctions and influences the activity of carcinogen detoxifying enzymes, adding to its multifaceted anti-carcinogenic properties [12]. These multiple mechanisms of beta-carotene action collectively make it a promising agent in

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the prevention of cancer, and its incorporation into a well-balanced diet rich in fruits and vegetables may offer substantial health benefits.

5.2.4 Role of Beta-carotene in Cancer Prevention and Treatment

Epidemiological studies have consistently demonstrated that a high intake of fruits and vegetables containing abundant beta-carotene or elevated blood levels of beta-carotene are associated with a reduced risk of certain cancers. The evidence is particularly strong for lung and stomach cancers, while the findings are less consistent for breast and prostate cancers. Regarding colon carcinoma, beta-carotene's impact appears to be moderate.However, the results from intervention trials using high-dose beta-carotene supplements have been less promising. Three out of four such trials did not show a protective effect against cancer. In fact, in these trials involving high-risk populations like smokers and asbestos workers, an increase in cancer and angina cases was observed. This suggests that while carotenoids, including beta-carotene, may have health benefits when consumed at dietary levels, caution should be exercised when taking high doses of supplements, especially for individuals who smoke or are exposed to asbestos [13].

5.3.1 Astaxanthin

Astaxanthin is a red-orange carotenoid pigment with powerful biological antioxidant properties, naturally occurring in various living organisms. Its potential and promising applications in human health and nutrition have garnered significant attention. Notably, astaxanthin plays a vital role as a colorant in the crustacean and salmonid aquaculture feed industry. It belongs to the xanthophyll group of carotenoids, which includes AST, β-cryptoxanthin, canthaxanthin, lutein, and zeaxanthin. Initially discovered in lobsters by Kuhn et al. in 1938, astaxanthin was initially used for pigmentation in aquaculture. However, in 1991, it gained approval as a supplement for human food due to its reported biological activities, antioxidant features, and its role as a precursor of vitamin A in rats and fish. Astaxanthin can be sourced from various microorganisms, phytoplankton, marine animals, and seafood, such as shrimp, lobster, asteroidean, algae, fish, crustacean, trout, krill, red sea bream, and salmon. The primary source for human consumption is the *GreenmicroalgaeHaematococcuspluvialis*, which has the greatest potential for providing astaxanthin from recommended sources. The specific semi-systematic name for astaxanthin is 3, 3’-dihydroxy-beta, beta-carotene-4, 4’-dione [14].

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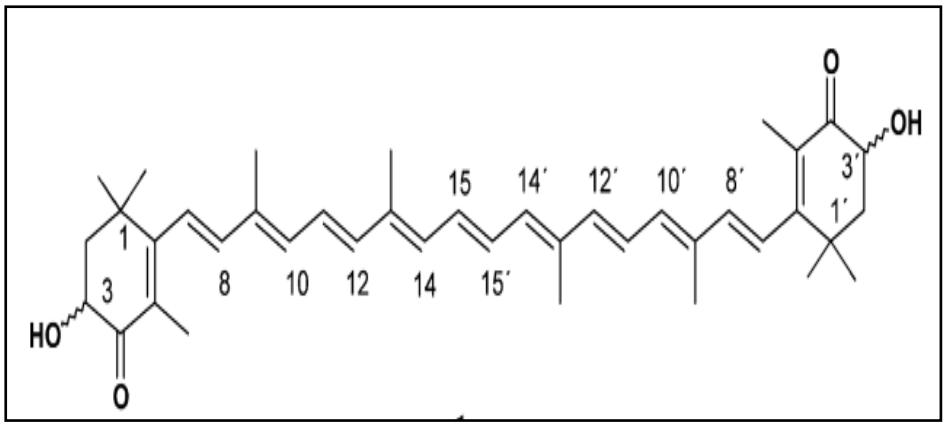

Figure 4: Biochemical Structure of Astaxanthin [Hussein, G.,*etal*, (2006), [14]

5.3.2 Sources

Astaxanthin, the predominant carotenoid pigment in aquatic organisms, is also present in certain bird species like flamingos and quails. This carotenoid is abundant in various seafood, including algae, salmon, trout, red sea bream, shrimps, lobster, and fish eggs. Similar to other carotenoids, animals cannot synthesize astaxanthin and must obtain it through their diet.

5.3.3 Mechanism of Action

AST (astaxanthin) serves as an effective defense against oxidative damage through various mechanisms, making it a valuable nutraceutical for human nutrition and healthcare. Its antioxidant capacity is remarkable due to its ability to neutralize singlet oxygen, scavenge radicals to halt chain reactions, protect cell membrane integrity by inhibiting lipid per-oxidation (LPO), enhance immune system function, and regulate gene expression. The unique molecular structure of AST allows it to capture radicals both within and outside the cell membrane. Compared to other carotenoids like α-carotene, lycopene, lutein, and β-carotene, AST exhibits greater antioxidant activity, surpassing vitamin E by over 100 times in combating LPO and approximately 550 times in neutralizing singlet oxygen. Its antioxidant activity outperforms other photochemical agents and is notably higher than alpha-tocopherol, zeaxanthin, lutein, canthaxanthin, and β-carotene. The beneficial effects of AST are attributed to its activation of the PI3K/AKT and ERK signaling pathways. This leads to the dissociation of Nrf2 from Keap1; facilitating Nrf2's nuclear translocation and activation of the Nrf2 antioxidant response elements (ARE) signaling pathway. Consequently, Nrf2-regulated enzymes like heme oxygenase-1 (HO-1), glutathione-S-transferase-α1 (GST-α1), and NAD(P)H quinine oxidoreductase-1 (NQO-1) are up regulated, providing protection against oxidative stress both in vitro and in vivo. Furthermore, AST intake has been shown to elevate antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), thiobarbituric acid reactive substances (TBARS), and peroxidase in rat liver and plasma, reinforcing its role in counteracting oxidative stress [15].

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5.3.4 Role of Astaxanthin in Cancer Prevention and Treatment

AST (astaxanthin) exhibits superior and more potent antitumor activity compared to other antioxidant carotenoids like β-carotene and canthaxanthin. It plays a crucial role in maintaining cell-to-cell communication via gap junctions, which is often lacking in human tumor cells, thereby reducing tumor cell proliferation. AST achieves this effect by up regulating the connexin-43 gene, leading to an increase in connexin-43 protein levels in mouse embryo fibroblasts. Multiple studies have reported the effectiveness of AST in inhibiting the growth of various cancer cells, including breast cancer, fibro sarcoma, melanoma, prostate cancer, liver cancer, and chemically-induced cell death. AST has also demonstrated its potential in curbing mammary tumor proliferation in both female and male mice and rats. Studies have highlighted the role of AST in enhancing the immune response by reducing lipid per-oxidation induced by stress. It exerts its anti- proliferative and anti-invasive effects through various pathways and molecules such as NF-κB, STAT3, and PPARγ. AST's down regulation of MKK1/2-ERK1/2-mediated thymidylate synthase (TS) expression is vital in enhancing pemetrexed-induced cytotoxicity in non-small cell lung cancer (NSCLC). AST has also been shown to possess significant preventive effects against large bowel carcinogenesis induced by azoxymethane and tongue carcinogenesis in rats induced by 4-nitroquinoline-1-oxide. Moreover, AST has demonstrated potential as a chemo preventive agent for bladder cancer in male ICR mice and oral cancer in male F344 rats, partly due to its ability to suppress cell proliferation [15].

5.4.1 Zeaxanthin

Zeaxanthin, a xanthophyll carotenoid, is prominently found in dark-green leafy vegetables and egg yolks. It exhibits wide distribution in various tissues, with its highest concentration in the eye lens and macular region of the retina. Although Zeaxanthin is recognized for its antioxidant properties, the specific molecular mechanisms underlying its actions remain inadequately elucidated. Nevertheless, epidemiological studies have shown a potential protective role of xanthophyll intake or status in reducing the risk of cataracts and age-related macular degeneration. Observational studies have also indicated an inverse relationship between xanthophylls, including Zeaxanthin, and the risk of specific cancers, particularly breast and lung cancers. Furthermore, emerging research suggests a potential contribution of lutein and zeaxanthin in the prevention of heart disease and stroke. Zeaxanthin exists in three stereo-isomeric forms, with (3R, 30R)-zeaxanthin being the principal form found in nature. Another form, (3R, 30S)-Zeaxanthin or meso-zeaxanthin, is absent from dietary sources, the liver, and circulation, but it is present in ocular tissues. It is important to note that humans are unable to synthesize zeaxanthin endogenously and must rely on dietary sources for its acquisition [16].

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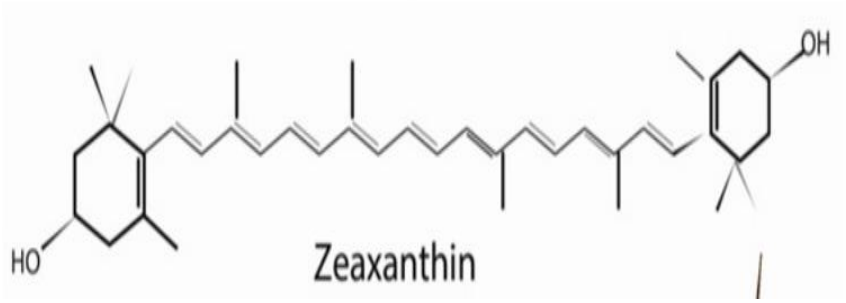

Figure 5: Biochemical Structure of Zeaxanthin [Murillo, A. G., *et al.*,(2019), [16]

5.4.2 Sources

In various food sources, lutein and zeaxanthin are commonly found together. Foods such as kale, parsley, spinach, Swiss chard, pistachios, green peas, egg yolks, cheese, wheat, red grapes, and sweet corn are notably rich sources of zeaxanthin.

5.4.3 Mechanism of Action

Zeaxanthin may have potential antimutagenic and anticarcinogenic properties, suggesting possible role in cancer prevention and treatment beyond its well-known benefits for eye health. Research studies related to carcinogenesis and cancer risk have provided insights into the potential effects of zeaxanthin in various body tissues.Studies have demonstrated that zeaxanthin, along with lutein and other carotenoids can inhibit the invasive action of rat ascites hepatoma AH109A cells when co-cultured with rat mesentery-derived mesothelial cells, showing a dose-dependent effect.In a study conducted in Finland, a lower risk of breast cancer was inversely related to serum concentrations of zeaxanthin plus lutein, and this relationship was not influenced by the presence or absence of a p53 mutation.In a cohort of male smokers, higher intake of lutein plus zeaxanthin was associated with a reduced risk of lung carcinoma. Similar findings were reported in a case-control study in Switzerland, where higher intake of lutein plus zeaxanthin was inversely associated with the risk of colorectal cancer.However, it's important to note that zeaxanthin and lutein were found to be less effective than other carotenoids like beta-carotene, canthaxanthin, or lycopene in inhibiting the growth of human DU145 prostate cancer cells [17]

6. Conclusion

It has been concluded that antioxidants, such as carotenoids like beta-carotene, lutein, and zeaxanthin, play a crucial role in neutralizing free radicals and reactive oxygen species, which are known to contribute to cellular damage and carcinogenesis. The mechanisms of action of these antioxidants involve scavenging free radicals, protecting cellular components from oxidative damage, modulating gene expression, enhancing immune function, and promoting cell

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differentiation and apoptosis.Fruits, vegetables, and other plant-based foods are abundant sources of antioxidants, and incorporating them into a balanced diet is essential for maintaining optimal health and reducing cancer risk. It is crucial to note that the outcomes of intervention trials using high-dose antioxidant supplements have been mixed, with some trials even reporting adverse effects in specific populations. Thus, it is essential to exercise caution when considering antioxidant supplementation and to focus on obtaining antioxidants through a varied and nutritious diet. Further research is required for better elucidating the complex interactions between antioxidants and cancer development, enabling the development of targeted and effective preventive strategies.

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