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Chemopreventive and therapeutic efficacy of astaxanthin against cancer: A comprehensive review

Keshamma E[1], Sridhar B T[2], Anil Kumar[3], Laxmi Kirana Pallathadka[4], Harikumar Pallathadka[4]

[1] Assistant Professor, Department of Biochemistry, Maharani Cluster University, Palace Road, Bangalore, Karnataka, India
[2] Department of Chemistry, Maharani Cluster University, Palace Road, Bangalore, Karnataka, India
[3] Department of Botany, DDU Gorakhpur University, Gorakhpur, Uttar Pradesh, India
[4] Manipur International University, Imphal, Manipur, India

Abstract
Astaxanthin is a natural product with oxidant-quenching and anti-inflammatory properties. Inflammation plays a crucial function in the propagation and survival of cancer. It can reduce the spread of malignant cells and prevent the development of inflammatory mucosal ulcers and pockets. It has been selected as a novel metastasis inhibitor. Astaxanthin causes apoptosis in several *in vitro* studies, including both oral and liver cancer cells. In the early stages of these studies, very promising findings have been produced, with expectations that human application is likely validated. Cancer-fighting evidence shows the ability of astaxanthin to combat cancer. Cancer cells expand rapidly, penetrate, migrate, and attach to healthy tissues and organs. The study is required to understand the mechanisms of action further and identify novel targets for the molecule. The author would like to clarify that this is not an endorsement of astaxanthin's actions in cancer, but rather a recommendation that further research is needed to confirm the beneficial effects of this natural product on cancer treatment. It can be used as a novel therapeutic agent for chemotherapy-induced oral mucositis. It has been selected as a Novel metastasis inhibitor. AXT inhibits the EMT pathway in colon cancer cells and can reduce breast cancer cells' proliferation and growth. In mice with AD, we observed that AST could exacerbate dermatitis and pruritus. Astaxanthin can address human health problems, including cancer, cardiovascular, and neurodegenerative diseases. It is hoped that human application is likely to be validated for use in cancer treatment. Astaxanthin can address human health problems, including cancer, cardiovascular, and neurodegenerative diseases. It can be used as a novel therapeutic agent for chemotherapy-induced oral mucositis.

Keywords: astaxanthin, cancer therapy, anti-inflammatory, apoptosis, mechanism of ast

Introduction

Astaxanthin is a bright red carotenoid pigment. It is a member of the carotenoid family and a fat-soluble oxygenated pigment. The double-stranded polyene chain with a six-stranded polar end ring, this unusual molecular structure has the excellent antioxidant ability. Astaxanthin is more polar than beta-carotene. Astaxanthin protects the cell nucleus in microalgae such as *Euglena* from high salinity, pH imbalance, and U.V. Oxidative stress caused. "Astaxanthin, a pink-colored ketocarotenoid (oxygenated derivatives of carotenoids) with chemical nature of 3,3'-dihydroxy-β, β'-carotene-4, 4'-dione occurs naturally in a wide variety of living organisms such as aquatic animals, fungi, bacteria, marine algae and even in some bird species" (Neuroprotective effect of Astaxanthin on H2O2-induced).

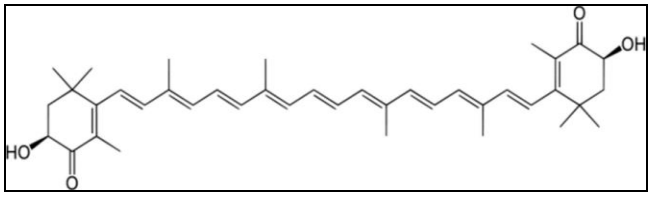

Fig 1: Astaxanthin Chemical Formula- C40H52O4 Exact Mass- 596.39 Molecular Weight- 596.84

Astaxanthin, a potent antioxidant carotenoid, is highly effective in mopping up free radicals as it possesses antioxidative properties. It also has anticancer effects because of antioxidative property. This study aimed to investigate the cytotoxic effects of Astaxanthin on breast cancer (MCF7) cells *in vitro* (Naji *et al*., 2019) [18]. Astaxanthin, a xanthophyll carotenoid, is a secondary metabolite spontaneously synthesized by various microbes, microalgae, and yeast. Traditionally, the commercial development of this pigment has been chemically synthesized. Nonetheless, the *Haematococcus pluvialis* microalgae have all the earmarks of being the most powerful type of mechanical natural creation. Because of its distinctive shared parts in skin science, there is verification that Astaxanthin has various medical advantages and critical nutraceutical applications in the dermatology area. While still being talked about, Astaxanthin potential pathways that may affect skin homeostasis have been recommended, including photoprotective, cancer prevention agent, and mitigating action (Davinelli *et al*., 2018) [7].

Astaxanthin, a carotenoid family member, is a dim red color and is the essential carotenoid present in the submerged climate of green growth and sea-going creatures. Astaxanthin is found in a few types of fish, including salmon, trout, red ocean bream, shrimp, lobster, and feathered creatures, for example, flamingo and quail. Manufactured Astaxanthin controls the world market, however ongoing interest in characteristic color sources has risen significantly. Mainstream causes of characteristic Astaxanthin incorporate green growth, *Haematococcus pluvialis*, red yeast, *Phaffia rhodozyma*, and scavenger side-

effects. Astaxanthin has remarkable cancer prevention agent properties, which have made a spike in the nutraceutical area of typified things. Various exploration has indicated that Astaxanthin has conceivable wellbeing advancing impacts in the counteraction and therapy of various infections, for example, tumors, ongoing provocative illnesses, metabolic condition, asthma, diabetic nephropathy, coronary sicknesses, gastrointestinal sicknesses, liver illnesses, neurodegenerative illnesses, eye infections, skin sicknesses, work out a prompted shortcoming, male barrenness. The most recent open exploration writing on the main exercises of Astaxanthin is talked about in this report (Dhankhar Jyoti, Kadian Sumita & Sharma Asha, 2012) [9].

Astaxanthin (ATX) is a xanthophyll carotenoid approved by the United States Food and Drug Administration (USFDA) as a food colorant in animal and fish feed. It is commonly found in algae and aquatic animals and has a significant anti oxidative effect. Previous studies have shown that ATX, with its antioxidant properties, is effective as a therapeutic agent for different diseases without any side effects or toxicity. Also, ATX demonstrates preclinical antitumor efficacy in multiple cancer models *in vivo* and *in vitro*. Several studies have shown that ATX exercises its antiproliferative, anti-apoptosis, and anti-invasive power through different molecules and pathways, including signal transducer and transcription activator 3 (STAT3), nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB), and peroxisome proliferator-activated gamma receptor (PPARγ). As a result, ATX is very promising as a chemotherapy agent in cancer. Here, we study the fast-moving area of ATX in cancer therapy and some molecular targets for ATX (Zhang & Wang, 2015) [31].

Physical properties of the astaxanthin

The physical properties of the Astaxanthin were defined based on its possible absorption of visible light and conversion of optical light energy into heat for thermal treatment. Due to its high light absorption, AXT isolated from marine content may be used for photothermal therapy. The thesis explored marine-based AXT's efficacy for chemo-photothermal therapy (PTT) by testing photothermal sessions in both cells and tumor tissues. An 80 W532 nm laser device was used to cause *in vitro* and *in vivo* thermal necrosis. Cytotoxicity analysis of AXT was conducted on a cell line, VX2, and macrophage (246.7) cell lines. *In vivo*, PTT studies were conducted on 17 rabbits administered with or without in tratumoral injection of AXT at a dosage of 100µl accompanied by laser irradiation at a low irradiance of $0.11W/cm^2$. Fluorescence microscopy images demonstrated apoptosis and necrosis due to the dual chemo-photo thermal effects of AXT. *In vivo* studies showed a 30.4^0C rise in tumor temperature following radiation therapy for 4 minutes. The tumors treated with both AXT and laser irradiation totally vanished within 14 days of treatment, but tumors treated under other conditions steadily developed. AXT-assisted laser treatment is a successful thermal therapy for multiple drug-resistant cancers (Nguyen *et al*., 2017) [21].

Apoptosis caused by astaxanthin to stop the malignant cell growth

Interest has risen in the efficacy of natural compounds and their impact on human health, particularly the performance of those that treat cancer. Natural compounds such as Taxol, Vincristine, and Vinblastine are used in chemotherapy to destroy cancer cells. Astaxanthin showed various biological activities among the carotenoids, including antioxidant, anticancer, and anticancer proapoptotic impact. It can cause apoptosis by downregulating anti-apoptotic proteins and up-regulating proapoptotic proteins. It might apply anticancer consequences for colorectal malignant growth, melanoma, and gastric carcinoma cell lines. It has anticancer action in a few trial models and is effective against tumor cells adding to conceivable future application. In this investigation, the creators depicted the anticancer capacity of Astaxanthin by adjusting numerous sub-atomic targets. While it has been unmistakably shown to execute a few diverse harmful cells *in vitro* and preclinical preliminaries, further clinical examination is needed to assess its viability as an anticancer specialist (Faraone *et al*., 2020) [10].

Table 1: Effects of ATX on cancers.

Cancer	*In vitro In vivo*	Molecular targets	Functions
Oral Cancer	*In vivo*	JAK-2/STAT-3, NF-κB, ERK, AKT(PKB)	Abrogate cell proliferation, invasion and angiogenesis, induce intrinsic apoptosis
Bladder Carcinogenesis	*In vivo*	/	Reduce the incidence of cancer and suppression of cell proliferation
Colon Carcinogenesis	Both	NF-κB, ERK, JNK, p38, AKT	Inhibit cell growth, invasion and inflammation, induce apoptosis, arrest cell cycle progression
Leukemia	*In vitro*	PPARγ, Nrf2	Decreased cell viability, induce apoptosis and interfere with cell cycle progression
Hepatocellular Carcinoma	Both	JAK-1/STAT-3	Attenuate cell proliferation and invasion, induce mitochondria mediated apoptosis
Lung Cancer	*In vitro*	/	Inhibit cell proliferation

JAK: Janus kinase; STAT: Signal transducers and activators of transcription; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; ERK: Extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinases; PKB: protein Kinase B; PPARγ: Peroxisome proliferator-activated receptor-gamma; Nrf2: NF-E2-related factor 2. (Zhang & Wang, 2015) [31]

Chemopreventive viability of astaxanthin on lipid peroxidation

(Prabhu *et al*., 2009) [25] assessed chemopreventive viability of Astaxanthin on lipid peroxidation, cancer prevention agent status, the complete number of aberrant crypt foci (ACF), and cell multiplication in 1,2-dimethylhydrazine (DMH)- initiated colon carcinogenesis utilizing a rodent

model. DMH was instigated subcutaneously at a portion of 40 mg/kg body weight, double seven days for about fourteen days. Astaxanthin was controlled orally when the DMH enlistment at centralization of 15 mg/kg body weight during the exploratory span. Toward the finish of about four months, pretreatment with Astaxanthin significantly diminished the level of histological injuries, the development of ACF, and the measure of argyrophilic nucleolar sorting out locales. Our discoveries likewise indicated diminished degrees of colon catalyst and non-chemical cell reinforcements and expanded lipid peroxidation markers in DMH-initiated rodents, which were considerably turned around when directed Astaxanthin. This examination showed that Astaxanthin has a positive and helpful effect against synthetically intervened pre-neoplastic colonic movement in DMH-prompted rodents.

Role of astaxanthin to decrease the tumour cell proliferation

Identifying agents that suppress STAT-3, a cytosolic transcription factor implicated in the activation of multiple genes involved in tumor development, is a fruitful cancer chemoprevention technique. In this research, the impact of dietary Astaxanthin on JAK-2/STAT-3 signaling in the 7, 12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch (HBP) carcinogenesis model was investigated by mRNA and protein expression of JAK/STAT-3 and its target genes. Quantitative RT-PCR, immunosuppressive and immunosuppressive analyses showed that Astaxanthin supplementation prevents core events in JAK/STAT signaling, particularly STAT-3 phosphorylation and subsequent STAT-3 nuclear translocation. Besides, Astaxanthin decreased the expression of target STAT-3 genes involved in cell proliferation, invasion and angiogenesis, and reduced micro vascular density, thus preventing tumor progression. The molecular docking study verified the inhibiting influence of Astaxanthin on STAT signaling and angiogenesis. Cell culture studies with the ECV304 endothelial cell line demonstrated the function of Astaxanthin in the suppression of angiogenesis. Taken together, our findings provide substantial proof that dietary Astaxanthin inhibits the production and progression of HBP carcinomas by inhibiting JAK-2/STAT-3 signaling and its downstream events. Astaxanthin, which acts as a powerful inhibitor of tumor growth and proliferation by targeting JAK/STAT signaling, could be the perfect candidate for cancer chemoprevention (J. Kowshik *et al*., 2014) [15]. Astaxanthin has been shown to inhibit NF-κB and Wnt signaling through deregulation of the primary regulating enzymes IKKβ and GSK-3β. Examination of gene expression and docking interactions showed that inhibition of these pathways could be regulated by inactivation of the upstream signaling kinases Erk/Akt by Astaxanthin. Astaxanthin also caused caspase-mediated mitochondrial apoptosis by deregulation of anti-apoptotic expression Bcl-2, p-Bad, and surviving and up-regulating proapoptotic Bax and Bad, with efflux of Smac/Diablo and cytochrome-c in the cytosol, and induced cleavage poly (ADP-ribose) polymerase (PARP). The findings offer convincing proof that Astaxanthin exerts chemopreventive effects by simultaneously inhibiting transcription and signaling kinase phosphorylation and inducing intestinal apoptosis. Astaxanthin targets main molecules in oncogenic signaling pathways that cause apoptosis and is a potential candidate for cancer prevention and therapy (Kavitha *et al*., 2013) [13].We assessed intragastricAstaxanthin's effectiveness on PCa cell formation, apoptosis, microRNA (miRNA) overexpression, and micro bacteria composition improvement. Nude mice have been inoculated subcutaneously with androgen-independent PC-3 cells of prostate cancer. The intervention began when tumors were 0.5–0.6 cm in diameter. Mice administered Astaxanthin (HA) 100 mg/kg, Astaxanthin (LA) 25 mg/kg of olive oil and administered intragastrically (TC). The findings revealed that 100 mg/kg Astaxanthin strongly inhibited tumor growth relative to the TC group, with an inhibitory rate of 41.7%. Decreased Ki67 and proliferating cell nuclear antigen (PCNA) and increased cleaved caspase-3 were observed in HA-treated tumors and increased apoptotic cells obtained by TUNEL assay. HA greatly raised the levels of miR-375 and miR-487b tumor suppressors in tumor tissues and the volume of *Lactobacillus* sp. and *Lachnospiraceae* in mice stools, but there was no substantial gap between LA and TC classes. These findings include a promising regimen to improve a dietary supplement (Ni *et al*., 2017).

Therapeutic efficacy of astaxanthin against cancer

Over the last decades, interest in the efficacy of natural compounds and their effects on human health has gradually grown, especially among those shown to benefit cancer. Natural compounds are currently used in chemotherapy, such as Taxol, Vincristine, or Vinblastine, and many other natural agents have been involved in reducing cancer cell progression and migration. Astaxanthin, xanthophyll red carotenoid, had a range of biological activities, including anti-inflammatory, antioxidant, proapoptotic, and anticancer impact. Apoptosis may be caused by lower control of anti-apoptotic protein (Bcl-2, p-Bad, and surviving) expression and upregulation of proapoptotic proteins (Bax/Bad and PARP). Anticancer effects may be exerted on colorectal cancer, melanoma, or gastric carcinoma cell lines. It also exhibits ant proliferative function in several animal models and increases the potency of traditional chemotherapy medications in tumor cells under its possible future application. This study offers an analysis of existing information on the anticancer capacity of Astaxanthin by modulating a variety of molecular targets. Although its multi-target role in the prevention and regression of malignant cells has been clearly shown *in vitro* or preclinical trials, more clinical trials are required to determine its potential as an anticancer in humans (Faraone *et al*., 2020) [10]. There is a debate in the oncology sector over the usage of antioxidants with chemotherapeutics. This research aimed to examine the impact of a potent antioxidant, (Astaxanthin), co-treatment with a successful anticancer medication, (carbendazim), on breast cancer cell proliferation. MCF-7 cells were treated with carbendazim, Astaxanthin, or variations of the two. Treatment was tested at various time points of infection with replication, cell cycle development, and reactive oxygen species output. Both studied combination improved antiproliferative activity of Carb and increased G2/M phase cell cycle arrest in cells treated with Cell Death Marker Alone. Astaxanthin decreased the elevated intracellular ROS levels caused by the carbendazim procedure. Our results indicate that Astaxanthin and carbendazim function in conjunction to inhibit cell proliferation while reducing ROS production in breast cancer cells. This study may create interest in the

usage of antioxidants combined with cancer chemotherapy (Atalay *et al*., 2019) [2].

The effects of astaxanthin on cyclophosphamide-induced oxidative stress

(Tripathi & Jena, 2010) [28] investigate the effects of Astaxanthin on cyclophosphamide-induced oxidative stress, DNA damage, cell death, and induction of GST-P foci in rat liver. Further attempts have been made to research the effect of Astaxanthin on the antioxidant response element (ARE) and transcription factor Nrf2 (nuclear factor E2-related factor 2) in the induction of step II NAD (P) H enzymes: quinine oxidoreductase-1(NQO-1) and hemoxygenase-1 (HO-1). Pre-and post-treatment with Astaxanthin (25 mg/kg) decreased oxidative stress-induced cyclophosphamide and DNA damage to the liver as demonstrated by the recovery of malondialdehyde glutathione as well as updated param-eternal comet assays. A substantial decrease in both the amount and the GST-P foci region in rat hepatocytes was observed with Astaxanthin post-treatment. Astaxanthin therapy greatly decreased the expression of p53 and p38 relative to the cyclophosphamide treatment community. It was also observed that the levels of Nof2 and Phase II enzymes, i.e., NQO-1 and HO-1, have been improved with Astaxanthin. The present study confirms that Astaxanthin is a powerful antioxidant and attenuates oxidative stress, DNA injury, cell death, and early hepatocarcinogenesis induced by cyclophosphamide in rats. Our findings provide proof that one of the chemoprotection pathways provided by Astaxanthin is regulated via the Nof2-ARE pathway

AXT prevents the cancer by inhibiting pi3k/akt and the associated downstream nf-κb and stat-3 signaling pathways in scc131 and scc4 oral cancer cells

Aberrant activation of the PI3K/Akt signaling pathway, a major driving force of diverse cellular processes, has been implicated in tumour development and progression. (Jaganathan Kowshik *et al*., 2019) [16] report that Astaxanthin (AXT), a potent antioxidant ketocarotenoid prevents cancer hallmarks by inhibiting PI3K/Akt and the associated downstream NF-κBand STAT-3 signaling pathways in SCC131 and SCC4 oral cancer cells as well as in the hamster buccal pouch carcinogenesis model. Using small-molecule inhibitors of NF-κB, STAT- 3, and PI3K and by overexpression of PI3K, we provide evidence to show that AXT inhibits NF-κB and STAT-3 signaling and cancer hallmarks by restraining the kinase activity of PI3K/Akt. Additionally, AXT down regulated the non-coding RNAs (ncRNAs), miR-21, and HOTAIR that influence PI3K/Akt signaling emphasizing its modulatory effects on epigenetic regulation. Ethyl cellulose-based AXT nanoparticles showed greater chemotherapeutic efficacy in the hamster oral carcinogenesis model compared to native AXT. We suggest that AXT prevents cell proliferation, apoptosis evasion, invasion, and angiogenesis by intercepting the crosstalk between the PI3K/Akt, NF-κB, and STAT-3 signaling circuits both *in vitro* and *in vivo*. Astaxanthin abrogates the PI3K/Akt signaling axis, a central hub that orchestrates the acquisition of cancer hallmarks and is a promising candidate for anticancer drug development Twenty weeks of Astaxanthin administration meant that the production of hepatocellular neoplasms (liver cell adenoma and hepatocellular carcinoma) and hepatic expression of cyclin D1 mRNA was substantially inhibited relative to the basal diet community in DEN-treated DB/DB mice. The administration of Astaxanthin in DEN-treated laboratory mice substantially decreased. Derivatives of the reactive oxygen metabolite/biological antioxidant potential ratio, which is a serum marker of oxidative stress, increasing the mRNA expression of the antioxidant enzymes superoxide dismutase 2 glutathione peroxidase 1 in the liver and white adipose tissues. The serum levels of adiponectin increased following Astaxanthin administration in these mice.Dietary Astaxanthin inhibited liver tumorigenesis in obese mice by improving oxidative stress and improving the amount of serum adiponectin. Astaxanthin can also benefit the chemoprevention of liver tumorigenesis in obese individuals (Ohno *et al*., 2016) [23]. The most famous UV-related DNA lesion is classified as "UV signature mutation."It is the creation of CPDs. As DNA is exposed to UV, neighboring pyrimidines (CC, CT, or TT) create a saturated bond that, if not repaired, contributes to DNA mutations that trigger tumorigenesis. UVB improves the activity of cutaneous ornithine decarboxylase (ODC). ODC, the first enzyme in the polyamine-biosynthesis pathway, can induce sustained proliferation and clonal expansion of the initiated cells, contributing to tumorigenesis. E.g., high levels of ODC are critical to the promotion of squamous cell carcinomas by driving a persistent proliferation and clonal expansion of V-Ha-ras-initiated cells. Also, pretreatment with 5 μM ASX of human keratinocytes (HaCaT) 24 h before UVB exposure or topical application of 0.02 percent ASX gel following chronic UVB irradiation on male Wistar mice (3 irradiations a week per 4 weeks) prevented oxidative DNA damage (Catanzaro *et al*., 2020) [4].

Astaxanthin (ASX) is a red xanthophyll carotenoid present in numerous micro-organisms and aquatic mammals. ASX is often referred to as the "super antioxidant" since it has the strongest antioxidant activity of current carotenoids. Studies have demonstrated antioxidant and antimicrobial, immunomodulatory, hepatoprotective, anticancer, and antidiabetic effects of ASX. There are, however, a small number of research investigating the selective cytotoxic impact of ASX on cancer cells. This analysis aimed to establish the cytotoxic effects of ASX on cells representing common forms of cancer. For this reason, human breast (MCF-7), lung (A549), liver (HepG2), melanoma (VMM917), colon (WiDr), and regular fibroblast cells were handled with different concentrations of ASX for 72 h. Then the MTT assay protocol was implemented. Cisplatin has been used as a supportive control in cytotoxicity studies. The findings revealed that ASX had a dose-dependent cytotoxic impact on all cancer cell lines tested. However, the greatest selective cytotoxic effect of ASX was calculated in A549 and WiDr cells compared with fibroblast cells. This research indicates that the selective cytotoxic activity of ASX should be more extensively studied, in particular concerning lung and colon cancer (DEMİR *et al*., 2020) [8].

Anti-inflammatory effects of astaxanthin

While Astaxanthin (ASTX) anti-inflammatory effects have been proposed, the underlying mechanisms have not been fully understood. In particular, the modulatory action of ASTX in the relationshipbetween nuclear factor E2-related factor 2 (NRF2) and nuclear factor κB (NFκB) to impose its anti-inflammatory activity in macrophages is unclear. The impact of ASTX on mRNA and protein expression of pro-

inflammatory and antioxidant genes and/or cellular reactive oxygen species (ROS) accumulation was calculated in RAW 264.7 macrophages, bone marrow-derived macrophages (BMDM) of wild-type (WT) and Nrf2-deficient mice, and/or splenocytes and peritoneal macrophages of obese mice fed ASX. The impact of ASTX on M1 and M2 macrophage polarization in BMDM was evaluated. ASX substantially decreased LPS-induced mRNA production of interleukin 6 (Il-6) and Il-1β by inhibiting nuclear translocation of NFiB p65; and attenuated LPS-induced ROS by increasing NRF2 nuclear translocation, simultaneously decreasing NADPH oxidase 2 expressions in RAW 264.7 macrophages. In WT and Nrf2-deficient mice BMDM, ASTX reduced basal and LPS-induced ROS accumulation. The activation of Il-6 mRNA by LPS was inhibited by ASTX in both forms of BMDM, whereas Il-1β mRNA was diminished only by WT BMDM. Also, ASTX intake decreased the LPS vulnerability of splenocytes in obese mice. ASX lowered the M1 polarization of BMDM, thus rising the polarization of M2. ASX exercises its anti-inflammatory effect by inhibiting the nuclear translocation of NFκB p65 and preventing the aggregation of ROS in NRF2-dependent and independent pathways. Consequently, ASTX is an anti-inflammatory and antioxidant agent that may be used to reduce inflammatory conditions (Farruggia *et al*., 2018) [11].

Growth-inhibiting properties of astaxanthin-rich *Haematococcus Pluvialis*

Growth-inhibiting properties of Astaxanthin-rich *Haematococcus Pluvialis* have been studied in HCT-116 colon cancer cells. *H. Pluvialis* extract (5-25 mg/ml) inhibited cell growth in a dose-dependent and time-dependent way, by preventing cell-cycle development and by inducing apoptosis. 25 lg/ml of *H. Pluvialis*extract, an improvement in p53, p21WAF-1/CIP-1, and p27 expression (220 percent, 160 percent, 250 percent, respectively) was reported, concomitantly with a decrease in cyclin D1 expression (58 percent) and AKT phosphorylation (21 percent). At the same dosage, the extract strongly up-regulated apoptosis by changing the Bax/Bcl-2 and Bcl-XL ratios and increased p38, JNK, and ERK1/2 phosphorylation 160 percent, 242 percent, and 280 percent, respectively. Growth-inhibiting effects of *H. Pluvialis*has also been identified in HT-29, LS-174, WiDr, SW-480 cells. This research indicates that *H. Pluvialis* can protect against cancer of the colon(Palozza *et al*., 2009).This research examined the use of astaxanthin as an anticancer agent to improve melanoma cell inhibition (A375 and A2058). Wound healing and invasion assays have demonstrated that astaxanthin therapy decreases melanoma cell proliferation in a dose-dependent manner. Effects on melanoma cell migration have been conferred by blocked expressions of matrix metalloproteinases 1, 2, and 9. Dichlorofluorescein diacetate assay also found that astaxanthin treatment decreased the development of cell-reactive oxygen species. Cell proliferation assay showed potent dose-dependent inhibiting effects on melanoma cells. One-dimensional flow cytometric research has shown that astaxanthin mediated cell cycle arrest in the G1 step. Double fluorescence staining of annexin V-fluorescein isothiocyanate and propidium iodide has been confirmed through apoptosis pathways. The antitumor effects of astaxanthin dramatically reduced tumor size in the xenograft model. In summary, the experimental findings revealed that astaxanthin had potent *in vivo* and *in vitro* inhibiting effects on tumor growth of melanoma for development as a chemotherapeutic agent (Chen *et al*., 2017) [5]. Astaxanthin mono-(AXME) and diester (AXDE) were described and evaluated for anticancer potency with complete carotenoid (TC) and astaxanthin (AX) anti-UV-7,12-dimethylbenz(a)anthracene (DMBA)-induced skin cancer model in rats. At 200 μg/kg BW, AXDE, and AXME decreased the occurrence of UV-DMBA-induced tumors by 96 and 88 percent, respectively, relative to AX (66 percent) and TC (85 percent). UV-DMBA has been reported to induce high amounts of free radicals and tyrosinase enzyme, contributing to typical signs of skin pigmentation and tumor initiation. Intriguingly, a 7-fold rise in tyrosinase and a 10-fold decline in antioxidant amounts have been normalized by AXDE and AXME compared to a single 1.4−2.2-fold increase in AX and TC. This finding, along with the appearance of 72 and 58 ng/mL of retinol in the serum of the respective AXE-treated (AXDE + AXME) and AX-treated animals, indicated that enhanced AXE anticancer potency might be attributed to increased bioavailability (Rao *et al*., 2013) [26].

Besides, numerous investigations have shown the anticancer effects of astaxanthin, but the action mode remains widely unclear. However, few studies have proposed altering gap junction communications as a potential route by which astaxanthin exerts its anticancer action. Gap junction communications are essential to homeostasis, cell growth regulation, and cell production. This intercellular distance is disrupted in cancer cells, and studies have shown that astaxanthin influences channel functions by modifying the phosphorylation pattern of the gap junction enzyme connectivity. Phosphorylation/dephosphorylation of functional membrane communication proteins can affect channel gating and regulate channel activity. While the data indicates the advantages of astaxanthin in preventing many chronic diseases, further study is also needed to elucidate the mechanisms of action involved in the reported therapeutic properties. Such awareness may include novel targets for the molecule of astaxanthin (Adeyemi, 2014) [1].

The exploration offers molecular proof of apoptotic and cell reinforcement viability of astaxanthin. Indicate results that astaxanthin can hinder expansion and instigate apoptosis in LS-180 cell lines by advancing the activity of cancer prevention agent chemicals, decreasing malondialdehyde advancement, and developing the statement of qualities that are powerful in apoptosis. In any case, research with more information, including interrelated sub-atomic pathways, may give additional proof (Hormozi *et al*., 2019) [12].

Recent study depicts that's astaxanthin may also play a role in cancer treatment

In the most recent decade, astaxanthin preliminaries as a strong remedial specialist have created promising execution. Astaxanthin might be utilized to determine various human medical conditions, including malignancy, cardiovascular and neurodegenerative problems, and maturing. These issues are regularly worried about irritation inferable from the relationship of nucleic acids and proteins with poisonous responsive species. These impacts are because of the particular properties of astaxanthin atomic structure, which cause the responsive species to be rummaged and the singlet oxygen to be extinguished. Late examinations have exhibited different astaxanthin isomers' commitment to

cancer prevention agent work, both *in vitro* and *in vivo*. Be that as it may, there is a deficiency of study into astaxanthin and its amalgamation in organic frameworks. Future investigations should focus on the physicochemical properties of different astaxanthin structures, their ingestion measures, and the office for coordination into metabolic pathways. Sub-atomic analyses, remembering for vitro and *in vivo* models, may likewise be embraced to investigate nutraceutical and restorative employments of various astaxanthin isomers (Brotosudarmo *et al*., 2020) [3]. Atopic dermatitis (AD) is caused by various causes, including immunological disorders and susceptibility to allergens. AST is a carotenoid that has recently been shown to have anti-inflammatory properties and control inflammatory cytokines. We investigated whether AST could enhance dermatitis and pruritus in a murine model of AD. The effects of AST on AD were calculated by clinical skin severity ranking, serum IgE stage, histological analyses of skin, and reverse transcription-PCR and Western blotting to express inflammation-related factors. Rats were handled with AST (100 mg/kg) or vehicle (olive oil) once a day for 26 days. When contrasted with the vehicle-treated community, administering AST decreased the magnitude of the psychiatric effects. Also, anti-seizure medication administered decreased spontaneous scratching in AD mice. The serum IgE level was slightly decreased after oral administration of AST relative to vehicle-treated mice. The number of eosinophils, complete and degranulated mast cells in the skin of AST-treated mice decreased dramatically. mRNA and protein amounts of eotaxin, MIF, IL-4, IL-5, and L-histidine decarboxylase were dramatically decreased in the skin of AST-treated mice. These findings indicate that AST enhances skin lesions by controlling the inflammatory mechanism and releasing inflammatory cytokines (Yoshihisa *et al*., 2016) [30]. Astaxanthin is a significant method to diminish the multiplication and advancement of bosom malignancy cells. Astaxanthin has shown a reliable capacity to limit a few types of malignancy. These outcomes can rouse a few unique types of clinical examination that could influence current disease care (McCall *et al*., 2018) [17].

Colorectal cancer (CRC) is the third most normal tumour and is related to numerous malignancy related passings around the world. Moreover, the achievement pace of treatment in CRC patients relies basically upon the status of the metastases. New drugs or restorative strategies for the treatment of metastatic CRC ought to likewise be found. In this examination, we chose Astaxanthin (AXT), quite possibly the most well-known carotenoids, as a novel metastasis inhibitor through high-throughput invadopodia staining drug screening. We affirmed the counter transient and against the obtrusive activity of AXT. We have indicated that AXT raises the articulations miR-29a-3p and miR-200a and consequently smothers the articulations MMP2 and ZEB1, individually. Accordingly, AXT smothers the epithelial-mesenchymal transformation (EMT) of CRC cells. Through an unthinking investigation, we found that AXT displays hostile to metastatic conduct through the MYC record factor's transcriptional concealment. At long last, we likewise affirmed that AXT smothers colon malignancy cells' metastatic capacity *in vivo* utilizing the mouse model. Altogether, we have found the novel job of AXT in repressing EMT and invadopodia improvement, which remembers the novel restorative capability of AXT for metastatic CRC patients (Kim *et al*., 2019) [14]. Astaxanthin slowed cancer growth and balanced invulnerable reaction, however just when astaxanthin was given before tumor inception. This demonstrates that satisfactory blood astaxanthin status is needed to secure against the commencement of a tumor; on the other hand, astaxanthin supplementation after the inception of a tumor might be contraindicated (Nakao *et al*., 2010) [19]. Results demonstrate a wide scope of assurance from cisplatin harm in fibroblasts by astaxanthin, suggesting its conceivable use as a novel helpful specialist against chemotherapy-induced oral mucositis (Yamaguchi *et al*., 2019) [29]. Normal AST considerably smothered esophageal malignant growth occurrence by expanding the cancer prevention agent limit and mitigating limit by repressing the articulation levels of NFκB and COX2 proteins (Cui *et al*., 2019) [6].

Mechanism of action of astaxanthin on prostate cancer

Astaxanthin can adequately hinder the multiplication and cloning development of DU145, advance the apoptosis of the DU145 cells, and debilitate the intrusion and relocation capacity of DU145. Also, astaxanthin can lessen the statement of STAT3 and the outflow of the connected proteins of STAT3 in protein and mRNA levels. When astaxanthin and si-STAT3 were joined, all the impacts were improved. The aftereffects of creature tests are predictable with the consequences of cell tests. Subsequently, we reasoned that astaxanthin restrains DU145 tumor cells by diminishing the degree of STAT3. It very well might be a planned medication that can adequately smother forceful tumor cells (Sun *et al*., 2020) [27].

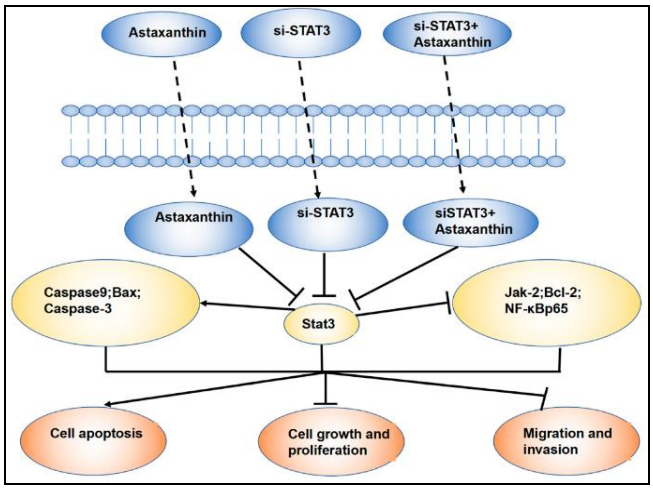

Fig 2: Schematic representation of the mechanism of action of astaxanthin on prostate cancer DU145. Astaxanthin inhibits DU145 tumor cells by reducing the levels of STAT3 and its related proteins. When astaxanthin and si-STAT3 are combined, the effects are better (Sun *et al*., 2020) [27]

Conclusion

Astaxanthin (ASX) is a red xanthophyll carotenoid present in numerous micro-organisms and aquatic mammals. ASX is often referred to as the "super antioxidant" since it has the strongest antioxidant activity of current carotenoids. Studies have demonstrated antioxidant and antimicrobial, immunomodulatory, hepatoprotective, anticancer, and anti diabetic effects of ASX. The study found that ASX had a dose-dependent cytotoxic impact on all cancer cell lines tested. The authors say it should be more extensively

studied, particularly concerning lung and colon cancer. The study was conducted on human breast, lung, liver, melanoma, colon, and fibroblast cells for 72 h and was published in the journal Cancer Epidemiology, Biomarkers and Therapeutics, and was peer-reviewed by the American Cancer Society. Astaxanthin (ATX) is a xanthophyll carotenoid approved by the U.S. Food and Drug Administration as a food colorant. It is commonly found in algae and aquatic animals and has a significant anti oxidative effect. The authors conclude that ATX is very promising as a chemotherapy agent in cancer and should be used in the future for the treatment of lung and skin cancers. The researchers found that dietary Astaxanthin inhibits HBP carcinomas' production and progression by inhibiting JAK-2/Stat-3 signaling and its downstream events. Identifying agents that suppress STAT-3, a transcription factor implicated in tumor development is a fruitful cancer chemo preventive technique, the authors say. The study authors say further clinical research is required to evaluate its effectiveness as an anticancer agent. This analysis indicated that Astaxanthin has a favorable and beneficial impact against chemically mediated pre-neoplastic colonic progression in DMH-induced rats. Astaxanthin exerts chemo preventive effects by simultaneously inhibiting transcription and signaling kinase phosphorylation and inducing intestinal apoptosis. Also caused caspase-mediated mitochondrial apoptosis by deregulation of anti-apoptotic expression Bcl-2, p-Bad, and surviving and up-regulating proapoptotic Bax and Bad. Colorectal cancer is the third most common cancer and is associated with many cancer-related deaths worldwide. New medications or therapeutic methods for the treatment of metastatic CRC should also be discovered. Astaxanthin (AXT) inhibits DU145 tumor cells by reducing the level of STAT3. It may be a prospective drug that can effectively suppress aggressive tumor cells, authors say. They say AXT exhibits anti-metastatic behavior through the transcriptional suppression of the MYC transcription factor and suppresses colon cancer cells' metastatic ability *in vitro* using the mouse model. The authors conclude that AXT has the potential to be a new treatment for metastatic cancer patients. Atopic dermatitis (AD) is caused by various causes, including immunological disorders and susceptibility to allergens. AST is a carotenoid that has recently been shown to have anti-inflammatory properties and control inflammatory cytokines. We investigated whether AST could enhance dermatitis and pruritus in a murine model of AD. The number of eosinophils, complete and degranulated mast cells in the skin of AST-treated mice decreased dramatically. These findings indicate that ASIST enhances skin lesions by controlling the inflammatory mechanism and releasing inflammatory cytokine. Astaxanthin may be used to resolve numerous human health problems, including cancer, cardiovascular and neurodegenerative disorders, and aging. These disorders are often concerned with inflammation owing to the association of nucleic acids and proteins with toxic reactive species. These effects are due to the specific properties of astaxanthin's molecular structure in which causes reactive species to be scavenged and the singlet oxygen to be quenched. Future studies should concentrate on the physicochemical properties of various astaxanthin structures, their absorption processes, and the facility for integration into metabolic pathways, say the authors. The research offers molecular evidence of apoptotic and antioxidant efficacy of astaxanthin, but more data with more data is needed to provide further evidence, they say. The author would like to clarify that there is a shortage of study into astaxanthin and its synthesis in biological systems. Astaxanthin mono-(AXME) and diester (AXDE) were evaluated for anticancer potency with UV-7,12-dimethylbenz(a)anthracene (DMBA)-induced skin cancer model in rats. UV-DMBA has been reported to induce high amounts of free radicals and tyrosinase enzyme, contributing to typical signs of skin pigmentation and tumor initiation. Examined the defensive influence of Astaxanthin (ASX) on apoptosis-induced 6-hydroxydopamine (6-OHDA) in the human neuroblastoma cell line SH-SY5Y. The antitumor effects of astaxanthin in this model dramatically reduced tumor size in the xenograft model. The study found that Asx had potent *in vitro* and *in vitro* inhibiting effects on tumor growth of melanoma for development of chemotherapeutic agent for development as a chemotherapeutic agent. The authors conclude that the defensive effects of Asx on carcinoma cells could be at least partly due to its potent antioxidant capacity. The researchers conclude that astaxanthin has potent *in vitro* and *in vivo* inhibited effects on melanoma growth and tumour growth and tumor growth in a xenografted skin cancer model and cancer-like tumors in humans. The researchers conclude that the study successfully reduced tumor size and the development of cell-reactive oxygen species.

List of abbreviations

Asx- Astaxanthin, 6-OHDA- 6-hydroxydopamine, MAPK-activated protein kinase, *c-jun*- NH2- terminal kinase, PTT-chemo-photothermal therapy, AXT-Astaxanthin, USFDA-United States Food and Drug Administration,ACF-aberrant crypt foci, DMH- 1,2-dimethylhydrazine, DMBA-7,12-dimethylbenz [a] anthracene, HBP-hamster buccal pouch, ARE-antioxidant response element, COD-cutaneous ornithine decarboxylase, ROS-reactive oxygen species, BMDM-bone marrow-derived macrophages,CRC-Colorectal cancer, EMT-epithelial-mesenchymal transition, AD-Atopic dermatitis

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