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# Astaxanthin – mechanism of action in oral cancer pre cancer

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**Abstract**

Astaxanthin (ATX) is a xanthophyll carotenoid which has been approved by the United States Food and Drug Administration (USFDA) as food colorant in animal and fish feed. It is widely found in algae and aquatic animals and has powerful anti-oxidative activity.

Previous studies have revealed that ATX, with its anti-oxidative property, is beneficial as a therapeutic agent for various diseases without any side effects or toxicity. In addition, ATX also shows preclinical anti-tumor efficacy both in vivo and in vitro in various cancer models.

Several researches have deciphered that ATX exerts its anti-proliferative, anti-apoptosis and anti-invasion influence via different molecules and pathways including signal transducer and activator of transcription 3 (STAT3), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and peroxisome proliferator-activated receptor gamma (PPARγ).

Hence, ATX shows great promise as chemotherapeutic agents in cancer. Here, we review the rapidly advancing field of ATX in cancer therapy as well as some molecular targets of ATX.

**Keywords**: Astaxanthin; Cancer; Molecular Target

## Introduction

Cancer of the oral cavity and lip, a major global health concern with an annual incidence of over 350,000 newly diagnosed cases, is the second most common cancer in India.[1] Aberrant activation of oncogenic signaling kinases and transcription factors plays a crucial role in the acquisition of hallmarks of cancer.[2] The PI3K/Akt signaling pathway that orchestrates multiple cellular processes including cell growth, metabolism migration and angiogenesis is one of the most commonly dysregulated pathways in malignant tumours including oral squamous cell carcinomas.[3,4]

About 67% of anti-cancer drugs are derived from natural products or natural product derivatives [5]. Astaxanthin is a natural product that is safe and possesses anti-cancer properties. It is primarily found in marine organisms such as algae, phytoplankton and shrimp.

It is the final form of carotenoid synthesis with a strong ability to quench singlet oxygen and clear free radicals

[6-8]. Recently, many in vivo and in vitro studies have confirmed that astaxanthin inhibits the growth of various tumor cells, such as neuroblastoma, lung cancer, gastric cancer, oral cancer, colon cancer, breast cancer, bladder cancer, liver cancer and leukemia [9-15]. Anti-cancer effects include anti-proliferation [16], enhancing apoptosis [17], anti-oxidation [18,19], anti-inflammation [20,21], preventing migration and invasion, and so on [20].

Although the mechanisms of astaxanthin mediating anti-cancer action have not yet been fully clarified, a number of molecular targets of astaxanthin have been proposed, which may explain the anti-tumor effects of this drug, such as NF-κB, STAT3, PI3K/AKT, MAPKs, PPARγ, and so on [20–23]. However, whether astaxanthin suppresses prostate cancer through STAT3 is yet to be elucidated. Herein, whether astaxanthin can effectively inhibit the proliferation, cloning ability, invasion and migration ability and increase the apoptosis of DU145 cells by inhibiting the expression of STAT3 and its related proteins at protein and mRNA levels is evaluated.

**Anti-cancer effects of ATX in oral cancer**

**Anti-Proliferation of Cells**

Tumor formation is characterized by rapid proliferation of cancer cells. Cancer cells proliferate promotes its invasion, migrate and adhere to target tissue. These steps allow the tumor cell to obtain metastatic phenotype. Cell proliferation depends on the signals transmitted by growth factors and adhesion proteins [24] and is usually regulated by signaling pathway such as mitogen-activated protein kinase (MAPK) and phosphatidylinositide 3-kinases (PI3K) cascades [25–28].

The processes of proliferation and further invasion, migration and adhesion require the rearrangement of actin cytoskeleton. It involves the release of pre-existing cell-matrix contacts and formation of new integrin substratum contacts [29].

The effect of ATX on cell proliferation in cancer cells has been explored by many researchers. Song et al. [30] have observed the anti-proliferative effect of ATX against CBRH-7919 (human hepatoma), SHZ-88 (rat breast) and Lewis (mouse lung) cells. They reported a strong correlation between ATX concentration and anti-proliferative effect on these cells at 24 h.

However, of these cells, CBRH-7919 was the most sensitive cell line to ATX with an IC50 value of 39 μM. In a separate study, Zhang et al. [18] compared the growth inhibitory effect of ATX with other carotenoids such as β-carotene, capsanthin and bixin on K562 leukemia cells.

They found that when K562 cells were treated with low concentrations of carotenoids (5 and 10 μM), ATX was the most effective to inhibit cell growth among the four kinds of carotenoids, followed by bixin, β-carotene and capsanthin in order.

In addition, ATX was shown to impede proliferation in a hamster model of oral cancer by regulating the expression of cyclin D1 and proliferating cell nuclear antigen (PCNA) [27] and decrease cell viability in human HCT-116 colon cancer cells in dose- and time-dependent manners [31].

Therefore, ATX exhibits an obvious anti-proliferative effect in cancers. Furthermore, several studies indicated that the normal cells were unaffected/less affected than cancer cells by ATX. For example, although ATX significantly inhibited the proliferation of CBRH-7919, SHZ-88 and Lewis's cell lines, it had little effect on HL-7702, a normal human hepatocyte line [30], indicating differential effects of ATX and focused targeting of cancer cells.

**Apoptosis**

Apoptosis is the process of programmed cell death (PCD) that takes place in multicellular organisms and comprises of many cellular events including nuclear fragmentation, cellular blebbing, chromosomal DNA fragmentation and ultimately cell death [32,33].

In physiological state, apoptosis is carried out in a regulated process, conferring advantage during an organisms life cycle occur. However, if apoptosis occurs in tumor cells, the tumor volume would decline, thus diminishing tumor burden and raising life expectancy [34,35].

In this regard, the effect of ATX on apoptosis is of interest and has been studied by researchers. The results obtained by Song et al**.** [30] showed that a significant peak of hypodiploid indicative of apoptosis was detected by flow cytometry when the cells were treated with ATX.

Moreover, ATX caused changes in mitochondria morphology, transmembrane potential and respiratory chain and regulated apoptotic proteins in mitochondria such as B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X protein (Bax). In a hamster model of oral cancer**,** Kavitha et al**.** [36] reported that ATX could induce caspase-mediated mitochondrial apoptosis by down-regulating the expression of anti-apoptotic Bcl-2,p-Bcl-2-associated death promoter (Bad) and surviving and up-regulating pro-apoptotic Bax and Bad, accompanied by efflux of Smac/Diablo and cytochrome c into the cytosol and cleavage of poly (ADP-ribose) polymerase (PARP).

In another study, ATX decreased the expression of Bcl-2, B-cell lymphoma-extra-large (Bcl-xL) and c-myc while increased the level of Bax and non-metastasis23-1 (nm23-1) in a hepatocellular carcinoma cell line [20]. Taken together, these data suggests that ATX could induce mitochondria-mediated apoptosis in cancer cells.

Interestingly, although ATX induced apoptosis in various cancers, it suppressed 6-OHDA-induced apoptosis and strikingly inhibited 6-OHDA-induced mitochondrial dysfunctions, including lowered membrane potential and the cleavage of caspase-9, caspase-3, poly (ADP-ribose) polymerase (PARP) in a human neuroblastoma cell line SH-SY5Y [5]. The discrepancies may be due to the complex and diverse interplays between ATX and apoptosis. Depending on different cell types, ATX may have different effects on apoptosis.

**Anti-Oxidation**

Oxidative stress is initiated by the production of free radicals and reactive oxygen species (ROS). Redox imbalance, due to aberrant ROS production and/or anti-oxidant functionality, contributes to tumor progression and is a hallmark of several types of cancer [37,38].

ROS may participate in cancer initiation, progression and spreading acting as secondary messengers in the activation and maintenance of specific signaling pathways [38].

This type of oxidative molecules can be inhibited by endogenous and exogenous anti-oxidants such as ATX. It has been shown that ATX attenuated intracellular $O_2^-$ production by restoring the anti-oxidant network activity of superoxide dismutase (SOD) and catalase (CAT), thus reversing lipopolysaccharide (LPS)-induced toxicity and ROS production in U937 cells [39].

In another case, ATX inhibited cell proliferation, induced cell apoptosis and interfered with cell cycle progression in leukemia K562 cells via activation of Nrf2-mediated anti-oxidant pathway [18]. Thus, oxidative stress could be key intermediates linking ATX and proliferation, apoptotic commitment.

However, recent studies have reported the pro-oxidant effects of some carotenoids on cancer cells with the

generation of free radicals. Kim et al. [40] have observed the growth inhibition in leukemia cell lines by fucoxanthin and have attributed it to ROS generation by fucoxanthin that leads to apoptosis.

Therefore, ATX may also exhibit its anti-cancer effects through activation of ROS. However, none studies have shown this action so far. Therefore, further studies are needed to clarify these mechanism

**Anti-Inflammation**

The role of inflammation in the development of cancer was firstly described by Rudolf Virchow in 1863 [41]. Inflammation is part of the complex biological response of body tissues to harmful stimuli and is characterized by a general increase in plasma levels and cell capability to produce pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) [42,43].

This generalizes pro-inflammatory status, interacting with the genetic background and environmental factors, potentially triggers the onset of cancer [44,45].

Abundant evidence supports the preposition that various cancers are triggered by inflammatory disease [44–46] and anti-inflammatory drugs such as aspirin or cyclooxygenase-2 (COX-2) inhibitors could reduce tumor recurrence [46,47].

The effect of ATX on inflammation has also been explored in cancer. Speranza et al. [48] have reported that in U937 cell line, ATX inhibited ROS-induced activation of nuclear factor-κB (NF-κB) transcription factor, which then in turn effectively suppressed the production of inflammatory cytokines such as IL-1β, IL-6 and TNF-α, through a restoration of physiological levels of SHP-1.

Furthermore, Yasui et al. [17] suggested that dietary ATX significantly inhibited the occurrence of colonic mucosal ulcers, dysplastic crypts and colonic adenocarcinoma which were related to colitis and colitis-related colon carcinogenesis in mice.

They proposed that the suppression of inflammatory cytokines such as nuclear factor-κB (NF-κB), TNF-α, IL-1β, IL-6 and COX-2 contributed to the anti-cancer effect of ATX. Since inflammation affects all stages of cancer, for example, increasing the onset risk, starting the initial genetic mutation, supporting tumor progression and promoting invasion and metastasis, it could be the key target of ATX.

**Invasion and Migration**

Invasion and migration are two pivotal processes in the development of cancer [49]. To invade surrounding tissue and metastasize, malignant cancer cells break away from the primary tumor, attach to and degrade proteins that make up the surrounding extracellular matrix (ECM) [50].

Then cancer cells escape the original tumor site and migrate to other parts of the body via the lymphatic system, bloodstream or by direct extension [51]. In this process, matrix metalloproteinases (MMPs) play a crucial role. MMPs are zinc-binding endopeptidases that can promote tumor cell migration and invasion by breakdown of the ECM [53]. In contrast, tissue inhibitor of metalloproteinases (TIMPs) are the endogenous inhibitors of the zinc-dependent endopeptidases of the MMPs [52].

In a hamster model of oral cancer, Kowshik et al. [53] studied the effects of ATX on the expression of MMP-2 and MMP-9. These MMPs were overexpressed in cancer cells and degraded ECM during cancer invasion. ATX treatment resulted in decreased mRNA and protein levels of MMP-2 and MMP-9. Besides MMPs, they also studied TIMP-1 and reversion-inducing-cysteine-rich protein with kazal motifs (RECK), the endogenous inhibitors of MMPs.

ATX increased the protein levels of TIMP-1 and RECK, suggesting the inhibition effects of ATX on invasion and metastasis. ATX was also found to suppress invasion in experimental rat colon carcinogenesis [16] and AH109A rat ascites hepatoma cell line [54] via modulating the expressions of MMPs. Thus, by inhibiting invasion factors, ATX may be valuable in preventing cancer cell invasion and metastasis.

**Future perspective**

**Autophagy**

Autophagy is a process by which cells conserve and recycle their organelles when in a nutrient-deprived or stressed state [55]. During autophagy, targeted cytosolic proteins and organelles are isolated within the autophagosomes, which are then fused with lysosomes, the contents of the autophagosome are degraded via acidic lysosomal hydrolases [56].

Under physiological conditions, autophagy ensure cellular survival by maintaining cellular energy levels [57,58]. However, extensive or inappropriate activation of autophagy can lead to cell death (type II PCD).

Nowadays, the relationship between autophagy and apoptosis is a hot research point in cancer. Recent studies have shown that some chemotherapeutics known to induce apoptosis also activate autophagy.

However, depending on different stimulus and cell types, autophagy acts not only as a protector—it prevents cells from undergoing apoptosis [59] but also as a promoter—it promotes cell apoptosis [60].

Therefore, autophagy may be considered as a double-edged sword in cancer. Depending on cell types, environment and stimulation manners, autophagy and apoptosis may have inhibitory, additive or even synergistic effects.

There were also studies demonstrating that ATX could affect autophagy. Shen et al. [61] reported that ATX significantly improved the pathological lesions of liver fibrosis by decreasing the levels of alanine aminotransferase aspartate aminotransferase and hydroxyproline.

Moreover, they found that the protective effect of ATX on liver fibrosis was through down-regulation of energy production in hepatic stellate cells (HSCs) by autophagy.

In another study conducted by Li et al. [62], they observed decreased immune liver injury in concanavalin A (ConA)-induced autoimmune hepatitis by ATX.

And this mode of action appeared to be down-regulation of JNK/p-JNK-mediated apoptosis and autophagy. Since autophagy played a key role in cancer and ATX has been shown to affect autophagy in liver injury model, therefore further studies are needed to estimate whether ATX could regulate autophagy in cancer.

**Angiogenesis**

Angiogenesis is the physiological process through which new blood vessels form from pre-existing vessels. Angiogenesis is a crucial part of tumor growth [63]. When a tumor reaches approximately 1–2 mm in diameter, it requires neovascularization for further development [64].

In addition, angiogenesis is a fundamental step in the invasion and metastasis of tumors. Therefore, disruption of tumor angiogenesis has been researched for developing alternative anti-tumor strategies. A number of studies have emphasized the major role of angiogenesis in cancer and agents that inhibited neovascularization could suppress the development of tumor [65,66].

To date, antibodies targeting the VEGF, such as bevacizumab, have proved therapeutically viable [66]. However, the role of ATX played in tumor angiogenesis has not been fully understood.

Recently, Kowshik et al**.** [53] found that ATX significantly modulated the expression of VEGF, VEGFR2 and decreased HIF-1a nuclear translocation, resulting in decreased number of vessels in oral cancer. This study indicated the anti-angiogenic potential of ATX, which may provide a novel research idea for the treatment of ATX in other cancers.

**Conclusion**

A number of studies show that ATX emerges as a key player in cancer therapy. It also influences a multitude of molecular and cellular processes. In this review, we have described the effects of ATX on oral cancer as well as some molecular targets of ATX involved in cancer-associated processes (such as apoptosis and inflammation).

These observations make ATX an attractive therapeutic agent for developing novel treatment protocols, and possibly for combining with other chemotherapeutics to overcome drug resistance and achieve better outcomes.

It is clear that further studies are required to elucidate the full spectrum of direct and downstream cellular targets of ATX. Ultimately, ATX may hold promise for clinical cancer therapy.

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