Astaxanthin in cancer therapy and prevention (Review)

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Abstract. Astaxanthin (AXT), a carotenoid primarily derived from marine organisms such as shrimp, krill and the microalga *Haematococcus pluvialis*, has gained significant attention for its potent antioxidant, anti-inflammatory and anti-proliferative properties. The present comprehensive review explored the role of AXT in cancer prevention and treatment, emphasizing its cytotoxic mechanisms and modulation of key molecular pathways involved in cancer progression. AXT has demonstrated efficacy across a variety of cancer types, including nervous system, breast and gastrointestinal cancers, through its ability to induce apoptosis, inhibit metastasis and disrupt cell growth. The present review detailed both *in vitro* and *in vivo* studies highlighting the effectiveness of AXT in sensitizing cancer cells to chemotherapy, thereby enhancing therapeutic outcomes and potentially reducing treatment-related side effects. The incorporation of AXT in nanoparticle-based delivery systems has further improved its bioavailability and targeted action, showcasing its potential in advanced cancer therapies. However, despite promising experimental results, more comprehensive *in vivo* studies and clinical trials are necessary to validate the efficacy and safety of AXT in human populations. Such research would help standardize dosing, confirm interactions with conventional treatments and support the integration of AXT into clinical oncology as a natural, complementary approach to existing cancer treatments.

Contents

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1. Introduction

Carotenoids have gained significant attention for its potential therapeutic and preventive benefits against various types of non-communicable diseases including diabetes, obesity, cardiovascular disease, cancers, respiratory disorders, as well as impaired neurodevelopment outcomes (1-6). In preventive medicine, diet and nutrition, play a crucial role as they are important risk factors for non-communicable diseases (7-10). Therefore, they should be prioritized in public health policies and programs. Moreover, promoting healthier diets could lead to substantial savings in health care costs and gains in quality-adjusted life years (11,12).

Astaxanthin (AXT) is derived from various sources, including marine organisms such as shrimp and krill, as well as freshwater microalgae, particularly *Haematococcus pluvialis* (13,14). It exhibits strong antioxidant properties, which contribute to its anti-inflammatory, anti-proliferative and possibly anticancer effects which are discussed in the present review. These sources are critical not only for their high AXT content but also for their role in sustainable production practices, which are crucial in the current global push for environmentally friendly and ethically sourced supplements. In a search for more sustainable and healthy food systems, microalga is one of the most auspicious sustainable sources of food ingredients with a great potential in promoting healthy diet and nutrition, thanks to the numerous pigments and nutrients that contain, which can be used as dietary supplements and functional foods (15-18).

In addition, microalgae are rich in bioactive compounds with different chemical structures that can be extracted from numerous species and can be used in the pharmaceutical field for therapeutic purposes or to formulate drug delivery systems (19). Nevertheless, 95% of AXT available in the market is produced synthetically using petrochemicals, due to cost-efficiency for mass production (20) and the natural production is facing challenges of a limited yield and high cost of cultivation and extraction, both with an increasing demand for a more and more sustainable economy, promoting biological production processes; which until now, have been associated with very high costs (21).

The present review, gathered and summarized the main findings on the application of AXT in preventive and therapeutic oncology, focusing on the hypothesized mechanisms of action underlying its cytotoxic effects on cancer cells. It

highlighted the anti-proliferative features of AXT, particularly its ability to induce cell death, inhibit metastasis and modulate key molecular pathways involved in cancer progression. The present review emphasized cancers with the most substantial body of research, providing a clearer understanding of how AXT can be effectively leveraged in combating these prevalent and impactful malignancies.

2. Protocol

A comprehensive literature search was conducted using the PubMed (https://pubmed.ncbi.nlm.nih.gov) and Scopus (https://www.scopus.com) databases, following a clearly defined retrieval strategy. The keywords 'Astaxanthin', 'Cancer' and 'Tumor' were used for searches within the Title and Abstract fields. The exact search string applied was: [Astaxanthin (Title/Abstract)] AND [cancer (Title/Abstract)] OR [cancers (Title/Abstract)] OR [tumor (Title/Abstract)] OR [tumors (Title/Abstract)]. Filters were set to include only peer-reviewed articles published from 2014 onwards. The inclusion criteria encompassed studies published in English, conducted *in vitro* or *in vivo*, with a minimum of five experimental articles for each type of cancer and peer-reviewed articles providing detailed insights into the cytotoxic mechanisms of AXT and its applications in cancer treatment or prevention. Exclusion criteria included articles not written in English and studies on types of cancer with fewer than five published experiments, with the exception of matters concerning central nervous system tumors. Additionally, studies conducted on carotenoid mixtures containing astaxanthin were excluded to maintain a sole focus on the specific effects of AXT. Initial screening of titles and abstracts was performed to assess relevance, followed by full-text reviews to confirm the eligibility of the selected studies. Data extraction was independently conducted by two reviewers to ensure accuracy and consistency. The synthesized data emphasized the role of astaxanthin in promoting cell death, inhibiting metastasis and modulating key molecular pathways involved in cancer progression. The flowchart summarizing the process of the present review is in Fig. 1.

3. Astaxanthin and cancer

Nervous system tumors. AXT has been investigated for its potential in treating some nervous system tumors, including glioblastoma multiforme (GBM) and neuroblastoma. Furthermore, phytochemicals, secondary metabolites in food, have been reported to protect neuronal cells from death in neurodegenerative disorder models through anti-oxidant and anti-inflammatory activities, opening potential multifaceted perspectives for their application (22).

GBM is one of the most aggressive forms of primary brain cancer, with very low survival rates and a significant impact on the patient's quality of life. As the most prevalent primary malignant brain tumor, glioblastoma accounts for 57% of all gliomas and 48% of all primary malignant central nervous system tumors (23). Patients diagnosed with glioblastoma often experience a rapid deterioration in neurological function, suffering from significant symptoms caused not only by the tumor but also by the side effects of various treatments (24).

When human GBM cell lines U251-MG and T98-MG, but not CRT-MG and U87-MG, are pretreated with AXT their sensitivity to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is significantly enhanced; thereby increasing the apoptotic response (25). Furthermore, the combined treatment shows improved effectiveness in inducing apoptosis compared with AXT or TRAIL alone, especially in the more responsive cell lines such as U251-MG and U87-MG, indicating that AXT may sensitize tumor cells to apoptosis-inducing agents. The differing sensitivity of these cell lines likely stems from distinct mechanisms, such as antioxidant expression and mitochondrial dynamics. U251-MG cells have lower Superoxide dismutase 2 (SOD2) expression and enzymatic activity compared with CRT-MG. Overexpression of SOD2 in U251-MG eliminates the AXT-induced sensitization to TRAIL treatment, indicating that SOD2 plays a critical role in the differential response between the two cell lines (25). These findings underscore that the ability of AXT to enhance cancer treatment may depend on the genetic and metabolic profile. Additionally, AXT exhibits hormetic effects on U251-MG, T98G and CRT-MG cell lines, where low doses stimulate cell proliferation by upregulating markers such as cyclin-dependent kinases, while higher doses induce apoptosis by triggering a dose-dependent oxidative stress response, significantly increasing reactive oxygen species (ROS) levels and promoting apoptosis (26). Targeting cyclin-dependent kinases with specific inhibitors could potentially improve treatment efficacy by reducing chemoresistance and enhancing the response to chemotherapy, as indicated also by Patel *et al* (27) for colorectal and oral cancers.

Further investigations into the effects of AXT on glioblastoma were conducting both *in vitro* in U251MG and GL261 cell lines and *in vivo* in C57BL/6J mice model. The *in vitro* results indicate that AXT could suppress cell viability and proliferation in a concentration-dependent manner, reducing cell migration and influencing key signaling molecules (ERK1/2, Akt and p38 MAPK) involved in tumor progression (28). The combined treatment of AXT with temozolomide, a standard chemotherapy drug for glioblastoma, enhanced the antitumor effects compared with AXT alone. *In vivo*, AXT significantly suppressed glioblastoma tumor growth, demonstrating its capacity to accumulate in brain tissue and effectively inhibit tumor progression (28).

Neuroblastoma is a common and aggressive pediatric cancer that originates in nerve tissues, responsible for a significant number of childhood cancer mortalities and presenting challenges for effective treatment due to its diverse genetic, morphological and clinical presentations; it most often begins in the adrenal glands but can also develop in other areas such as the neck, chest, abdomen, or spine (29). The effects of AXT were explored on SK-N-SH neuroblastoma cell line both *in vitro* and *in vivo*. *In vitro* AXT revealed strong anti-tumor activity by inhibiting proliferation, migration and invasion, while also promoting apoptosis (30). When AXT was combined with small interfering (si)RNA targeting the STAT3 signaling pathway, a synergistic effect was observed, further enhancing the reduction of tumor cell viability and aggressive behavior *in vivo* (30) The STAT3 pathway is implicated in resistance to chemotherapy and the ability of AXT to inhibit STAT3 could theoretically help counteract this resistance,

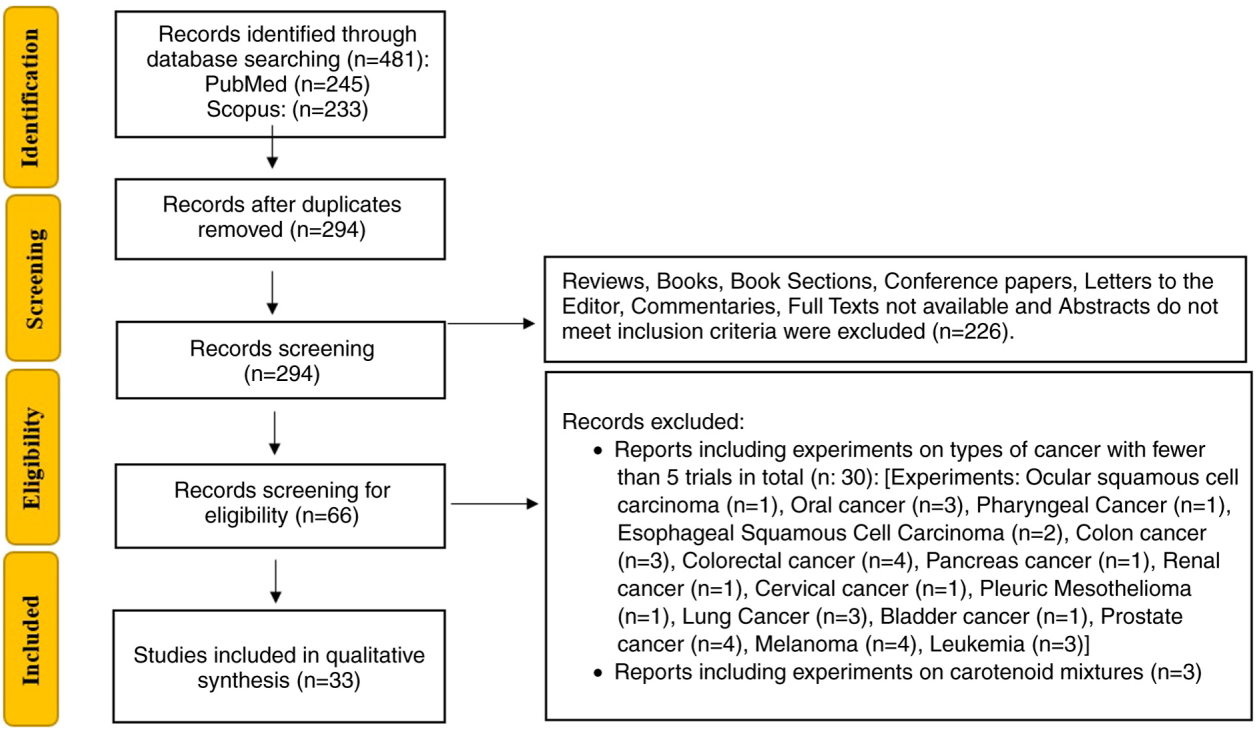

Figure 1. Flowchart of literature search.

making it a promising candidate for further investigation in chemoresistant cancer models.

AXT is known for being able to modulate cell survival, redox biology and bioenergetics status by influencing key signaling pathways (31). García *et al* (32) demonstrate that AXT reduces mitochondrial superoxide (O2-•) production in SH-SY5Y cells exposed to N-methyl-D-aspartate. Zhang *et al* (33) found that AXT activates the PI3K/Akt/GSK3β pathway, leading to the upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor, in SH-SY5Y cells under oxygen and glucose deprivation conditions. More recently AXT was shown being able to reduces mitophagy through the Akt/mTOR pathway, suggesting its potential in preventing neurotoxicity in neurodegenerative diseases (34). As a matter of fact, the regulation of mitochondrial membrane pore formation has been previously proposed as a neuroprotective mechanism of AXT in aging and neurodegenerative disorders and thus also explains their dual functions in neuronal and cancer cells (22). As an antioxidant, AXT has the potential to act as both an anticancer drug and a neuroprotectant. In cancer, AXT limits tumor growth by modulating ROS produced under stressful conditions in rapidly proliferating cells. Conversely, AXT protects against oxidative stress, which causes mitochondrial dysfunction and apoptosis, thereby reducing the detrimental effects associated with neurodegenerative diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (35).

Breast cancer. Breast cancer is the most frequently diagnosed type of cancer in women worldwide, with higher incidence rates in high High Development Index (HDI) countries and markedly lower in medium and low HDI countries. Survival rates also vary markedly between developed and less developed countries, highlighting disparities in healthcare quality and access to healthcare (36). Research findings reveal that AXT treatment of human breast cancer cell lines effectively reduces cancer progression in a dose-dependent manner by inhibiting cell growth and inducing apoptosis without affecting non-tumorigenic cell lines. AXT alleviates inflammation and the immunosuppressive environment within tumors, creating less favorable conditions for cancer growth and its spread, reducing cancer cell migration and metastasis formation (37-43). AXT may modulate various pathways involved in the activation of apoptosis, targeting key signaling pathways critical in breast cancer progression, including angiogenesis, cellular stress response, lipid metabolism and the regulation of inflammation (40,41,44).

In vitro, AXT significantly reduces cell proliferation and migration in both the MCF7 (ER-positive) and MDA-MB-231 (triple-negative) breast cancer cell lines in a dose-dependent manner. However, the MDA-MB-231 cell line was more sensitive to the anti-migratory effects of AXT due to its higher metastatic potential and apoptotic gene expression was also more prominently observed in these cells (45). In SKBR3 cells, AXT decreased the expression of human epidermal growth factor receptor 2 (HER2) and other related oncogenic proteins that are typically overexpressed in SKBR3 cells (40). This downregulation of HER2 and associated signaling pathways indicates that AXT may interfere with survival and proliferation signals in HER2-positive breast cancer cells. Astaxanthin treatment also significantly reduces the expression of pontin in T47D and BT20 cell lines (37) and mutant p53 (mutp53) in T47D, BT20 and SKBR3 cell lines (37,40). Notably, the knockdown of pontin through siRNA mirrors the effect of AXT on gene expression and markedly reduces the proliferation, migration and invasion of cancer cells. Therefore, by lowering both pontin levels and ROS, AXT also reduces

mutp53. Sowmya *et al* (46) studied the effects of AXT derived from shrimp, alone and combined with β-carotene and lutein from greens, on MCF-7 breast cancer cells. This combination exhibits enhanced cytotoxicity and oxidative stress compared with individual treatments or saponified shrimp carotenoid extract. This combination selectively killed MCF-7 cancer cells by modulating key proteins involved in cell cycle regulation and apoptosis leading to cell cycle arrest in the G_0/G_1 phase, with no adverse effects on normal breast epithelial cells (MCF-10A).

In vivo, Yuri *et al* (47) examined dietary AXT effects on mammary carcinogenesis in female Sprague-Dawley rats treated with N-methyl-N-nitrosourea; higher concentrations of AXT significantly reduces the incidence of palpable mammary tumors compared with the control group. AXT's anticarcinogenic effects are also associated with decreased adiponectin expression in mammary adipose tissues, which is linked with anti-inflammatory and anti-tumor properties and its upregulation may help reduce tumor progression (47). Furthermore, a protective effect on tissue is shown by histological analysis, indicating that AXT preserves tissue integrity in mammary glands, exerting a protective role against cellular damage caused by carcinogens (47).

Combined treatments were tested to enhance the efficacy of cell death induction in breast cancer cells. The synergistic cytotoxic effect of AXT with melatonin showed enhanced efficacy in the T47D cell line compared with the MDA-MB-231 line (39). The increased effectiveness in T47D cells is attributed to its triple-positive receptor status (expressing estrogen, progesterone and HER2 receptors), which may increase the sensitivity of these cells to apoptosis-inducing effects. By contrast, MDA-MB-231, being a triple-negative breast cancer line, exhibited lower sensitivity to the combined treatment. This variability suggested that receptor status and genetic differences between cell lines play a significant role in the differential response to astaxanthin and melatonin (39). Fouad *et al* (48) investigated the combined effects of eugenol (EUG) and AXT with doxorubicin (DOX) on MCF7 cells, a hormone receptor-positive breast cancer cell line. Key findings showed that EUG and AXT markedly increased the cytotoxic effect of DOX on MCF7 cells through epigenetic modifications and immune modulation. Notably the EUG and AXT combination increased histone acetylation and histone acetyltransferase expression and decreased aromatase and EGFR expression which is critical in breast cancer cell proliferation and survival. Vijay *et al* (44) studied the combined effects of AXT and other carotenoids with low doses of DOX on MCF-7 and MDA-MB-231 breast cancer cells; combining carotenoids with a minimal cytotoxic dose of DOX resulted in greater cytotoxic effects, more significantly in MCF-7 cells, than either higher doses of DOX alone or carotenoids alone through the modulation of redox balance. This combination not only promoted apoptosis and arrested the cell cycle in the G0/G1 phase but also exhibited minimal cytotoxicity in normal breast epithelial cells (MCF 10A). Atalay *et al* (49) focused on the effects of AXT combined with carbendazim on MCF-7 breast cancer cells; this combination significantly increased the anti-proliferative effects compared with carbendazim and AXT alone and increased cell cycle arrest in the G_2/M phase. Furthermore, co-treatment with AXT reduced the elevated ROS levels induced by carbendazim, potentially lessening oxidative stress-related side effects while maintaining the anti-cancer efficacy, suggesting that combining ATX with carbendazim could enhance anti-cancer effects while mitigating some of the oxidative stress typically induced by chemotherapy agents (49). Malhão *et al* (45) investigated the effects of AXT on breast cancer cells, both as a standalone treatment and in combination with conventional chemotherapy drugs (cisplatin and DOX). AXT alone did not show significant cytotoxic effects on the cancer cell lines tested, including luminal MCF7 SKBR3 (HER-2 positive) and MDA-MB-231 (triple-negative), as well as a non-tumoral breast cell line, MCF12A. However, in combination with cisplatin or DOX, the effect of AXT is varied. In some instances, it reduces the cytotoxicity of cisplatin, particularly with cisplatin on the SKBR3 breast cancer cell line, indicating a potential protective effect. In certain cases, AXT enhances the cytotoxic effect of the chemotherapy drugs, specifically when combined with DOX on the MCF7 cell line. The results suggest that while AXT itself does not directly induce strong cytotoxic effects against breast cancer cells, its interactions with chemotherapy drugs can influence treatment outcomes, though not always in a favorable way. This highlights the need for further research to improve understanding of the role of AXT in combination therapies.

Research also shows promising potential for using functionalized nanoparticles in breast cancer therapy. A nanoparticle formulation combining DOX with low-molecular-weight heparin (LMWH) and AXT, known as LMWH-AST/DOX nanoparticle (LA/DOX NP), has been studied. The findings highlight that LA/DOX NPs effectively suppressed liver metastasis by inhibiting the formation of neutrophil extracellular traps (NETs) (41). Furthermore, ATX-reduced gold nanoparticles (ATX-AuNPs) were studied in MDA-MB-231 human breast cancer cells, showing dose-dependent cytotoxic effects and significant antiproliferative activity, indicating potent efficacy in inhibiting cell growth. The results illustrate that ATX-AuNPs exhibit enhanced cytotoxic effects compared with free ATX alone, indicating that these nanoparticles can induce programmed cell death more effectively than free AXT and improved cellular uptake (50). ATX-loaded chitosan oligosaccharide/alginate nanoparticles (ATX-COANPs) also offer a promising solution to the challenges of low solubility, bio accessibility and bioavailability of ATX. By encapsulating ATX within COANPs, the bioactive properties of astaxanthin are enhanced, with improved *in vitro* anti-inflammatory activity and significant cytotoxic effects on MCF-7 breast cancer cells. This nanostructure, optimized using Box-Behnken design and response surface methodology, presents an effective delivery mechanism for ATX in nutraceutical and functional food application (51).

Gastrointestinal cancers. Gastrointestinal cancers encompass a diverse group of malignancies affecting the digestive system, including the esophagus, stomach, liver, pancreas, gallbladder and intestines. The incidence of gastrointestinal cancer is rising, with age-standardized diagnosis rates showing significant global variations, with the highest rates observed in South America, Eastern Asia and Central and Eastern Europe (52). Due to delayed detection and the lack of effective treatments,

GC has a poor prognosis, with a number of patients diagnosed at advanced stages and mortality often occurring within the first year of diagnosis (53). Understanding the specific characteristics and risk factors of each type is crucial for early detection, effective treatment and improving patient outcomes. The chemo preventive and cytotoxic potential of AXT has been extensively studied in relation to oral, liver and gastric cancers, demonstrating promising results and showcasing AXT's ability to inhibit tumor growth and induce apoptosis in cancer cells.

Liver cancer. Liver cancer, or hepatocellular carcinoma (HCC), is a major cause of cancer-related mortality worldwide and its increasing incidence, particularly in patients with cirrhosis, poses significant treatment challenges (54). The complexity of HCC treatment arises from the variability in tumor size, number of nodules and patient liver function. Liver transplantation is considered the most effective long-term treatment, but is limited by strict eligibility criteria and organ availability (55). AXT has been extensively studied for its potential therapeutic and preventive benefits primarily focusing on various HCC cell lines and animal models. *In vitro* and *in vivo* studies are mainly based on the HepG2 hepatoma cell line. By using Kunming mice, Shao *et al* (56) demonstrate that AXT inhibits the proliferation of H22 hepatoma cells *in vitro* and *in vivo* and induces both apoptosis and necrosis as indicated by nuclear condensation and fragmentation analysis in treated cells. Although the apoptosis rate did not vary significantly between low- and high-dose groups, cell necrosis increased markedly, with high-dose AXT performing similarly to cisplatin. Additionally, AXT effectively reduced tumor size and the number of cancer cells in mice, supporting its potential anti-tumor activity. These findings highlight AXT's role in inhibiting tumor growth and inducing cell death. Zhang *et al* (57) encapsulated AXT in biodegradable calcium alginate microspheres to enhance its bioavailability and stability, protecting it from degradation in harsh environmental conditions such as gastric acids. This study demonstrates that AXT treatment reduces ROS levels specifically in HepG2 cells, leading to significant inhibition of cell growth. Notably, this cytotoxicity was selective, sparing normal hepatocytes (THLE-2 cells), thereby highlighting AXT's potential for targeted cancer therapy without harming healthy cells (57). Thus, encapsulated AXT in calcium alginate microspheres enhances stability, enables controlled release and improves selective cytotoxicity toward cancer cells, minimizing effects on healthy cells. This approach reduces oxidative stress in normal cells, improves cellular uptake in cancer cells and offers a safer, more effective delivery method, making encapsulated AXT a promising option for targeted cancer therapy.

Another approach involves using natural sources of AXT, as in the study by Messina *et al* (58), which assesses the bioactive properties of AXT extracted from shrimp by-products on hepatoma cells (Hep-G2). This research shows dose-dependent anti-proliferative effects, where increasing concentrations of AXT decreased cell vitality and induced apoptosis, marked by the increase in p53 protein levels and activation of caspase-3 Considering that 53 is among the most well-known tumor progression inhibitors. it is reasonable that AXT activates apoptosis modulating p53 expression/activity.

These markers are critical in the cellular apoptotic pathway, reinforcing AXT's potential to induce programmed cell death in cancer cells (58). Further extending the scope of the effect of AXT on liver cancer, Li *et al* (59) examined both natural and synthetic forms of AXT on different human hepatoma cell lines, LM3 and SMMC-7721. Their findings highlight that AXT inhibits growth by downregulating critical signaling pathways such as NF-κB p65 and Wnt/β-catenin. These pathways are instrumental in the regulation of gene expression linked to cell proliferation and survival. AXT stabilizes IκB-α, preventing the nuclear translocation of NF-κB p65 and thus inhibiting this pathway and the consequent survival of cancer cells. Additionally, AXT influences the Wnt/β-catenin pathway, further strengthening its role in reducing proliferation and inducing apoptosis in a dose-dependent manner, with significant effects observed at higher concentrations (59). The study observed that AXT was comparably effective in both LM3 and SMMC-7721 HCC cell lines, demonstrating dose- and time-dependent inhibition of cell proliferation and induction of apoptosis in both of the lines (59). The anti-proliferative effects of carotenoid mixture extracted from microalgae (*Monoraphidium* sp. and *Scenedesmus obliquus*), includes AXT as a major component, was also explored using the HCC cell line HUH7 (60). The study highlights that *Monoraphidium* sp., which had the highest amounts of AXT, exhibits stronger antioxidant and anti-proliferation activities compared with *Scenedesmus obliquus*. This underscores the significance of exploring freshwater microalgae as a source of high-yielding AXT for pharmaceutical applications (60).

AXT's potential in combination with chemotherapy drugs is confirmed in studies from animal studies. Ren *et al* (61), in an *in vivo* mouse mode, shows that combining AXT with sorafenib enhances anti-tumor immune responses in hepatocellular carcinoma. AXT increases CD8+ T cell infiltration, polarizes macrophages towards the M1 phenotype, boosts anti-tumor cytokines and positively alters gut microbiota, improving overall immune function and treatment efficacy, thus reducing some of the systemic and gut-related side effects of sorafenib (61). By enhancing immune responses, AXT may overcome some of the mechanisms that allow chemo-resistant tumors to evade treatment. Subsequently, the same authors demonstrated *in vivo* that AXT combined with sorafenib enhances tumor suppression more significantly than *in vitro*, indicating that the efficacy of AXT may depend on mechanisms beyond direct cytotoxicity observed in cell culture, such as its role in modifying the tumor microenvironment or impacting pathways relevant to *in vivo* models (62). Furthermore, the combination treatment appeared to reduce symptoms linked to cachexia; such as muscle wasting, which are typically observed with sorafenib alone (62). By enhancing the effectiveness of a lower, subclinical dose of sorafenib, AXT potentially allows for a reduction in the standard sorafenib dose, thereby decreasing the likelihood of its associated toxicities.

Gastric cancer. Gastric cancer is a significant global health issue, with >1 million new cases estimated annually, making it the fifth most diagnosed cancer worldwide. Due to often being diagnosed at an advanced stage, gastric cancer has a high mortality rate, ranking as the third leading cause of cancer-related deaths with 784,000 deaths reported globally

in 2018 (63). *Helicobacter pylori* is the primary risk factor for gastric cancer, being the main cause of chronic gastritis and peptic ulcer disease. Despite decreasing infection rates in a number of countries due to improved living standards, its prevalence remains high, particularly in the Far East and is linked to socioeconomic status and hygiene levels (64).

The effects of AXT on gastric cancer were studied using the AGS adenocarcinoma cell line to investigate how *H. pylori* infection markedly alters gene expression, upregulating genes associated with inflammation, cell proliferation and cancer pathways (65-67). Kim *et al* (65) found that AXT administration results in altered expression of several genes involved in cell motility and cytoskeleton remodeling, notably c-MET, PI3KC2, PLCγ1, Cdc42 and ROCK1, which are critical for these processes. The role of AXT in mitigating the effects of *H. pylori* infection was further studied by Lee *et al* (66) on human gastric epithelial cell line AGS. AXT effectively inhibits *H. pylori*-induced apoptosis in AGS cells as demonstrated by the reduction in key cell death markers such as DNA fragmentation, caspase-3 activity and the cytochrome *c* release. Furthermore, the study indicates that, in *H. pylori*-stimulated AGS cells, AXT enhances autophagy, through increasing the phosphorylation of AMP-activated protein kinase (AMPK) and consequently downregulating mTOR. It was also found that pretreatment of AGS cells with AXT counteracted *H. pylori*-induced changes by reducing the expression of key genes involved in the Wnt/β-catenin pathway (67). This includes the downregulation of porcupine, Fos-like 1 and c-myc, which are associated with cancer cell proliferation and survival (67). In addition, AXT reversed *H. pylori*-induced repression of tumor suppressor genes such as SMAD4 and BAMBI, which are involved in the regulation of cell proliferation and survival, and reduced expression of spermine oxidase (SMOX) involved in oxidative stress (67).

AXT effectively inhibits the expression of MMP-7 and MMP-10 in *H. pylori*-infected gastric epithelial cells. These enzymes are crucial for degrading the extracellular matrix, which typically facilitates tumor invasion and metastasis. By reducing the invasive and migratory capabilities of these cells, AXT limits their ability to spread following *H. pylori* infection (68). Furthermore, *H. pylori* infection increases the expression of integrin α5 in AGS cells, which in turn enhances cell adhesion and migration, key processes in cancer metastasis. This increase is linked to elevated ROS levels and activation of the JAK1/STAT3 signaling pathway (69). AXT effectively lowers ROS levels in AGS cells and suppressed the activation of JAK1/STAT3. Consequently, AXT also decreases the expression of integrin α5, leading to reduced cell adhesion and migration in the *H. pylori*-stimulated AGS cells (69).

A dose-dependent inhibition of cell proliferation was also documented for a number of other adenocarcinoma cell lines including AGS, KATO-III, MKN-45 and SNU-1. When administered to KATO-III and SNU-1 cells, AXT has a more pronounced effect, inhibiting cell proliferation in a dose-dependent manner and decreasing the percentage of cells in the S phase. Accordingly p27kip-1 expression, a cyclin-dependent kinase inhibitor that regulates the cell cycle, is increased, thereby contributing to the observed G_0/G_1 arrest (70). By contrast, AXT shows minimal effects on the viability of AGS and MKN-45 cells and did not significantly alter cell cycle progression in these cell lines (70). Others mechanisms explaining the antiproliferative features of AXT in AGS cancer lines have been reported, including the involvement of ERK and the activation of necroptosis-related proteins such as NADPH oxidase, receptor-interacting protein kinase (RIP) 1, RIP3 and mixed lineage kinase domain-like protein (71).

In vivo, on male C57BL/6 mice used as animal model, AXT was observed to reduce oxidative stress, as indicated by decreased lipid peroxide levels and myeloperoxidase activity and suppression of inflammatory cytokine IFN-γ, as well as oncogene expression, such as c-myc and cyclin D1, which are associated with cancer progression (72). The study suggests that AXT can help to protect against oxidative damage, inflammation and oncogene activation in gastric tissues, potentially offering a preventive strategy against *H. pylori*-associated gastric carcinogenesis.

4. Conclusions

In conclusion, AXT holds considerable promise as a bioactive compound with therapeutic and preventive potential in cancer management. Extensive *in vitro* and *in vivo* research underscores its efficacy across multiple cancer types, including nervous system, breast and gastrointestinal cancers, largely due to its antioxidant, anti-inflammatory and anti-proliferative properties. AXT exerts significant effects by modulating various key molecular pathways involved in cancer progression, cellular stress responses and neuroprotection. It has been shown to activate the PI3K/Akt/GSK3β pathway, leading to the upregulation of Nrf2, a transcription factor crucial for oxidative stress regulation. It also modulates the Akt/mTOR pathway, influencing mitophagy and preventing excessive apoptosis, thus exhibiting potential in reducing neurotoxicity and affecting cancer cell behavior. It was also found to inhibit the JAK1/STAT3 pathway, which is associated with cell adhesion and migration, particularly in the context of cancer metastasis. Additionally, it downregulates the Wnt/β-catenin pathway, thereby reducing cancer cell proliferation and survival. The NF-κB pathway is also affected by AXT, as it stabilizes IκB-α to prevent the nuclear translocation of NF-κB p65, thereby inhibiting survival signals in cancer cells. Likewise, p53, the most well-known tumor progression inhibitor may be influenced by AXT in several cancers preventing cancer growth and invasiveness. By targeting cyclin-dependent kinase pathways, AXT promotes cell cycle arrest, contributing to reduced cancer cell proliferation.

Furthermore, AXT enhances autophagy through the AMPK/mTOR pathway, reducing cell proliferation in cancer models. Last, AXT affects the ERK1/2 and p38 MAPK signaling pathways, which are involved in tumor suppression, as demonstrated in studies on glioblastoma. These regulatory effects underscore AXT's potential as a multifaceted agent in cancer therapy and neuroprotection, warranting further clinical research to fully validate its therapeutic role. The synergy observed when AXT is combined with chemotherapeutic agents highlights its role in enhancing treatment efficacy and minimizing adverse effects, especially in breast

and liver cancers. Moreover, innovations in AXT delivery, such as encapsulation in nanoparticles, have further improved its bioavailability and targeted action, enabling more effective cancer cell targeting and potentially reducing systemic side effects. However, despite promising laboratory results, further *in vivo* studies and clinical trials are essential to validate AXT's therapeutic effects in human populations. These studies would allow the establishment of standardized dosing regimens, confirm safety profiles and AXT's interactions with conventional therapies across diverse cancer populations. It is important to note that research on certain types of cancer remains limited. Therefore, the conclusions drawn for these specific cancers should be interpreted with caution, as they may not be as robust or comprehensive as those for more extensively studied malignancies.

As a future direction, it would be valuable to conduct comparative studies between natural and synthetic AXT to improved understand their respective efficacies and potential differences in biological activity. Additionally, further research combining AXT with other bioactive compounds from natural sources would be beneficial, as these combinations can exhibit synergistic effects that enhance its overall therapeutic potential. This synergy can result in superior antioxidant, anti-inflammatory and anticancer effects compared with synthetic AXT alone. Investigating these synergistic interactions and exploring the potential of combining AXT with other naturally occurring compounds could pave the way for more effective, multi-targeted cancer treatments and preventive strategies.

Continued research into the bioavailability, delivery mechanisms and role of AXT in combination therapies could facilitate its incorporation into clinical oncology, potentially offering a natural, complementary approach to current cancer treatments.

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Not applicable.

Authors' contributions

CC and MF contributed to the study design; CF and CS developed the methodology; CC and MFT were responsible for data curation and original draft preparation; AG, HGD and GOC reviewed and edited the manuscript; MF supervised the project and secured funding for the study. Data authentication is not applicable. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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