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REVIEW

Pharmacotherapeutic Efficacy of Astaxanthin Toward Breast Cancer: A Systematic Review

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ABSTRACT

Background: Breast cancer (BC) is one of the most common malignancies in women, characterized by the malignant proliferation of breast epithelial cells that significantly impairs patients' quality of life. Astaxanthin (ASN), a marine-derived xanthophyll carotenoid, is known for its antioxidant and anti-inflammatory properties. Emerging evidence suggests that ASN may exert anti-neoplastic effects by inhibiting tumorigenesis and suppressing the growth and progression of BC cells. This systematic review aims to critically evaluate the therapeutic potential of ASN as a pharmacological agent in the prevention and management of breast cancer.

Methodology: Following PRISMA 2020 guidelines, a comprehensive literature search was conducted in PubMed, Web of Science, and Google Scholar using keywords (e.g., "astaxanthin", "carotenoid", "breast cancer"). Studies were screened based on predefined inclusion and exclusion criteria with a focus on recent mechanistic insights. Ten studies meeting these criteria were included for analysis.

Results: The included studies (nine in vitro and one in vivo) demonstrate that ASN exerts significant antiproliferative, pro-apoptotic, and cytotoxic effects on BC cells. Mechanistically, these effects involve downregulation of mutated p53 and upregulation of pro-apoptotic markers. ASN also suppressed metastasis and angiogenesis, associated with increased expression of metastasis-suppressor genes such as BRMS1, maspin, MKK-4, and CD-82.

Conclusion: ASN shows promising anti-cancer potential in BC by targeting key pathways in cell proliferation, apoptosis, and metastasis. Additionally, it may enhance chemosensitivity and reduce chemotherapy-induced toxicity. These findings support the potential role of ASN as an adjuvant therapeutic candidate in BC treatment strategies.

Keywords: Astaxanthin, Breast cancer, Antioxidant, Apoptosis, Metastasis, Chemotherapy, Carotenoid

1. Introduction

When malignant cells grow within the tissues of the breast, the condition is referred to as breast cancer (BC). It is important to be considered because of its severity (He et al., 2020). BC is the most common cancer in women and ranks as the second most repetitive type of cancer among other female organ cancers. As hereditary patterns and environmental factors interact together in order to induce BC (Zhu et al., 2023). The condition starts when normal cells become aging and are no longer needed, they will undergo apoptosis, or self-destruction. Up until that point, a number of protein clusters and pathways protect the cells from programmed death (Liu et al., 2024). However, RAS/MEK/ERK mechanism and the

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phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway (PI3K/AKT pathway) are two different examples of protective pathways that inhabit cell destruction (Nunkoo et al., 2024). Additionally, GATA-3 is a differentiation marker that regulates the expression of genes associated with epithelial differentiation, including the oestrogen receptor (ER). Its absence leads to a loss of differentiation and this is linked to poor prognosis, cancer cell invasion, and tumour spread (Asch-Kendrick and Cimino-Mathews, 2016). Regarding the treatment, the age of the patient and the cancer's stage are two important variables that have an impact on how BC is managed (McGuire et al., 2015). BC is usually treated with surgical intervention that may be followed by radiation therapy chemotherapy, or both. Also, Monoclonal antibodies, or other immune-modulating treatments, may be administered in certain cases of metastatic and other advanced stages of BC. Another controversial treatment for breast cancer in general is the utilization of antioxidants. Astaxanthin (ASN) is a potent antioxidant with notable effects against various cancer types, particularly BC cell lines (Grinan-Lison et al., 2021; McCall et al., 2018). ASN is an accessory pigment found in plants with several reasonable traits. It is frequently considered as of the most powerful anti-inflammatory with its antioxidant properties. It has the potency to lessen the risk of cancer or eradicate the spread of tumour proliferation. ASN is mainly notable since it has been said to strengthen mitochondrial redox state and functional integrity. The insertion into the lipid bilayers form this complex which preserves cell membrane integrity (McCall et al., 2018; Donoso et al., 2021). ASN inhibits oxidative stress and inflammatory responses by triggering Nrf2-ARE and other signaling pathways (Davinelli et al., 2022). It also inhibits cancer cell invasion, migration, and intercellular communication by modulating intracellular signaling pathways. These mechanisms contribute to its potential in preventing breast and other types of cancer (Ebran Safahi and Nikoonahad Lotfabadi, 2024). Moreover, ASN has the ability to reduce the levels some inflammatory markers such as IL-6, TNF-α, and IFN-γ by the suppression of NF$\kappa\beta$ (Chang and Xiong, 2020). Because ASN reduces oxidative stress and exerts anti-inflammatory effects, it plays a key role in regulating apoptotic signalling. ASN promotes intrinsic apoptosis by modulating Bax/Bcl-2, activating cleaved caspase-3 and -9, and phosphorylating ERK1/2, JNK, and p38. Therefore, supplementing with ASN may positively influence cancer outcomes. Additionally, ASN suppresses proliferation in a dose-dependent manner, causes cell apoptosis, and stops cell cycle progression at G0/G1 (McCall et al., 2018; Donoso et al., 2021). ASN induces cell death, as proven by the decreased expression levels of mutp53 and the cleaved PARP-1 fragment sequentially. It also changes the expression of superoxide dismutases and the anti-apoptotic factor Pontin, as it decreases the production of ROS inside cells. ASN prevents oxygen-mediated cytotoxicity, modifies tumour immunity, and induces intrinsic apoptosis by inhibiting the signaling of PI3, AKT, and mitogen-activated protein kinase (MAPK). It also has cytotoxic properties on the human breast tumour cell line MCF-7, that contains progesterone, estrogen, and glucocorticoid receptors (Kim et al., 2020). Furthermore, ASN possesses other properties such as photo-protective, antioxidant, anti-inflammatory, and anti-apoptotic effects that work at various levels and benefit in the skin, heart, eyes, neurons, and immune system (Donoso et al., 2021). ASN mechanisms are illustrated in Fig. 1. Recent synthetic anti-cancer medications have various disadvantages which limit their usage because of their cytotoxic harmful consequences on normal cells. Therefore, the natural medicinal compounds that hinder the development of cancer cells without resulting in significant damage are under investigation in an attempt to discover potential therapies with less cytotoxic effect (Ebran Safahi and Nikoonahad Lotfabadi, 2024; Lin et al., 2020).

The purpose of this review was conducted systematically by collecting to collect extensive and detailed information regarding ASN's potential application as a pharmacotherapeutic agent for prevention and treatment of BC. By highlighting its efficacy, safety profile, and mechanism of action, the evaluation of this study will help to guide future research by offering insightful details about ASN's clinical usage.

2. Materials and methods

2.1. Eligibility criteria

To discover suitable and reasonable studies analyzing ASN's pharmacotherapeutic prospect in BC patients, an extensive and comprehensive review of the literature was carried according to PRISMA 2020 guidelines (Tugwell and Tovey, 2021). Only original in vitro and in vivo studies were explicitly targeted in the search, which was limited to English-language journal articles published between 1st January, 2010 and 31st December, 2022. Several exclusion criteria were applied to ensure the quality and relevance of the selected data: conference papers and proceedings, documentary reports, letters to the editor, narrative reviews, systematic or meta-analyses, and articles without full-text access.

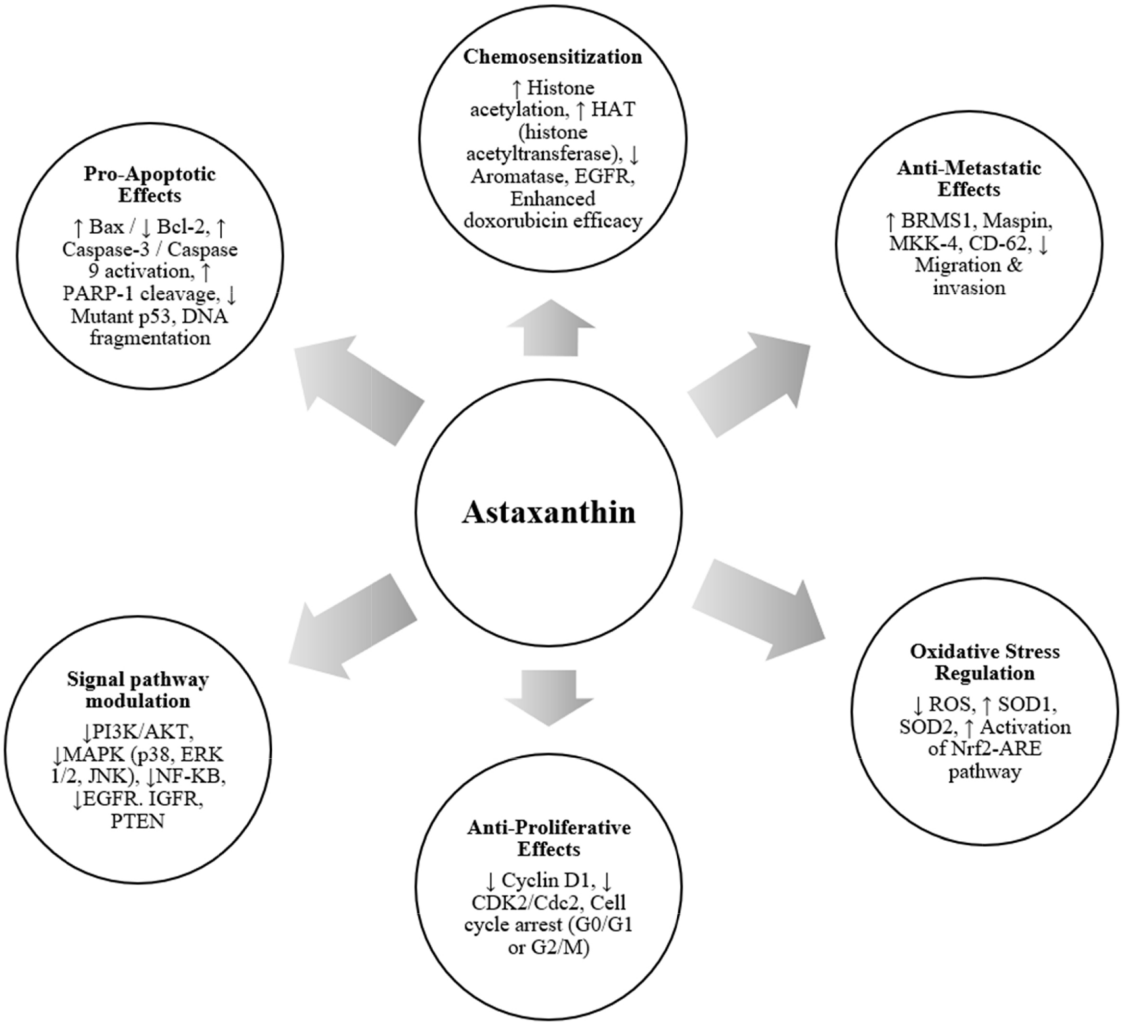

Fig. 1. Schematic representation of the multifaceted anticancer mechanisms of astaxanthin (8–13).

2.2. Study selection

The following key words “astaxanthin”, “antioxidant”, “carotenoid”, and “breast cancer” used to search studies from major scientific databases such as Web of Science (WoS), PubMed, ScienceDirect, and Google Scholar. Likewise, the authors team carried out the selection process in an independent manner. This is done in order to avoid bias and being sure whether all of the requirements fulfilled.

2.3. Data extraction and quality assessment

All studies included in this systematic review were assessed independently by two reviewers to ensure methodological rigour and relevance. Data extraction was conducted using a predesigned form that captured essential study details, including publication year, experimental model (in vitro or in vivo), breast cancer cell lines used, astaxanthin concentration, mechanisms of action, and therapeutic outcomes.

The process of study identification, screening, eligibility assessment, and inclusion is summarised in the PRISMA 2020 flow diagram, Fig. 2. This figure outlines the total number of records identified from databases, duplicates removed, records screened, full texts assessed for eligibility, and studies included in the final analysis.

To evaluate the methodological rigor and reliability of the included studies, we applied the Office of Health Assessment and Translation (OHAT) risk of bias tool, which is recommended by the U.S. National Toxicology Program for assessing both in vitro and in vivo evidence (23). This tool is advantageous because it provides a consistent framework for evaluating diverse study designs, which was essential given that our dataset comprised both cell culture experiments and one animal model study.

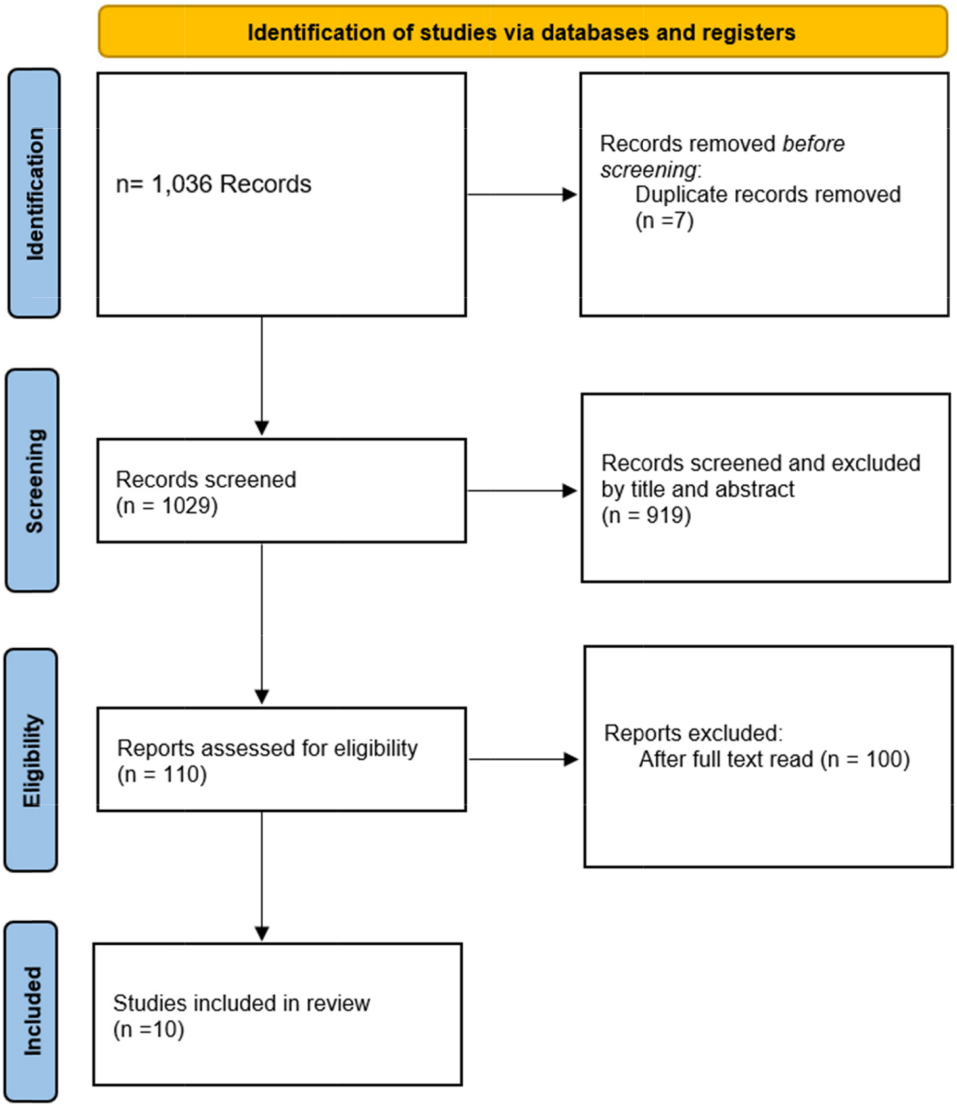

Fig. 2. Flow chart for literature search of study selection.

The OHAT tool assesses potential biases across six main domains which are: selection bias performance bias, attrition/exclusion bias, detection bias, selective reporting bias, and other sources of bias including conflicts of interest, funding influence, or methodological flaws. Each study was evaluated within these domains and categorized as having definitely low, probably low, probably high, or definitely high risk of bias. An overall judgment was then made for each study, summarizing its risk of bias/quality rating as Low, Low–Moderate, Moderate, or High.

Using this approach, most of the included in vitro studies were rated as Low–Moderate risk of bias, reflecting generally sound methodology, but limited reporting of blinding, randomization, or sample size justification. The single in vivo study (Nakao et al., 2010) was classified as Moderate, due to insufficient details on randomization and blinding, despite clear reporting of outcomes. Only one preprint study (Fouad et al., 2020) was judged to be at High risk of bias, primarily due to the absence of peer review and incomplete methodological reporting.

3. Results and discussion

This search resulted in 1036 records from various databases mentioned above. After removing duplicates, 1,029 records were screened. Based on predefined inclusion criteria, 717 were excluded, and 202 more were removed after title and abstract review. The remaining 110 full-text articles were assessed for eligibility. The reasons for the removal or exclusion of full-text articles were clearly defined to

ensure the quality and relevance of included studies. A total of 100 articles were excluded for various reasons, including being narrative reviews, systematic or meta-analyses, general review articles, documentary reports, letters to the editor, case reports, or conference papers. Articles without full-text availability were also excluded. After this rigorous screening and eligibility evaluation process, eventually ten studies were included in the final analysis. The full identification, screening, and selection of studies in accordance with the PRISMA 2020 guidelines was shown in Fig. 2.

Additionally, Table 1 has shown the fundamental characteristics of the ten studies which were evaluated for this particular review. The key information extracted from each included study comprised: (1) type of the study (in vitro or in vivo), (2) type of breast cancer or cell line used, (3) the medication (astaxanthin) and its concentrations, (4) the proposed mechanism of action, (5) the main outcomes of the study, and (6) quality appraisal results. The ten included studies comprised nine in vitro and one in vivo investigation. These studies examined the pharmacological potential of ASN in BC through a variety of mechanistic assays. Table 1 provides a structured summary of the experimental models, breast cancer cell lines (e.g., MCF-7, SKBR3, MDA-MB-231, T47D, BT20), ASN concentrations (ranging from nanomolar to 300 μM), proposed mechanisms of action, and therapeutic outcomes.

The in vitro studies consistently demonstrated that ASN exerts potent anti-proliferative and pro-apoptotic effects in BC cell lines. For instance, Kim *et al.* used SKBR3 cells to show that ASN activates the MAPK cascade (ERK1/2, JNK, p38), induces cleaved PARP-1, and suppresses mutant p53, suggesting involvement in intrinsic apoptotic signaling. This was further supported by reduced ROS levels and upregulated SOD1/2, highlighting ASN's capacity to balance oxidative stress (Kim et al., 2020). Similarly, McCall *et al.* demonstrated that ASN selectively induces apoptosis in cancer cells (MCF-7, MDA-MB-231), while sparing normal epithelial cells (MCF-10A), through modulation of BAX and BCL-2 (McCall et al., 2018). These results suggest a degree of therapeutic selectivity, as essential feature for clinical applicability. Karimian *et al.* reinforced these findings using low-dose ASN (0.005 – 300 μM), which triggered DNA fragmentation and apoptotic events in T47D and MDA-MB-231 cells (Karimian et al., 2022). Notably, Ahn *et al.* explored the effect on breast cancer stem cells (BT20 and T47D), revealing that ASN suppressed stemness-related markers such as Pontin and mutant p53 (Ahn et al., 2020), underscoring its potential to target resistant subpopulations.

Moreover, several studies revealed ASN's role in suppressing metastasis and enhancing chemosensitivity. Badak *et al.* reported that ASN upregulated BRMS1, Maspin, MKK-4, and CD-82, genes associated with metastasis suppression in T47D cells (Badak et al., 2021). ASN's ability to inhibit cellular migration and angiogenesis further supports its anti-metastatic potential. Fouad *et al.* provided compelling evidence of chemo-sensitization: ASN co-administered with doxorubicin significantly increased histone acetylation and HAT expression, while reducing aromatase and EGFR expression (Fouad et al., 2020). This implies that ASN may potentiate standard chemotherapy efficacy via epigenetic modulation. Subsequently, Gardaneh *et al.* confirmed, through molecular docking simulations, that ASN exhibits high binding affinity for key oncogenic receptors (e.g., EGFR, IGF1R, AKT, ERK1/2, PTEN), supporting its pleiotropic molecular interference (Gardaneh et al., 2020).

The sole in vivo study, conducted by Nakao *et al.*, used BALB/c mice bearing WAZ-2T mammary tumors. Oral ASN administration led to significant activation of NK cells and increased IFN-γ levels, resulting in a measurable reduction in tumor growth (Nakao et al., 2010). Although preliminary, these results validate the immune-enhancing and cytotoxic potential of ASN in an animal model. However, the absence of long-term safety, pharmacokinetics, and survival analyses limits translational conclusions. Despite methodological variability (e.g., cell lines, doses, endpoints), a convergent trend emerges: ASN exerts multi-level antitumor activity. Its ability to influence cell proliferation, apoptosis, oxidative stress, stemness, epigenetics, and immune modulation makes it a strong candidate for further exploration. Importantly, ASN's differential impact on cancer vs. normal cells suggests a favorable therapeutic index (Alugoju et al., 2023).

Nevertheless, differences in experimental designs, particularly in ASN source (synthetic vs. natural), solvent systems, and duration of exposure, may account for variability in potency. Standardized protocols would improve the reproducibility and comparability of future research. Despite extensive preclinical support, no clinical trials investigating ASN in breast cancer patients were identified.

In summary, ASN demonstrates good anti-breast cancer effects in preclinical models via multiple mechanisms: inducing apoptosis, halting cell cycle progression, reducing oxidative stress, and suppressing metastasis. The summarized evidence in Table 1 and the selection process in Fig. 2 underscore the consistency of these outcomes across diverse models. However, the translational gap remains significant.

Table 1. Summary of studies characteristics, mechanisms of action, outcomes, and OHAT-based quality assessment of included studies.

Serial Number	Authors	Type of the study	Type of breast cancer cell-line	Concentration of medication	Mechanism of action	Outcome of the study	Study quality (OHAT Assessment)
1	(Ahn et al., 2020)	*In vitro*	BT20 and T47D Breast Cancer Stem Cells	60–100 μM ASN	Inhibiting Expression of Pontin and Mutant p53	Anti-proliferative effect	Low–Moderate
2	(Atalay et al., 2019)	*In vitro*	MCF-7	5–30 μg/mL ASN with 8–30 μM carbendazim	Induction of mitotic arrest and increase the G2/M phase cell cycle arrest.	Inhibit breast cancer cell proliferation	Low–Moderate
3	(Badak et al., 2021)	*In vitro*	T47D cell	0–2000 μM ASN	Increase BRMS1, maspin, MKK-4 and CD-82 expression	Inhibit metastasis and angiogenesis	Moderate
4	(Fouad et al., 2020)	*In vitro*	MCF7	40 μM ASN with 0.0625–0.75 μM doxorubicin	Combination with astaxanthin significantly increased the level of histones acetylation and histone acetyl transferase expression, while reduced the expression of aromatase and epidermal growth factor receptor (EGFR) when compared with doxorubicin alone.	Astaxanthin significantly increased doxorubicin cytotoxicity	High
5	(Gardaneh et al., 2020)	*In vitro*	MCF-7, BT-474, SKBR3 and MCF-10	8–80 μM ASN	Strong binding of astaxanthin to EGFR, IGF1R, AKT, ERK1/2, and PTEN.	Induce apoptosis.	Low–Moderate
6	(Karimian et al., 2022)	*In vitro*	T47D, MDA-MB-231, and MCF10A	0.005–300 μM ASN	Reduced the expression of Bcl2 proteins	Very low doses of astaxanthin reduced survival rate, induced apoptosis, and destroyed the DNA in cancerous cells	Low–Moderate
7	(Kim et al., 2020)	*In vitro*	SKBR3 cells	0–80 μM ASN	•Induce Cell Cycle Arrest and Apoptosis of the SKBR3 Cells, •Reduce the Level of Mutp53 Expression and Generate a PARP-1 Fragment in the SKBR3 Cells, •Induce Intrinsic Apoptosis Through Activation of the MAPKs in the SKBR3 Cells, •Decrease Intracellular ROS Level and 7Modulated SOD1 and SOD2 Expressions in the SKBR3 Cells, •Decrease the Expression Level of Pontin and Reduce Association between Mutp53 and Pontin in the SKBR3 Cells.	Inhibit breast cancer cell proliferation, change cellular morphology of SKBR3 cells and induce apoptosis.	Low–Moderate
8	(McCall et al., 2018)	*In vitro*	MCF-7, MDA-MB-231, MCF10A	10–50 μM ASN.	Effect on gene expression of two mediator of apoptosis BAX and BCL-2	Inhibit breast cancer cell migration and induce apoptosis	Low–Moderate
9	(Nakao et al., 2010)	*In vivo*	Mice were inoculated with WAZ-2T (-SA) mammary tumor cells	0.005% ASN	Activation of NK cells and IFN- γ production in mice in-vivo	Cytotoxic effect	Moderate

Future research must focus on bridging this gap through well-designed animal and clinical studies, with emphasis on dosing strategies, bioavailability, and long-term safety. ASN stands as a promising adjuvant or complementary therapy in breast cancer management, but its full therapeutic potential awaits confirmation in clinical settings.

4. Conclusion

This systematic review aims to explore ASN's pharmacotherapeutic efficacy against BC. The collected data indicates that ASN exerts multifaceted anti-cancer effects. Multiple in vitro studies have confirmed that ASN induces apoptosis, causes cell cycle arrest, and inhibits the proliferation of BC cells. The medication also mitigated chemotherapy-induced toxicity and enhanced tumour cell sensitivity to standard chemotherapeutic agents. These outcomes suggest that ASN could serve as a valuable adjunct to conventional BC therapies. Moreover, these findings might support the idea of using ASN an adjuvant to lessen the probability of anticancer treatment resistance. To fully realize the clinical potential of ASN, further research is required. Additional in vivo studies should investigate ASN's anticancer activity and safety in animal models to validate the in vitro mechanisms observed. Given the current lack of clinical evidence, rigorous randomized, double-blind, placebo-controlled trials in BC patients are essential to evaluate ASN's efficacy and safety. Such future clinical investigations will be critical for determining whether ASN can be effectively integrated into standard treatment regimens as an adjuvant therapy for BC.

Author's contribution

H.A.A, B.H.M; conceptualization, methodology design, and literature search. B.H.M.: supervision H.A.A; data extraction. H.A.A, L.I.S, R.M.K, S.M.D; data analysis, interpretation of results, preparation of the table and figure, and manuscript editing. All authors have approved and revised the final version and agreed to be published.

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Conflict of interest

The authors affirm that they hold no conflicting interests related to this research.

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