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In Vivo Studies of Anticancer Peptides for Breast Cancer Therapy

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Abstract

Context: Breast cancer is a major cause of mortality worldwide. It involves the proliferation of cells within breast tissues and metastasis to other organs. Currently, several strategies exist to address this challenging disease, but none are both promising and safe, often exposing patients to complications. Consequently, alternative therapeutic agents are urgently needed. Anticancer peptides (ACPs), due to their considerable efficacy and low toxicity, hold high therapeutic value in combating breast cancer. Reviewing the activity, toxicity, and mechanisms of ACPs, as reported in original articles from this era, can lead to better judgment regarding their implementation in clinical trials.

Evidence Acquisition: We conducted a search in the PubMed database for original articles published in English from 1963 to 2025. The search strategy is outlined in Appendix 1 in Supplementary File. This study included original articles that investigated the anticancer effects of peptides in vivo. Excluded from the analysis were studies conducted only in vitro or those that investigated other properties of the peptide, such as delivery, imaging, or vaccination, without examining the anticancer effects of the peptide on tumors. Additionally, articles written in languages other than English, as well as reviews and duplicates, were excluded.

Results: A search of the PubMed database yielded 3,552 articles. After removing duplicates and review papers, 3,147 articles were deemed suitable and qualified for analysis. Following a screening process based on titles and abstracts, 3,080 publications were excluded due to lack of relevance, leaving 67 articles that met our inclusion criteria for full-text review (Appendix 2 in Supplementary File). The anticancer properties of the reviewed peptides are summarized in Appendix 3 in Supplementary File.

Conclusions: The development of ACPs represents a hopeful and innovative frontier in the fight against breast cancer. Through ongoing research, ACPs could emerge as a vital component of treatment options, providing new hope for patients worldwide.

Keywords: Breast Cancer, Anticancer Peptides, In Vivo, Mechanism, Cancer Therapy, Tumor

1. Context

Cancer is a complex and devastating disease affecting millions globally, characterized by the growth and spread of abnormal cells. It results from genetic changes that disrupt normal cell activities, leading to tumor formation, tissue infiltration, and metastatic disease. Cancer is the world's leading cause of death, with annual diagnosis rates rising, highlighting its growing global impact. Despite significant advances in cancer biology and treatment options, cancer poses enormous public health challenges due to its variety, drug resistance, and recurrence tendency (1-4).

Breast cancer is the most common cancer among women and one of the leading causes of cancer deaths worldwide. In the United States, the breast cancer death rate is 19.3 per 100,000 women as of 2024 (5). By 2040, the morbidity and mortality rates of breast cancer are predicted to exceed 3 million and 1 million cases annually due to aging and population growth (6). This

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condition features uncontrollable proliferation of cells within breast tissues, often associated with tumors that infiltrate adjacent tissues and metastasize to other organs (7-9).

Breast cancer is highly complex, with different molecular subtypes exhibiting distinct biological properties and treatment responses. The three main subtypes are hormone receptor-positive (HR+), HER2-positive (HER2+), and triple-negative breast cancer (TNBC). Hormone receptor-positive tumors, which express estrogen or estrogen receptors, are often treated with hormones such as tamoxifen and aromatase inhibitors. HER2-positive malignancies, defined by overexpression of HER2 proteins, respond effectively to targeted therapies like trastuzumab (10-12). The TNBC, lacking HR and HER2 expression, is the most aggressive and difficult-to-treat subtype, often requiring chemotherapy. However, chemotherapy has limited effectiveness and serious adverse effects, including drug resistance and reduced patient quality of life.

Current breast cancer treatment options require a comprehensive approach tailored to the tumor's genetic characteristics, stage, and individual patient considerations (10, 13, 14). The main therapeutic methods include:

1. Surgery: Procedures such as lumpectomy and mastectomy are used to eradicate local cancer (15).

2. Chemotherapy: Drugs like doxorubicin and paclitaxel target rapidly dividing cancer cells but often cause systemic toxicity, resulting in serious side effects such as nausea, fatigue, and decreased function (16, 17).

3. Radiation therapy: Used post-surgery to eliminate residual cancer cells and reduce local recurrence risk. Although effective, it can damage healthy tissues and cause long-term consequences (18).

4. Hormone therapy: HR+ breast cancer responds well to selective estrogen receptor modulators (e.g., tamoxifen) and aromatase inhibitors (e.g., letrozole). However, resistance to these treatments remains a significant challenge (19, 20).

5. Targeted therapy: Monoclonal antibodies (e.g., trastuzumab) and small molecule inhibitors (e.g., lapatinib) target specific molecular pathways, especially in HER2-positive malignancies. Despite improved outcomes, high costs and limited availability pose obstacles (21).

6. Immunotherapy: Immune checkpoint inhibitors (e.g., pembrolizumab) enhance the immune system's ability to detect and destroy cancer cells, showing potential for treating TNBC. However, only a small number of patients respond to immunotherapy, which may have immune-related side effects.

Despite these advances, challenges such as drug resistance, cancer recurrence, and severe side effects necessitate the development of new, effective, and safe drugs for patients (22, 23).

1.1. Anticancer Peptides: A New Frontier for Breast Cancer Treatment

Anticancer peptides (ACPs) have emerged as a promising new category of treatment options for breast cancer. These short sequences of amino acids exhibit targeted toxicity against cancer cells while sparing healthy tissues. Their unique features, including high specificity, low toxicity, and the ability to evade drug resistance mechanisms, make them attractive candidates for further investigation (24, 25).

1.2. Physicochemical Properties of Anticancer Peptides and Supplementary Features

The ACPs, typically composed of 10 to 50 amino acids, possess a net positive charge due to the proximity of cationic residues like lysine and arginine. This cationic nature facilitates their interaction with the negatively charged membranes of cancer cells, which often have higher levels of anionic phospholipids, such as phosphatidylserine, compared to normal cells (26). Additionally, ACPs often exhibit amphipathic properties, allowing them to interact with both hydrophilic and hydrophobic environments. This duality enables them to penetrate cancer cell membranes, disrupt membrane integrity, and initiate apoptosis or necrosis (27).

The secondary structures of ACPs, including α-helices, β-sheets, or random coils, are crucial to their biological activity (28). For instance, α-helical peptides such as Melittin and LL-37 have demonstrated potent anticancer activity by forming pores in the cancer cell membrane, leading to cell lysis (29). Furthermore, β-sheet peptides exert anticancer effects by disrupting membranes and modulating immune responses (30).

1.3. Anticancer Peptide Sources

The ACPs can be derived from a wide range of sources, including microorganisms, plants, and animals. For example, peptides like magainin, isolated from the skin of African clawed frogs (Xenopus laevis), exhibit significant anticancer properties (31). The ACPs are also abundant in marine life, including mollusks

and marine anemones, with peptides such as pardaxin and dolastatin showing promising results in preclinical studies (27). Additionally, ACPs can be identified from human proteins, such as lactoferricin, which is produced by the enzymatic degradation of proteins in bodily fluids (32).

The diverse sources and configurations of ACPs provide an extensive pool of potential treatment options for breast cancer. Advances in peptide design and bioinformatics have enhanced ACP production strategies, improving their robustness, selectivity, and therapeutic viability (33). This underscores the potential of ACPs as versatile and powerful tools in the fight against breast cancer.

1.4. Action Mechanisms of Anticancer Peptides

The ACPs combat cancer through various mechanisms, including.

1.4.1. Membrane Rupture

Many ACPs interact with the negatively charged membranes of cancer cells, forming pores or disrupting lipid bilayers, which leads to cell death (34).

1.4.2. Initiation of Apoptosis

Some ACPs trigger apoptosis by engaging intrinsic or extrinsic pathways, affecting critical regulators such as BAX, BCL-2, and caspases (35).

1.4.3. Modulation of the Immune System

Certain ACPs enhance the immune response by activating cytokine production, attracting immune cells, and facilitating the presentation of tumor antigens (36, 37).

1.4.4. Suppression of Angiogenesis

The ACPs can inhibit the formation of new blood vessels, thereby restricting the supply of nutrients and oxygen to tumors (24, 38, 39).

2. Anticancer Peptides for Breast Cancer Therapy

2.1. Bovine Lactoferricin and Its Derived Peptides

Bovine lactoferrin (bLF), a 77 kDa iron-binding glycoprotein found in bovine breast milk, exhibits various bioactive functions, including antimicrobial, anticancer, and immunomodulatory properties. Lactoferrin is a cancer-fighting agent that is safe and well-tolerated when administered in vivo (40, 41). Lactoferricin B (LfcinB), a cationic and amphipathic peptide derived from lactoferrin through acid-pepsin hydrolysis, demonstrates antifungal, antibacterial, and anticancer properties (42-44).

2.1.1. Bovine Lactoferricin

This 25-amino acid peptide, LfcinB, induces apoptosis in various breast cancer cell lines, while MCF-10A cells remain insensitive to LfcinB. A Boyden chamber assay demonstrated LfcinB's potential to inhibit the invasion capability of breast cancer cell lines, showing a more pronounced effect in the MDA-MB-231 cell line (80%) compared to MDA-MB-468 cells (50%). Intratumoral injections of LfcinB in a mouse xenograft model significantly induced apoptosis in tumor cells, leading to reductions in tumor growth rate and size. Both tumor volume and weight decreased markedly following LfcinB treatment, highlighting its potential as a safe candidate for breast cancer therapy (40).

2.1.2. Dimeric peptide 26[F]

In 2017, it was demonstrated that the dimeric peptide LfcinB $(20 - 30)_2$, with the sequence $(20RRWQWRMKKLG30)_2$-K-Ahx, has the potential to inhibit MDA-MB-468 and MDA-MB-231 cell lines in vitro, with IC_{50} values of 5 μM and 14 μM, respectively, after a 2-hour incubation (45). According to Insuasty-Cepeda et al., the analogue 26[F], characterized by the sequence $(RRWQWRFKKLG)_2$-K-Ahx, exhibits cytotoxicity against the MCF-7 breast cancer cell line. In experiments conducted on mice, its lethal dose 50 (LD_{50}) was found to range from 70 to 140 mg/kg (46).

2.2. Melittin

Melittin, a water-soluble cationic polypeptide composed of 26 amino acids, is the principal toxic component of honeybee (Apis mellifera) venom (47-49). Duffy et al. demonstrated that both honeybee venom and melittin were selectively cytotoxic against triple-negative and HER2-enriched breast cancer cells compared to normal cells. According to immunoblot analysis results, melittin alone induced a greater degree of apoptosis than honeybee venom at both 18 and 24 hours post-treatment. In vivo results showed that melittin reduced tumor cell proliferation by 31.7 ± 1.3% and decreased the expression of the immune-

checkpoint protein programmed death ligand-1 (PD-L1) in tumors by 52.9 ± 2.4%. Both in vivo and in vitro, a reduction in the phosphorylation levels of EGFR and HER2 was observed (50).

2.3. p28

p28, an amphipathic, α-helical cell-penetrating peptide derived from azurin (51, 52), has demonstrated stability and tumor penetration consistent with selective entry into tumor cells, significantly inhibiting the growth of p53-positive tumors (53). The Azurin-p28 (p28) peptide produced significant dose-related decreases in the proliferation and growth of MDA-MB-231 xenografts, suggesting that a human trial in patients with solid tumors could begin with a starting dose of p28 at 10 mg/kg body weight (53).

2.4. NRC-03 and NRC-07

Pleurocidin-family cationic antimicrobial peptides (CAPs), NRC-03 and NRC-07, demonstrated minimal or no lysis of human dermal fibroblasts, umbilical vein endothelial cells, or erythrocytes. These peptides effectively killed various breast cancer cell lines in vitro. The study results indicate that peptide treatment, particularly with NRC-03, effectively inhibits tumor growth, maintaining it at a stable size compared to control tumors. The significant reduction in the size of NRC-03-treated tumors by day 12 suggests a strong therapeutic effect of this treatment. Furthermore, the absence of discernible adverse effects from the intratumoral administration of the CAPs indicates a favorable safety profile (54).

2.5. [D]-NRC-03

[D]-NRC-03, a D-amino acid analog of NRC-03, was designed to resist proteolytic degradation. Unlike its predecessor, [D]-NRC-03 remained stable in human serum and trypsin, resulting in enhanced efficacy against breast cancer cells, including those resistant to multiple drugs. However, it exhibited increased cytotoxicity towards certain normal cell types compared to NRC-03. Notably, in animal models, [D]-NRC-03 required only a quarter of the dosage to achieve similar growth-inhibitory effects on breast cancer xenografts in immunocompromised mice. Hematoxylin and eosin staining demonstrated a significant increase in necrosis in tumors treated with peptides, especially with [D]-NRC-03, which also correlated with a reduction in tumor growth. This inhibition suggests that [D]-NRC-03 is more effective in vivo compared to NRC-03. Importantly, treated mice did not exhibit any noticeable toxicity, such as changes in behavior or weight loss. Necropsy results confirmed the absence of damage to vital organs, indicating that the intratumoral administration of these peptides was well-tolerated (55).

2.6. A7R

The peptide ATWLPPR (A7R) has been found to effectively block the binding of VEGF165 to the neuropilin-1 (NRP-1) receptor, while leaving interactions with the tyrosine kinase receptors VEGFR-1 (flt-1) and KDR unaffected. Additionally, it does not interact with heparin. In vitro studies revealed that ATWLPPR reduced both the proliferation of human umbilical vein endothelial cells and their ability to form tubular structures on Matrigel and in co-culture with fibroblasts. In vivo experiments showed a decrease in the growth of A7R-treated tumors, alongside a reduction in blood vessel density and endothelial cell area. Importantly, there were no observable side effects throughout the A7R treatment period. After 35 days of administration, the body weight of the treated mice remained stable, and all survived until the end of the study. These findings suggest that ATWLPPR can inhibit VEGF165's binding to NRP-1 and suppress tumor angiogenesis and growth, highlighting NRP-1 as a potential target for antiangiogenic and antitumor therapies (56).

2.7. TE-64562

Boran et al. designed TE-64562, a peptide encoding EGFR 645-662 conjugated to the Tat sequence, which demonstrated anticancer effects in various human cancer cell lines, while showing reduced efficacy in cells lacking EGFR expression and in non-cancerous cells. Initial exposure to TE-64562 led to non-apoptotic cell death, progressing to caspase-3-mediated apoptosis with extended treatment. In studies with nude mice, TE-64562 successfully slowed the growth of MDA-MB-231 tumors and increased survival rates without causing toxicity. Additionally, TE-64562 inhibited the Akt and Erk signaling pathways in vivo (57).

2.8. DPT-C9h

The DPT-C9h peptide, developed by Arrouss et al. to target the caspase-9/PP2A interaction, induced caspase-9-dependent apoptosis in cancer cell lines. In preclinical studies, DPT-C9h exhibited notable tumor growth

inhibition (TGI) due to competition by the binding motif in breast cancer xenograft models (58).

2.9. SP2043

SP2043, a collagen IV-derived biomimetic peptide, effectively inhibited breast cancer growth and metastasis by targeting and blocking angiogenesis and lymphangiogenesis. Studies on MDA-MB-231 cancer cells have shown that SP2043 blocks HGF-induced phospho-Met. This peptide also inhibited tumor growth by preventing tumor angiogenesis in MDA-MB-231 tumor xenografts. In vivo experiments demonstrated that SP2043 significantly inhibited tumor growth by 77.8% and 90.7% at doses of 10 and 20 mg/kg, respectively, over a 33-day period, without causing significant toxicity, as evidenced by stable mouse body weights across treatment groups. Additionally, SP2043 inhibited the levels of p-Met and the formation of blood and lymphatic vessels, with reported inhibition rates of 57.8% for angiogenesis and 69.5% for lymphangiogenesis. Further analysis using MDA-MB-231 tumor-conditioned media (TCM) revealed that SP2043 inhibits TCM-induced lymphangiogenesis and angiogenesis in pre-metastatic organs and prevents metastasis to both the lungs and lymph nodes (59).

2.10. ES-SS and ES-Zn

To determine the roles of zinc binding and the N-terminal loop in endostatin's anticancer effects, Chamani et al. compared the native zinc-binding endostatin peptide (ES-Zn) with its variant ES-SS, which features a disulfide loop but lacks the ability to bind zinc. According to in vivo results on BALB/c mice, ES-SS significantly inhibited tumor growth compared to the control group, with treated tumors being smaller than those in the ES-Zn group at a low dosage of 50 μg/kg. The final tumor volumes for ES-SS treatments were approximately 680 mm^3, 635 mm^3, and 520 mm^3 at doses of 2.5 mg/kg, 0.5 mg/kg, and 50 μg/kg, respectively, while the ES-Zn and control groups showed larger volumes of 760 mm^3 and 980 mm^3, respectively. Tumor growth curves indicated that ES-SS treatments resulted in a notable delay in tumor growth compared to controls, with the most significant effect at 50 μg/kg. In contrast, ES-Zn did not significantly delay tumor growth. Additionally, analysis of tumor microvessel density showed a reduction in CD31-positive vessels in both ES-SS and ES-Zn-treated mouse tumors (60).

2.11. TAT- DV1–BH3 Polypeptide

The anticancer effect of the TAT–DV1–BH3 polypeptide, an antagonist of the CXC chemokine receptor 4 (CXCR4), was evaluated by Liang et al. both in vitro and in vivo. The TAT–DV1–BH3 polypeptide demonstrated a significant ability to inhibit the growth of breast cancer cell lines MDA-MB-231 and MCF-7, and it possesses a proapoptotic effect in these breast cancer cells, while not affecting non-cancerous HEK-293 cells. Additionally, this fused polypeptide suppressed the migration and invasion of MDA-MB-231 cells. Investigating the underlying mechanism in vitro revealed that TAT–DV1–BH3 effectively entered cells and was largely distributed in the cytoplasm. Notably, TAT–DV1–BH3 also colocalizes with mitochondria in MDA-MB-231, MCF-7, and HEK-293 cells. In vivo experiments confirmed its inhibitory effect on tumor growth and metastasis in MDA-MB-231 xenografts (61).

2.12. WVLGE-containing Polypeptide

A 35-amino acid polypeptide containing WVLGE, derived from the cell-penetrating peptide of the azurin protein, selectively targeted MCF-7 breast cancer cells rather than non-cancerous MCF-10A cells. This polypeptide was found to inhibit Rac1 activation, leading to cellular changes associated with Rac1 suppression. Notably, the WVLGE polypeptide demonstrated a Rac1-dependent ability to inhibit breast cancer growth in both in vitro and in vivo models. Colony formation assays indicated a significant reduction in the proliferation of MCF-7 and MDA-MB-231 cells. Luminescence imaging and tumor weight measurement confirmed its efficacy in suppressing tumor growth in MCF-7 tumor xenografts. Analysis of MCF-7 cells treated with the polypeptide showed a decrease in parenchymal cell presence at cancer foci, along with reduced β-catenin expression and fewer Ki-67-positive cells, suggesting its potential as a therapeutic agent in breast cancer treatment (62).

2.13. AD-01 and ALM201

McClements et al. investigated the anticancer potential of FK506-binding protein-like (FKBPL) peptide derivatives, AD-01 (a pre-clinical peptide) and ALM201 (a clinical peptide), in both ER+ and ER- breast cancer cells and in vivo models. The results showed that AD-01 and ALM201 peptides inhibited cancer stem cells (CSCs) in both MCF-7 and MDA-MB-231 cells. AD-01 reduced

migration and invasion in vitro, which was confirmed in vivo, where lung colonization of breast cancer cells was effectively inhibited following peptide treatment. Researchers also indicated that by reducing the number of CSCs, the clinical peptide ALM201 delayed tumor recurrence (63).

2.14. Sea Cucumber Intestinal Peptide

Sea cucumber intestinal peptide (SCIP), a small molecular oligopeptide rich in hydrophobic and branched-chain amino acids derived from sea cucumber intestines, has demonstrated potential as an anticancer agent both in vitro and in vivo. SCIP inhibited the proliferation of human breast cancer MCF-7 cells and induced apoptotic cell death through the inactivation of the PI-3K/AKT signaling pathway. Additionally, SCIP was able to inhibit the growth of zebrafish human breast cancer cell (MCF-7) xenografts under in vivo conditions (64).

2.15. M1-21

Cheng et al. have developed an interfering peptide, M1-21, which targets and binds to multiple regions of the transcription factor FOXM1, disrupting protein-protein interactions between FOXM1 and several of its known partner proteins, including PLK1, LIN9 and B-MYB of the MuvB complex, and β-catenin. Studies on its anticancer effects demonstrate that M1-21 effectively inhibits the proliferation, migration, and WNT signaling of multiple cancer types both in vitro and in vivo at concentrations of 20 μM or 30 mg/kg, respectively. Additionally, M1-21 exhibits low levels of hemolytic toxicity and immunogenicity in mouse models, highlighting its potential as a promising candidate for anticancer drug development targeting FOXM1 (65).

2.16. Mastoparan

Mastoparan, a peptide derived from wasp venom, is a promising anticancer agent that inhibits various human breast cancer cells, including MDA-MB-231, SKBR3, MDA-MB-468, T47D, and 4T1 mouse mammary carcinoma cells, through a lytic mechanism. The peptide demonstrated an inhibitory concentration (IC_{50}) of approximately 20 - 24 μM for breast cancer cells, while showing significantly lower toxicity to normal cells, with an IC_{50} of 48 μM for peripheral blood mononuclear cells (PBMCs). Under in vivo conditions, researchers observed that mice treated with Mastoparan exhibited a decrease in tumor volume and mass compared to those treated with saline, although these differences were not statistically significant (66).

2.17. TAT-NLS-BLBD-6

TAT-NLS-BLBD-6 has been shown to directly interact with β-catenin, leading to significant inhibition of breast cancer cell proliferation, invasion, migration, and colony formation. Additionally, it promotes sub-G1 cell cycle arrest and induces apoptosis. Gene expression analysis revealed that the downstream target genes of TAT-NLS-BLBD-6 are associated with the HER-2 and IL-9 pathways, and this peptide downregulated 27 key genes, which align with Wnt downstream target genes, in both MCF-7 and MDA-MB-231 breast cancer cell lines. In vivo studies using nude mice and zebrafish models demonstrated that TAT-NLS-BLBD-6 effectively reduced breast tumor growth without causing toxicity or affecting body weight (67).

2.18. Foxy5

In 2008, the WNT5A mimicking hexapeptide Foxy5 was shown to inhibit the migration and invasion of 4T1 breast cancer cells without affecting apoptosis or proliferation. In vivo studies demonstrated that when WNT5A-negative 4T1 cells were implanted orthotopically in mammary fat pads, Foxy5 inhibited metastasis to the lungs and liver by 70% to 90%. These findings suggest that reconstituting Wnt-5a signaling in breast cancer cells could serve as a strategy to impair breast tumor metastasis by targeting the motility of cancer cells (68).

2.19. PFISED

Ray et al. designed and synthesized a pro-apoptotic peptide, PFISED (69), from hemagglutinin protease secreted by V. cholerae, which was shown to have anticancer properties in their previous study (70). In vitro studies using annexin V and PI staining to explore the role of PFISED in inducing apoptosis showed that at a concentration of 100 μM, 90% of human MCF-7 and mouse EAC breast cancer cells underwent apoptosis. In contrast, at the same peptide concentration, PFISED did not affect normal cells, including MCF-10A, MCR-5, and normal mouse peritoneal macrophage cells. Additionally, peptide treatment of EAC mouse models revealed the peptide's ability to induce apoptosis in EAC cells, with survival rates of 100%, 80%, and 60% after 30, 60, and 120 days, respectively (69).

2.20. ([(LLKK)2]2κC)2

The in vitro cytotoxicity assessment of the 4-arm branched peptide, $([(LLKK)_2]_2\kappa C)_2$, demonstrated its ability to overcome drug resistance and induce apoptosis in both parent and resistant cancer cells, while maintaining selectivity with less cytotoxicity to HL-7702 cells. Analysis of the peptide's intracellular uptake revealed that the FITC-labelled 4-arm branched peptide, FITC-$([(LLKK)_2]_2\kappa C)_2$, successfully penetrated the cytoplasm and nucleus of live BCap37 cells, indicating its capability to enter these compartments for anticancer activity. In vivo experiments conducted on mice with breast tumors indicated that the branched peptide localized at tumor sites post-injection, significantly inhibiting tumor growth (17.3% and 33.7% for 10 and 20 mg/kg, respectively) while causing minimal toxicity to vital organs. The similar body weight change in peptide-treated and saline control groups suggests that the peptide was well tolerated (71).

2.21. PKHB1

Calvillo-Rodriguez et al. investigated the anticancer properties of PKHB1, a thrombospondin-1 peptide mimic, focusing on its effects on breast cancer cells. Research conducted in vitro, ex vivo, and in vivo explored PKHB1's potential as an anticancer agent and the mechanisms contributing to its effects. PKHB1 induced cell death with a CC_{50} (cytotoxic concentration 50%) of 200 µM for MDA-MB-231 and MCF-7 human breast cancer cells, and 300 µM for the 4T1 murine cell line. It also triggered mitochondrial alterations, increased reactive oxygen species (ROS) production, and led to calcium-dependent cell death in various breast cancer cells, including triple-negative subtypes. In vivo experiments demonstrated that PKHB1 significantly reduced tumor size and weight while enhancing the infiltration of CD8+ T cells within tumors. Control animals exhibited a tumor volume of 1500 mm^3 16 days after the 4T1 cell transplant, while mice treated with PKHB1 displayed a peak tumor volume of 890 mm^3 on day 8, followed by a notable reduction to 570 mm^3 by day 16. This decrease in tumor size corresponded with a significant drop in tumor weight, from 1.5 grams in the control group to just 0.40 grams in those receiving PKHB1 treatment. Importantly, the daily administration of PKHB1 did not impact the overall weight of the treated mice. Furthermore, the cancer cells killed by PKHB1 treatment successfully promoted the maturation of dendritic cells and stimulated T cell-mediated antitumor responses in ex vivo assays (72).

2.22. Juxtamembrane 2

Juxtamembrane 2 (JM2) peptide, which mimics the amino acid sequence of the juxtamembrane region of connexin 43 (Cx43), inhibited the proliferation and colony formation ability of 4T1 cells, arrested the cells at the S-phase of the cell cycle, and significantly suppressed tumor cell migration by down-regulating MMP2 and MMP9 gene expressions. This mimetic peptide stimulates mitochondria to gather near the microtubule-organizing center of tumor cells, leading to elevated levels of ROS. This increase contributes to mitochondrial dysfunction and triggers mitochondria-mediated apoptosis. In vivo studies have demonstrated that JM2 significantly suppresses breast tumor growth, with tumors in the control group treated with PBS being three times larger on average than those in the JM2-treated group (73).

2.23. NAF-144-67

NAF-1^{44-67}, a peptide derived from the human protein NAF-1/CISD2, was developed by Sohn et al. to target the mitochondria and endoplasmic reticulum (ER) of cancer cells. This peptide exhibited the ability to selectively penetrate the plasma membranes of breast cancer cells without causing any apparent damage to the membranes or nuclei. This selective permeability leads to the disruption of mitochondria and ER in cancer cells, ultimately inducing cell death through mechanisms characteristic of apoptosis, ferroptosis, and necroptosis. In fluorescence studies, a fluorescein-labeled version of the peptide (Fl-NAF-1^{44-67}) was predominantly localized outside the control MCF-10A cells, confirming its preferential targeting of the MDA-MB-231 cancer cell line. In vivo results demonstrated that NAF-1^{44-67} significantly inhibits tumor growth in MDA-MB-231 mouse xenografts without adversely affecting their body weight, indicating its non-toxic profile. Additionally, survival analysis showed improved outcomes for mice treated with the 3D-NAF-1^{44-67} peptide compared to those receiving saline (74).

2.24. NBD

The synthetic NBD peptide, which disrupts the interaction between the calcium-binding protein

S100A4 and methionine aminopeptidase 2 (MetAP2), has shown potential to inhibit cell motility and metastasis of aggressive human breast cancer cells. This peptide significantly downregulated matrix metalloproteinase-14 (MMP-14) levels, as evidenced by RT-qPCR, which also confirmed this at the protein level. In contrast, MMP-1 and TIMP metallopeptidase inhibitor 1 (TIMP-1) showed elevated expression levels. The NBD peptide was also found to reduce the expression of specificity protein 1 (Sp1), as confirmed by western blot analysis. Additionally, using the Sp1 inhibitor mithramycin A further confirmed Sp1's regulatory influence on MMP-14 in MDA-MB-231-Luc-D3H2LN cells, as it led to a decrease in MMP-14 expression, highlighting the potential impact of the NBD peptide on the Sp1/MMP-14 signaling pathway. Although NBD peptide-encapsulated glycoliposomes with sialyl Lewis X on their surface (NBD-GlycoLipos) did not inhibit primary tumor growth, their intravenous administration effectively inhibited pulmonary metastasis from mammary gland tumors, and a marked decrease in metastatic foci was observed in the treated group (75).

2.25. CPP-4-2

Li et al. conducted a phage display screening using the SN1/2 domain (amino acids 16-339) of staphylococcal nuclease domain-containing protein 1 (SND1) to discover a 12-amino acid peptide, 4-2, with the tryptophan 10 (W10) residue being essential for its ability to interact with SND1 and disrupt the SND1-metadherin (MTDH) interaction. To enhance its penetration potential, the peptide was modified into a cell-penetrating form (CPP-4-2) by attaching a hybrid cell-penetrating peptide (CPP) RR-TAT to its N-terminus. CPP-4-2 demonstrated the ability to penetrate and induce death in breast cancer cells by disrupting the SND1-MTDH interaction, with IC_{50} values of 22.4 ± 1.0 μM, 18.7 ± 0.2 μM, and 15.9 ± 6.2 μM for MDA-MB-231-GFP-Red-FLuc, MCF7, and MDA-MB-468, respectively. In vivo studies on xenograft mouse models also indicated that CPP-4-2 inhibited breast cancer growth by degrading SND1, leading to a reduction in tumor volume and weight without causing significant side effects such as weight loss or other toxic symptoms (76).

2.26. CST6-derived Peptides

CST6, a secretory protein notably downregulated in breast cancer cells with bone metastasis, has been shown to inhibit tumor invasion and metastasis to bone in animal studies (77). Further research aimed at identifying CST6-mimicking peptides has revealed their promising potential for treating breast-to-bone metastasis (78). The peptides GQ86 and DQ51, which contain the QLVAG sequence, effectively inhibit cathepsin B (CTSB) and reduce osteoclast formation in bone marrow cells. When tested in mice, both peptides demonstrated a notable ability to suppress bone metastasis of SCP2 cells at a dosage of 1 mg/kg, while also preventing the maturation of osteoclasts. Pharmacological assessments indicated that DQ51 has a longer plasma half-life compared to GQ86 and CST6, with a maximum tolerance dose (MTD) and median lethal dose (LD_{50}) of 250 and 360.10 ± 74.25 mg/kg, respectively, while GQ86 displayed MTD and LD_{50} values of 200 mg/kg and 377.70 ± 146.05 mg/kg, respectively. Significantly, these doses are much higher than the effective treatment dose of 1 mg/kg, and no adverse effects were noted in various organs or overall body weight after treatment, underscoring the safety of these peptides for treating osteolytic bone metastasis (78).

2.27. RF16

RF16, an antagonist peptide with positively charged residues that interact with the negatively charged N-terminal residues of CXCR1 and CXCR2, exhibited antiproliferative and antimetastatic properties against MDA-MB-231 cells, not due to cytotoxicity. When tested on MCF-7 cells, RF16 showed minimal impact on growth at 100 μM but reduced MDA-MB-231 cell proliferation in a dose-dependent manner. Wound-healing assays indicated that RF16 treatment substantially decreased the migratory abilities of both cell lines, achieving a 60 - 90% reduction in wound closure compared to controls. Furthermore, RF16 was found to inhibit IL-8-induced migration and epithelial-mesenchymal transition (EMT) in MDA-MB-231 cells. In vivo studies using SCID mouse xenograft models revealed that RF16 slightly enhanced survival rates and reduced tumor volume and weight without affecting body weight, indicating its potential as a therapeutic agent against breast cancer metastasis (79).

2.28. RP7

RP7 peptide, an antagonist of the receptor for advanced glycation end products (RAGE) highly expressed in TNBC, effectively inhibited cell viability, migration, and invasion of MDA-MB-231 cells in vitro. RP7 has been shown to inhibit ERK1/2, IKKα/β, IKBα, and p65

phosphorylation and the entry of p65 into the nucleus, resulting in reduced activity of the Erk1/2/NF-κB signaling pathway. Additionally, RP7 downregulates Bcl-2 levels while promoting the expression of Bax, leading to the release of cytochrome C from mitochondria into the cytoplasm. This process ultimately triggers caspase-9 and caspase-3 dependent apoptosis. HMGB1 expression levels were also reduced after RP7 treatment, suggesting an antimetastatic effect of RP7 through interference with the HMGB1/EMT signaling pathway. Under in vivo conditions, treatment of TNBC xenograft models with RP7 led to a notable decrease in both tumor volume and weight. Importantly, the body weight of mice across various dosing groups remained stable, and no obvious toxicity was observed. Furthermore, the results revealed that mice receiving RP7 treatment exhibited lower Ki67, HMGB1, and MMP-9 expression levels, alongside an increase in caspase-3 expression and a greater presence of apoptotic tumor cells, indicating RP7-induced apoptosis of TNBC in vivo (80).

2.29. PA3264

Recently, the anticancer properties of the PA3264 linear dipeptide, a potential active ingredient in Squama Manis (pangolin scale), have been investigated in both laboratory settings and animal models. The findings revealed that PA3264 caused damage to the plasma membrane and suppressed colony formation in breast cancer cells, with cell viability IC_{50} values of 23.03 mM and 25.17 mM for MDA-MB-231 and 4T1 cells, respectively. Additionally, wound healing assays indicated the inhibitory effect of PA3264 on 4T1 cell migration. The mechanism behind its anticancer activity was identified as the inhibition of the PI3K/AKT/NF-κB signaling pathway, leading to cell cycle arrest and enhanced apoptosis. Examination of the antitumor effects of PA3264 in vivo showed that the tumor volume and weight in PA3264-treated mice were reduced by 41% and 32%, respectively. Importantly, the administration of PA3264 did not lead to any notable changes in the body weight of the treated mice and did not cause any appreciable damage to the kidneys or liver (81).

2.30. 9S1R

Ali et al. investigated the anticancer potential of the 9S1R nullomer peptide, administered with a trehalose carrier (9S1R-NulloPT), against TNBC. In both mouse and human TNBC cell lines, 4T1.2-Luc and MDA-MB-231, 9S1R-NulloPT inhibited cell viability and reduced mitochondrial membrane potential, accompanied by an increase in mitochondrial ROS production. In vivo studies indicate that the 9S1R-NulloPT drug effectively inhibits growth in early-stage cancers, but not at late stages. Notably, toxicity assessments conducted on female BALB/c mice at doses of 5, 25, 50, and 100 mg/kg revealed no significant alterations in behavior, clinically observable signs of acute toxicity, or notable changes in body weight (82).

2.31. mL7N

In a recent study, Zhong et al. discovered a novel PD-1/PD-L1 immune checkpoint targeting peptide, mL7N, which successfully rejuvenated PD-1-suppressed T cells. The researchers tested four different doses of mL7N coupled to albumin-binding palmitic acid (PA-mL7N), ranging from 0.5 to 8 mg/kg, alongside a 2 mg/kg dose of mL7N on BALB/c mice with 4T1 tumors. Results indicated that doses of PA-mL7N between 0.5 and 4 mg/kg significantly inhibited tumor growth, showing comparable anti-tumor effects to the 2 mg/kg dose of mL7N (83).

2.32. Folligen

Folligen significantly suppresses tumor progression in DMBA-induced mammary carcinomas in rats, achieving nearly complete remission within three weeks. Its mechanism of action involves the inhibition of tyrosine kinase activity, with notable redistribution of protein kinase C activity, affecting crucial pathways that rapidly regulate cancer cell proliferation (84).

2.33. Peptide YY (PYY)

The antitumor effects of Peptide YY (PYY) were evaluated in vivo using an MCF-7 breast cancer xenograft model in athymic nude mice. Mice implanted with PYY-releasing pellets showed a significant reduction in tumor weight, nearly 50% less than controls, with a reduction to 67 mg. Tumor volume significantly decreased to roughly one-third of the control group volume, approximately 76 mm^3. PYY dramatically inhibits tumor growth by lowering intracellular cAMP levels (85).

2.34. Anastellin (III1-C)

Anastellin (III1-C) is a 76 amino acid peptide derived from the first type III repeat of fibronectin (Fn), with a documented capacity to inhibit tumor growth,

angiogenesis, and metastasis. Anastellin binds to fibrinogen and Fn, stimulating the formation of polymeric fibronectin (sFN) and polymeric fibrinogen (sFBG), which possess strong anti-tumor activity. In vitro, Anastellin significantly inhibited endothelial cell migration and proliferation by impairing integrin-mediated cell adhesion. The peptide also reduced tumor vasculature density by interacting with extracellular matrix (ECM) components and blocking integrin activation, thereby inhibiting angiogenic signaling pathways. In vivo, systemic administration of Anastellin (300 μg, intraperitoneally, every other day for 5 weeks) in MDA-MB-435 breast cancer xenograft-bearing nude mice resulted in a 50 - 90% reduction in tumor volume compared with controls, a 60 - 80% decrease in vascular density in the tumor (as shown by CD31 immunostaining), and no detectable systemic toxicity, indicating a good safety profile (86).

2.35. Alpha-Fetoprotein-Derived Peptides

Caceres et al. investigated the anticancer properties of two peptides derived from alpha-fetoprotein (AFP) in prostate and breast cancer models. In vitro and in vivo studies demonstrated that these peptides suppressed tumor growth by interfering with estrogen receptor signaling. Treatment with AFP-derived peptides significantly reduced tumor size in xenograft models of breast and prostate cancer, with reductions of up to 60% compared to controls ($P < 0.01$) (87).

2.35.1. AFPep

Bennett et al. evaluated the anticancer effects of AFPep, an 8-mer peptide derived from alpha-fetoprotein (AFP), in estrogen receptor-positive (ER^+) breast cancer models. In vivo, AFPep effectively prevented tumor growth in xenograft models, including tamoxifen-resistant ER^+ breast cancer, with complete suppression of tumor progression at a dose of 1 μg per injection ($P < 0.05$) (88).

2.35.2. Cyclo AFpep

Parikh et al. explored the anticancer properties of AFPep, a cyclic nonapeptide derived from AFP, in both in vitro and in vivo models. In vitro, AFPep inhibited the proliferation of ER^+ breast cancer cells (T47D, MCF-7) without affecting ER^- MDA-MB-231 cells, indicating a selective anti-estrogenic mechanism. The peptide suppressed ER phosphorylation while increasing p53 phosphorylation, leading to reduced tumor cell proliferation (89). In vivo, AFPep was tested in an N-methyl-N-nitrosourea (MNU)-induced breast cancer model in rats. Daily subcutaneous administration of 0.1 mg AFPep per animal significantly delayed tumor onset, reduced tumor incidence from 70% to 40%, and decreased tumor burden. Importantly, AFPep treatment showed no significant toxicity, as evidenced by stable body weight, organ weights, and overall animal health.

2.36. Growth-Inhibitory Peptide

In another study, the anticancer potential of growth-inhibitory peptide (GIP), a 34-amino acid peptide derived from AFP, along with its A-, G-, and S-analogs, was investigated. In vitro, the A-peptide showed the most significant growth inhibition in MCF-7 breast cancer cells, with 70% suppression at a 10^{-5} M concentration, while the G- and S-peptides exhibited only moderate inhibitory effects, ranging between 35 - 45% inhibition over a 10^{-5} to 10^{-7} M range. This differential activity was attributed to variations in oligomeric state and hydrophobicity, which influenced peptide binding and cellular uptake. In vivo, a syngeneic mouse mammary tumor model was used to assess tumor suppression by these peptides. The A-peptide at 1 μg/day for 12 days led to a significant reduction in tumor weight and ascitic fluid accumulation, correlating with 50 - 70% suppression of cancer cell numbers. The C-peptide and its trimers were also active, while dimeric forms displayed lower anticancer potency. Further analysis suggested that structural modifications, including increased α-helical content and hydrophobicity, contributed to enhanced tumor inhibition (90).

2.37. K237

Hetian et al. evaluated the effects of K237, a peptide isolated from a phage display library, on tumor growth and metastasis in vivo. In a SCID mouse xenograft model of breast cancer, administration of K237 led to a 70% reduction in tumor weight and a 53% reduction in lung metastases compared to the control group ($P < 0.05$). The peptide effectively disrupted the VEGF-KDR interaction, inhibiting angiogenesis and suppressing tumor progression (91).

2.38. Å6

Guo et al. examined the anticancer effects of Å6, an 8-mer peptide derived from the non-receptor-binding domain of urokinase (uPA), in a syngeneic breast cancer

model. In vivo studies showed that administration of Å6 at 75 mg/kg/day significantly reduced tumor growth by 50 - 60%, with an even greater 75% reduction when combined with tamoxifen (TAM). Additionally, Å6 alone led to a notable decrease in lung, liver, and lymph node metastases, whereas TAM showed no significant effect on metastasis. Histological analysis confirmed that Å6 treatment reduced blood vessel density and increased tumor cell apoptosis, supporting its anti-angiogenic and pro-apoptotic properties (92).

2.39. C16Y

In a groundbreaking study, Ponce et al. examined the anti-tumor effects of C16Y, a modified peptide derived from laminin-1, using in vivo models. Their results compellingly revealed that C16Y substantially inhibited the growth of MDA-MB-231 breast cancer tumors in xenografts. With daily intraperitoneal injections of C16Y (1 mg/day), there was a remarkable 33% reduction in tumor size after just one week of treatment ($P < 0.05$). Furthermore, histological analysis demonstrated a significant decline in tumor vascularization, highlighting that C16Y effectively targets tumor growth primarily through its robust anti-angiogenic mechanisms (93).

2.40. Valorphin

Blishchenko et al. studied the anticancer effects of valorphin, a β-hemoglobin-derived peptide, using both in vitro and in vivo models. In the in vitro tests, valorphin significantly inhibited murine fibrosarcoma by 53% at a concentration of 0.1 μM. Its mechanism of action involved inducing S-phase cell cycle arrest, which resulted in a prolonged refractory period that prevented rapid tumor cell division. Importantly, valorphin demonstrated minimal cytotoxicity to normal murine bone marrow cells, indicating its selectivity for tumor cells. In vivo, in a murine breast carcinoma model, treatment with 1 mg/kg of valorphin led to a 42% reduction in tumor growth compared to the control group, and a 22% reduction when compared to mice treated with epirubicin (94).

2.41. ATN-161

ATN-161 is a five-amino acid peptide derived from Fn, designed to inhibit tumor growth and metastasis by targeting integrins. Khalili et al. found that ATN-161 binds selectively to α5β1 and αvβ3 integrins but does not directly kill breast cancer cells. Instead, it reduces MAPK phosphorylation, disrupting integrin-mediated signaling. In a mouse model of breast cancer, ATN-161 (0.05 - 1 mg/kg, intravenously, three times per week for 10 weeks) significantly reduced tumor growth and metastasis, particularly to bones and soft tissues. It also lowered microvessel density, suggesting anti-angiogenic effects, while Ki-67 staining showed reduced tumor cell proliferation. Importantly, no significant toxicity was observed (95).

2.42. D-K6L9

D-K6L9 is a specialized peptide that targets cancer cells by binding to their membranes and causing necrotic cell death. Papo et al. demonstrated that D-K6L9 selectively attacked 22RV1 prostate carcinoma and MDA-MB-231 breast cancer cells while sparing normal cells. It induced rapid membrane depolarization, with LC_{50} values of 6 μM and 3 μM for prostate and breast cancer cells, respectively, whereas normal cells remained unaffected at concentrations up to 100 μM. In mice, intravenous administration (9 mg/kg, every other day for 9 doses) led to a threefold reduction in prostate tumor size, a 3.5-fold decrease in breast tumor size, and a fivefold drop in metastatic spread. Tumor vascularization decreased tenfold, yet no toxicity or weight loss was observed (96).

2.43. Hecate-βCG and Phor21-βCG

Hansel et al. studied the effectiveness of Hecate-βCG and Phor21-βCG, lytic peptide conjugates that target LH/CG receptors, in selectively destroying breast cancer cells and metastases. In vitro, both conjugates specifically targeted MDA-MB-435S and MCF-7 breast cancer cells, which express LH/CG receptors, causing rapid membrane disruption and necrosis. Hecate-βCG had an EC_{50} of 6.6 μM in rLHR-CHO cells, while much higher concentrations (50 - 100 μM) were needed in wild-type CHO cells. Among the conjugates, Phor21-βCG(ala) showed superior potency. In vivo, Hecate-βCG (8 mg/kg, intravenously, weekly for 3 weeks) resulted in a significant reduction in tumor size in mice with MDA-MB-435S xenografts, with a threefold decrease in tumor burden ($P < 0.001$). Phor21-βCG(ala) was equally effective at a lower dose (0.08 mg/kg). Histological analysis showed widespread tumor necrosis and intact vasculature, indicating minimal toxicity. Furthermore, metastases to lymph nodes, bones, and lungs were significantly reduced ($P < 0.05$), as shown by tumor

tracking. Even after primary tumor removal, Hecate-βCG effectively suppressed metastatic spread (97).

2.44. Resistin-13-Peptide

Pan et al. examined the anticancer effects of resistin-13-peptide, a 13-amino acid fragment of human resistin, in TNBC models. Resistin-13-peptide slowed down MDA-MB-231 cancer cell growth, adhesion, and invasion in a dose- and time-dependent manner. At 50 ng/mL for 96 hours, it reduced cell proliferation by 40% and also prevented colony formation. The peptide worked by inhibiting key enzymes, MMP-2 and MMP-9, that facilitate tumor spread. It also increased the levels of TIMP-1 and TIMP-2, natural inhibitors of these enzymes, which helped prevent cancer cell invasion. In mice, the peptide (2.5 or 5 mg/kg, every four days) led to a noticeable reduction in tumor size, with a 50% decrease at the higher dose. Importantly, no toxicity was observed in vital organs, including the ovaries (98).

2.45. EGEVGLG Peptide

EGEVGLG, identified via phage display, is a peptide that detects tumor response by selectively binding to therapy-responsive tumor vasculature. In vitro experiments revealed that EGEVGLG exhibited strong binding to MDA-MB-231 and MCF-7 breast cancer cells after sunitinib treatment, while showing minimal interaction with therapy-resistant B16 melanoma and BxPC3 pancreatic cells. The peptide also displayed affinity for endothelial cells undergoing vascular remodeling due to sunitinib exposure. In vivo, AlexaFluor-750-labeled EGEVGLG was injected into nude mice bearing MDA-MB-435 and MCF-7 tumors. Mice treated with 40 mg/kg sunitinib daily for 5 days showed a significant increase in peptide binding compared to controls, with imaging analyses correlating this binding to reduced tumor volume and delayed growth. Tumors unresponsive to sunitinib did not display enhanced peptide accumulation, underscoring its specificity for therapy-responsive cancers (99).

2.46. Melittin-Loaded Nanoparticles

Soman et al. (2009) explored melittin-loaded perfluorocarbon nanoparticles designed to target tumor cells while reducing the toxicity associated with free melittin. In vitro, these nanoparticles induced apoptosis in various cancer cell lines by preferentially binding to tumor cell membranes, triggering mitochondrial cytochrome c release and apoptosis, while also reducing hemolysis by nearly 20-fold compared to free melittin. In animal studies, these nanoparticles demonstrated strong anti-tumor activity. In C57BL/6 mice bearing MDA-MB-435 breast cancer xenografts, five doses (2.5 mg/kg every 3 days) resulted in a 24.68% decrease in tumor volume ($P < 0.05$). Histological analysis confirmed extensive necrosis in tumor tissues while healthy organs remained unaffected (100).

2.47. SP2012 Peptide

Rosca et al. (2011) developed SP2012, a modified 20-amino acid peptide derived from collagen IV, designed to inhibit tumor angiogenesis and improve stability for therapeutic applications. The peptide was optimized by replacing cysteine residues with L-α-amino-n-butyric acid, enhancing its resistance to oxidation while maintaining anti-angiogenic activity. In laboratory tests, SP2012 significantly slowed down the growth, adhesion, and migration of both endothelial and tumor cells. For example, in human umbilical vein endothelial cells (HUVEC), the IC_{50} for proliferation inhibition was 32.9 ± 4.7 μM. In microvascular endothelial cells (MEC), the IC_{50} values were 82.9 ± 7.4 μM for proliferation, 0.71 ± 0.21 μM for adhesion, and 1.88 ± 0.81 μM for migration inhibition. In TNBC cells, notable adhesion and migration inhibition was observed at 50 μM. Additional Matrigel tube formation assays confirmed that SP2012 effectively disrupted both new and existing vascular networks. Receptor-binding studies revealed that it selectively interacts with the αVβ1 integrin and downregulates VEGFR2 signaling at concentrations around 100 μM (101).

In animal studies, SP2012 was tested in SCID mice bearing MDA-MB-231 xenografts. Daily intraperitoneal injections of 10 mg/kg for 21 days led to a significant reduction in tumor volume and an impressive 80% drop in tumor microvascular density ($P < 0.05$), outperforming its parent peptide, SP2000. Importantly, no significant toxicity was observed in vital organs (57, 101).

2.48. SP6001 Peptide

SP6001 is a peptide derived from the serpin family associated with the DEAH box helicase protein. In vitro studies demonstrated that SP6001 successfully induced endothelial cell apoptosis through the activation of caspase-3/7, as well as promoting endothelial cell adhesion and inhibiting their migratory potential.

Notably, 10 μM SP6001 induced sustained phosphorylation of FAK, which was consistent with reduced cell motility. Furthermore, SP6001 at 1 μM exhibited a peak in endothelial apoptosis, indicating a biphasic response.

In vivo, administration of SP6001 once a day over 25 days via intraperitoneal or subcutaneous routes at 5 mg/kg in SCID mice bearing MDA-MB-231 TNBC xenografts led to strong inhibition of tumor volume. The subcutaneous route proved more effective than the intraperitoneal route, with tumor size shrinking from 1274 mm^3 in control groups treated with PBS to 453 mm^3 ($P < 0.01$). Immunohistochemical analysis confirmed a 43% reduction in CD34-positive microvessels, reflecting significant anti-angiogenic activity of the compound (102).

2.49. Nef-M1 Peptide

Bumpers et al. investigated the Nef-M1 peptide, a CXCR4 antagonist derived from the HIV-1 Nef protein, in breast cancer models. In vitro, Nef-M1 exhibited strong pro-apoptotic activity in CXCR4-positive breast cancer cells without affecting CXCR4-negative cells. At a concentration of 100 ng/mL for 24 hours, Nef-M1 significantly increased TUNEL-positive apoptotic cells in:

- MDA-MB-231 (CXCR4-positive, TNBC) to 89.3% apoptosis

- MCF7 (CXCR4-positive, ER-positive breast cancer) to 20.5% apoptosis

- DU4475 (CXCR4-positive, breast cancer) elicited an apoptotic response

- MDA-MB-468 (CXCR4-negative, TNBC) did not undergo apoptosis

- HME (normal human mammary epithelial cells, CXCR4-negative) did not show apoptosis

Caspase-3 activation assays confirmed strong cleavage of the 32 kDa pro-caspase-3 into its active 17 kDa and 12 kDa forms, confirming the induction of apoptosis selectively in CXCR4-expressing cells.

In vivo, systemic administration of Nef-M1 (2 μg, intraperitoneally, biweekly, starting at tumor implantation) in SCID mice bearing MDA-MB-231 xenografts resulted in:

- Complete abrogation of primary tumor growth in treated mice, whereas in control mice, metastases developed widely throughout the intraperitoneum

- Smaller tumor volumes at the endpoint (3.19 cm^3 vs. 4.29 cm^3, $P < 0.05$)

- A lower metastatic burden (0.39 cm^3 vs. 2.1 cm^3, $P < 0.05$) (103).

2.50. Chalone 19-peptide

Huang et al. investigated the use of Chalone 19-peptide, a tumstatin-derived peptide (amino acids 185 - 203 of the collagen IVα3 chain), for breast cancer treatment. In vitro, Chalone 19-peptide induced apoptosis in MDA-MB-231 breast cancer cells with minimal toxicity to normal hepatic cells. Western blot analysis confirmed that caspase-3 and PTEN were upregulated, while pAkt and PCNA were downregulated, indicating that the PTEN/Akt pathway was involved in the induction of apoptosis (104).

In vivo, the therapeutic effect of Chalone 19-peptide was assessed using a nude mouse xenograft model (MDA-MB-231 breast cancer). Mice were treated with Chalone 19-peptide alone (6.6 mg/kg, intraperitoneally, 8 doses over 28 days). Histological examination confirmed increased tumor necrosis and apoptosis in Chalone 19-peptide-treated tumors (104).

2.51. TP-Tox Peptide

TP-Tox is a bifunctional peptide combining the LTVSPWY cancer-targeting sequence with a toxic mitochondrial-disrupting sequence $(KLAKLAK)_2$, linked by a glycine-glycine linker. In vitro, TP-Tox exhibited high cytotoxicity against breast, prostate, and ovarian cancer cells with minimal toxicity to normal cells. The EC_{50} values for different cancer cell lines were:

- MDA-MB-435S (breast cancer, HER2-negative): 2.5 μM

- SKBR3 (breast cancer, HER2+): 2.5 μM

- MCF-7 (breast cancer, HER2-): 50 μM

- MDA-MB-453 (breast cancer, HER2+): 80 μM

- T47D (breast cancer, HER2+): 60 μM

Mechanistic investigations revealed that TP-Tox selectively damaged mitochondrial membranes, triggering apoptosis through the activation of caspase-3 and mitochondrial outer membrane permeabilization (MOMP). Cell uptake experiments indicated that cancer cells internalized TP-Tox through clathrin-mediated endocytosis, followed by localization in the nucleus.

In vivo, systemic administration of TP-Tox (250 μg/mouse, once weekly for 10 weeks) to nude mice

carrying MDA-MB-435S breast cancer xenografts resulted in:

- Statistically significant tumor growth inhibition compared to control groups.

- 80% survival at day 100, whereas the control mice were all dead by day 70.

- Enhanced apoptosis and tumor necrosis, as confirmed by histological analysis (105).

2.52. A7RC Peptide

Cao et al. investigated the use of the A7RC peptide (ATWLPPRC) for its potential applications as a tumor-targeting ligand due to its strong binding affinity for neuropilin 1 (NRP-1), a receptor overexpressed in the vasculature of tumors and some breast cancer cells. In vitro, A7RC bound selectively to MDA-MB-231 cells with high expression of NRP-1. Additionally, A7RC demonstrated significant inhibition of endothelial tube formation, suggesting intrinsic anti-angiogenic activity alongside its targeting capability.

In vivo, fluorescence imaging of nude mice bearing xenografts with A7RC showed rapid and sustained tumor accumulation of A7RC-labeled constructs. These findings support the notion that A7RC is an efficient NRP-1 targeting peptide that could be used in the future for tumor imaging, drug delivery, and anti-angiogenic therapy (106).

2.53. LDFI Peptide

LDFI, L-leucyl-L-aspartyl-L-phenylalanylleucine, was created by Catalano et al. in 2015 to obstruct leptin receptor signaling on breast cancer cells. This tetrapeptide was designed to inhibit the binding of leptin to its receptor. LDFI effectively blocked leptin-induced proliferation and migration in both MCF-7 and ERα-negative SKBR3 breast cancer cell lines. Notably, LDFI does not affect breast cancer cell lines that are not stimulated by leptin. Mechanistically, LDFI blocks JAK2/STAT3, AKT, MAPK phosphorylation, and cyclin D1 expression, which are leptin-stimulated processes leading to G1 cell cycle arrest.

In vivo, pegylated LDFI (1 and 10 mg/kg/day, intraperitoneally) was administered to nude mice with SKBR3 xenografts. The treatment resulted in a decrease in tumor volume compared to the control group and the other pegylated dose. Ki-67 staining showed a reduction in proliferating cells within the tumors. Furthermore, western blot analysis revealed decreased levels of active STAT3, AKT, and MAPK in tumors treated with LDFI. Remarkably, there were no serious local or general toxic effects, and no metabolic changes were observed (107).

2.54. Heparin-Binding Peptide

Choi et al. designed heparin-binding peptide (HBP), a peptide derived from BMP4, intended to suppress angiogenesis by inhibiting interactions between heparan sulfate proteoglycans (HSPGs) and growth factors. The HBP effectively inhibited endothelial cell (HUVEC) migration, invasion, and tube formation, which are key processes in tumor angiogenesis in vitro. The HBP downregulated FAK, ERK, and AKT phosphorylation and reduced the expression of MMP2 and MMP9, which are crucial for remodeling the extracellular matrix.

In vivo, intraperitoneal injection of HBP (1 mg/kg, three times weekly, for 5 weeks) in MDA-MB-231 xenograft-bearing nude mice resulted in notable inhibition of tumor volume and tumor vascularization, as indicated by reduced expression of CD31 and CD34 in tumor tissues. Notably, HBP preferentially accumulated in the tumor area, with minimal distribution in normal organs, demonstrating its tumor-targeting ability (108).

2.55. C2ORF40 Mimic Peptide (C2ORF40MPF)

The C2ORF40 mimic peptide, derived from a 16-amino acid sequence of the C-terminal of the C2ORF40 gene, identified as a tumor suppressor, was investigated by Li et al. in 2017 for its potential use as a therapeutic agent. In vitro tests confirmed that C2ORF40MPF potently inhibited the proliferation of BT549 and MDA-MB-231 breast cancer cell lines in a dose- and time-dependent manner. The IC_{50} values of C2ORF40MPF for MDA-MB-231 and BT549 cells were 93 μM and 106 μM, respectively. Moreover, transwell and Matrigel chamber assays demonstrated that C2ORF40MPF inhibited cancer cell migration and invasion. Similar to the action of full-length C2ORF40, C2ORF40MPF caused G2/M phase cell cycle arrest, as shown in flow cytometry experiments.

Following systemic treatment with C2ORF40MPF (30 mg/kg, intraperitoneally, for 23 days) on MDA-MB-231 xenograft-bearing nude mice in vivo, the following were observed:

- Significant tumor growth inhibition

- Reduced tumor weight and volume ($P < 0.05$)

- No observed systemic toxicity (109).

2.56. Pep5 Peptide

According to Russo et al., Pep5 is a Cyclin D2-derived intracellular peptide generated by proteasomal degradation. It has been found to induce selective apoptosis of MDA-MB-231 breast cancer cells through sustained activation of ERK1/2 signaling, primarily at the G1/S and S phase transition. Pep5 also showed rapid cellular internalization in vitro, with nuclear and cytoplasmic distribution occurring in as little as three minutes. Mechanistic investigations revealed that Pep5 interacts with plectin and chloride intracellular channel protein 1 (CLIC1), leading to destabilization of the cytoskeleton, sustained ERK1/2 activation, and ultimately, cell apoptosis. With no obvious toxicity to normal tissues, Pep5 conjugated with a cell-penetrating peptide (Pep5-CPP, 25 μM) effectively inhibited tumor cell viability when delivered in vivo (110).

2.57. GK-1 Peptide

Torres-Garcia et al. investigated the anticancer activity of GK-1, an 18-amino acid immunomodulatory peptide of parasitic origin. GK-1 induced the expansion of $CD8^+$ T-cells and cytokine secretion (IFN-γ, TNF-α, IL-12) in vitro through enhanced T-cell activation and antigen-presenting cell function, resulting in a stronger immune response against tumor cells. In vivo, GK-1 (10, 50, or 100 μg/mouse, intravenously, once weekly for 3 weeks) was administered to BALB/c mice bearing 4T1 breast cancer xenografts. GK-1 significantly decreased lung metastases ($P = 0.006$) and early tumor growth ($P = 0.014$) and volume ($P < 0.0001$). Histological analysis of treated tumors confirmed increased immune cell infiltration and increased tumor necrosis. Importantly, systemic toxicity was not observed (111).

2.58. UP-7 Peptide

The 14-amino acid peptide, UP-7 (PWCYVQVGLKPLVQE), derived from the kringle domain of urokinase (UK1), was identified by Kim et al. as a potent inhibitor of tumor angiogenesis and metastasis. In vitro, UP-7 was shown to potently inhibit endothelial cell migration and proliferation in a dose-dependent manner. The peptide significantly decreased the phosphorylation of FAK and ERK1/2, disrupting cytoskeletal organization and reducing the formation of focal adhesion complexes. Additionally, UP-7 selectively inhibited the growth, migration, and invasion of MDA-MB-231 and LM-MDA-MB-231 cells, but not NCI-H460 or U87 cells.

In vivo, UP-7 administration (10, 30, or 100 mg/kg, intraperitoneally, for 24 days) significantly decreased the LM-MDA-MB-231 lung metastatic burden by 92.5% ($P < 0.001$) in a metastatic breast cancer model (112).

2.59. NKp44-Pep8 Peptide

A PCNA-binding peptide, NKp44-Pep8, was discovered by Shemesh et al. to possess selective binding affinity towards PCNA in vitro, resulting in reduced viability of cancer cells and induction of apoptosis. For intracellular delivery, the peptide was conjugated with R11-NLS. In 4T1 breast cancer and B16 melanoma xenograft models, systemic administration of R11-NLS-Pep8 caused a significant decrease in tumor volume and enhanced apoptosis induction. NKp44-Pep8, an NKp44 immune receptor PCNA-binding peptide, specifically interacted with proliferating cell nuclear antigen (PCNA) in vitro, inhibiting cancer cell viability and causing cell death. In 4T1 breast xenograft models, treatment with R11-NLS-Pep8 resulted in a remarkable reduction in tumor volume with enhanced apoptotic activity (113).

2.60. Self-assembling Peptide for Tumor Suppression

Luo et al. synthesized a self-assembling peptide (KLVFF) that, upon contact with cancer cells, physically encapsulates the cells by forming β-sheet nanofibers, effectively isolating them from their surrounding environment. Hyaluronic acid-functionalized liposomes (KF-Lipos) were used to deliver this peptide into CD44-overexpressing breast cancer cells. KLVFF potently suppressed platelet aggregation around circulating tumor cells (CTCs), inhibited 4T1 breast cancer cell migration and invasion, and interrupted metastasis in vitro.

Systemic in vivo treatment with KF-Lipos (2 mg/kg, intravenously, every 4 days for 4 weeks) in BALB/c mice bearing 4T1 breast cancer xenografts exhibited a significant anti-metastatic effect. Fluorescence imaging confirmed long-term tumor retention of KLVFF (up to 72 hours post-injection), where the self-assembled nanofiber network physically separated the tumor cells from their microenvironment (114).

2.61. AXT201 Peptide

The 20-mer synthetic peptide AXT201 functions to regulate the tumor immune microenvironment (TIME) and interfere with pro-angiogenic signaling. AXT201

potently inhibited tumor vascularization in vitro by selectively inhibiting VEGFR2, cMet, and IGF1R phosphorylation in endothelial cells. This inhibition led to decreased endothelial cell migration and proliferation by interfering with integrin-mediated co-receptor interaction.

In vivo, significant tumor suppression was observed in TNBC models following systemic treatment with AXT201 (20 mg/kg, intraperitoneally). AXT201 decreased tumor volume by 47% on day 22 ($P < 0.001$) in 4T1 tumor-bearing BALB/c mice and reduced tumor size by 41% on day 38 ($P < 0.05$) (115).

2.62. AAN-FnBPA5

AAN-FnBPA5 is a dual-targeting peptide designed to target extracellular matrix (ECM) components, tumor-associated macrophages (TAMs), and cancer-associated fibroblasts (CAFs) to disrupt the tumor microenvironment (TME). AAN-FnBPA5 enhances the tumor-homing capacity of the ECM by binding with collagen I, Fn, and legumain, an enzyme overexpressed in TAMs.

In vitro, AAN-FnBPA5 demonstrated a strong capacity to suppress the viability of tumor cells in M2-polarized macrophages, CAFs, and 4T1 breast cancer cells. Immunofluorescence and flow cytometry confirmed the peptide's strong ability to target and kill CAFs, reducing the amount of collagen surrounding tumors. It effectively inhibited fibroblast activation triggered by TGF-β1, a critical process in tumor stromal remodeling and metastasis.

In vivo, AAN-FnBPA5 was administered to breast cancer-bearing BALB/c mice, resulting in 98.2% inhibition of tumor growth, suppression of ECM stiffness, inhibition of collagen fiber density, and suppression of immunosuppressive TAMs and CAFs. The treatment showed no obvious systemic toxicity, indicating its safety for potential clinical translation (116).

2.63. PDBAG1 Peptide

PDBAG1 is an artificial peptide derived from glycerol-3-phosphate dehydrogenase 1 (GPD1) that selectively targets and degrades the mitochondrial protein C1QBP, which is crucial for tumor metabolism and survival. The peptide acts as a potent inhibitor of mitochondrial oxidative phosphorylation (OXPHOS) and homologous recombination repair (HRR), thereby hindering the growth of TNBC.

In vitro studies demonstrated that PDBAG1 significantly suppressed the proliferation, invasion, and migration of MDA-MB-231 and MDA-MB-468 TNBC cells at a concentration of 30 μM. In vivo, PDBAG1 reduced tumor weight and disrupted mitochondrial homeostasis by reducing ATP levels and increasing ROS. Additionally, PDBAG1 showed synergistic activity with PARP inhibitors like PJ34-HCl, further enhancing tumor inhibition (117).

2.64. Mastoparan-M

Mastoparan-M (Mast-M), a 14-amino acid peptide from Vespa magnifica wasp venom, exhibits potent cytotoxicity against TNBC. To enhance its bioavailability and tumor targeting, a phytosome formulation (Phy-Mast-M) was developed. In vitro, Mast-M demonstrated strong inhibition of 4T1 and MDA-MB-231 breast cancer cells with an IC_{50} value of 2.7 μM, primarily by disrupting mitochondrial membranes, generating ROS, causing mitochondrial depolarization, and activating caspase-3, ultimately inducing intrinsic apoptosis.

In vivo, intravenous administration of Phy-Mast-M (2.7 mg/kg, every 4 days for 16 days) in 4T1 tumor-bearing BALB/c mice resulted in a 72.03% tumor inhibition rate compared to free Mast-M. The peptide localized within tumors for up to 72 hours, enhancing its apoptotic activity, as indicated by the increased Bax/Bcl-2 ratio and expression of cleaved caspase-3 in treated tissues. Importantly, no off-target effects on normal organs or systemic toxicity were observed, highlighting both its therapeutic utility and safety (118).

3. Conclusions

Our review highlights the various mechanisms through which ACPs combat breast cancer, including immune response modulation, apoptosis induction, and membrane disruption. Numerous promising ACPs identified have demonstrated strong anticancer efficacy in preclinical research. ACPs offer a promising new treatment option for individuals with breast cancer, particularly those with aggressive or resistant subtypes, due to their low toxicity and high specificity.

Future research should focus on enhancing the stability and bioavailability of ACPs, as well as understanding the mechanisms underlying their selectivity for cancer cells. Clinical trials are also necessary to evaluate the safety and efficacy of ACPs in human participants. Despite the great potential of ACPs, challenges such as drug resistance, delivery issues, and

the need for more comprehensive clinical data must be addressed. Overcoming these obstacles will be crucial for the successful translation of ACPs from the laboratory to the clinic.

In conclusion, the development of ACPs represents a hopeful and innovative frontier in the fight against breast cancer. Through ongoing research, ACPs could emerge as a vital component of treatment options, providing new hope for patients worldwide.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors' Contribution: P. G. and M. P. M. contributed to search, data analysis, writing abstract and results, and also developed search strategy. F. A. K. contributed to writing introduction. M. R. M. contributed to editing and reviewing of the article. K. P. B. contributed to quality control, writing abstract and conclusion, editing and redaction of the article.

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