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Review Article

Exploring the potential of anticancer peptides as therapeutic agents for cancer treatment

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Abstract

Despite great advances in cancer identification and treatment, malignancies remain the primary cause of high morbidity and mortality worldwide. The drawbacks of conventional chemotherapy, such as severe toxicity, lack of specificity related to actively dividing cells, and resistance, can warrant the urgent need to develop an alternative approach to treat this disease. To overcome the drawbacks, researchers are attempting to deliver drugs to the site of action (targeted delivery) or to identify drugs that specifically target tumor cells. In this regard, highly cationic and amphipathic antimicrobial peptides are attracting the attention of researchers due to their potent anticancer activity, low cost of manufacture, and, most critically, tumor-targeting activity. A growing number of documents have shown that some of the mentioned peptides exhibited a broad spectrum of cytotoxic activity against cancer cells but not normal mammalian cells entitled as anticancer peptides. Due to their solubility, low toxicity, strong tumor penetration, high selectivity, and ability to be used alone or in conjunction with other conventional medications, anticancer peptides have the potential to become very successful cancer treatments in the future. This review provided an overview of the studies concerning anticancer peptide classification, modes of action, and selectivity, and also summarized some of the anticancer peptides developed for targeting different types of malignancies. The role of *in silico* methods or artificial intelligence in the design and discovery of anticancer peptides was briefly explained. Additionally, the current review addressed challenges in utilizing anticancer peptides for cancer therapy and highlighted peptides currently undergoing clinical trials.

Keywords: Anticancer peptides; Antimicrobial peptides; Cancer; Cancer therapy; Targeted therapy.

INTRODUCTION

Cancer is a general term used to describe more than 100 distinct, mostly malignant diseases affecting many different tissues and cell types, characterized by the rapid growth of abnormal cells that results from the accumulation of a few inherited or environmentally-induced genetic mutations and epigenetic changes. To become cancerous, a cell must acquire 6 unique behaviors, including I. the ability to produce its growth factors; II. insensitivity to growth-inhibitory signals; III. resistance to cellular suicide mechanisms resulting in apoptosis; IV. the capacity for limitless replication; V. the ability to stimulate new blood vessel development (neo-vascularization or angiogenesis); and VI. the capacity to invade other organs and tissues, a process known as metastasis.

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Cancers including breast, lung, liver, prostate, and colorectal are the most commonly diagnosed forms of this disease (1-4). At the beginning of the 21st century, cancer remains one of the leading causes of mortality and morbidity worldwide and continues to take a toll on global public health systems. According to recent reports, it was estimated that 19.3 million new cancer cases and almost 10 million cancer deaths occurred in 2020 worldwide. The illness is the second most common reason for death throughout the world, and per official projections, it is predicted that there will be approximately 26 million new cancer cases and 17 million cancer-related deaths annually by 2030 (2,5). There are some curative therapies available to fight cancer, such as chemotherapy, surgery, and radiotherapy, which play an important role in increasing the life expectancy of cancer patients. Although localized/solid tumors can often be successfully treated by radiation therapy or surgery, chemotherapy is still the principal strategy applied to treat advanced or metastatic cancer. In addition, other therapeutic arsenals, including DNA-alkylating agents, natural products, antimetabolites, hormone agonists/antagonists, and specific inhibitors, such as kinase inhibitors, monoclonal antibodies, or small organic molecules, are available and are used for cancer therapy (6,7).

Current conventional chemotherapeutics, unfortunately, are not specialized for malignant cells and because such therapeutics do not present selective mechanisms to detect normal/abnormal cellular dividing rates, they have severe side effects such as alopecia, vomiting, rashes, and, in some cases, myelosuppression on other cells and organs throughout the body. Little or no tumor specificity, poor tumor penetration, cancer cell heterogeneity, insufficient drug accumulation into the tumors abound with the development of multidrug resistance (MDR) conferred by many factors, and finally, undesirable side effects are all crucial matters that contribute to the lack of effectiveness and eventually therapeutic failure observed in conventional cancer therapeutics. Studies performed on using current remedies have also shown a potential to create secondary malignancies as well as high chances of re-occurrence in many cases. Furthermore, owing to different reasons, a considerable number of cancer patients did not respond to these therapeutics efficiently (8,9). Considering that the number of individuals suffering from cancer-related disorders is growing by the day and since conventional therapies typically have a troubling number of deficiencies and drawbacks, it is critical to establish a new therapeutic strategy. Targeted therapeutic tactics may be useful in this case. Targeted therapy is one of the major modalities in cancer pharmacotherapy, which aims to selectively kill cancer cells and restrict side effects by enhancing the efficacy and specificity of medications. In this scenario, developing a new class of anti-cancer drugs with greater selectivity and specificity against the different types of tumors is highly desirable. Therefore, the efforts of academia and industry are directed toward the prospection of drug-candidate molecules (10,11).

Biopharmaceuticals like therapeutic peptides and proteins, fusion proteins, monoclonal antibodies, and antibody-drug conjugates are the key components of the targeted therapy approaches. Among the mentioned biopharmaceuticals, small bioactive molecules named antimicrobial peptides (AMPs) have drawn the attention of researchers in recent times. AMPs are short peptides and components of the innate immune system that play a vital role in the innate immune system with a wide spectrum of activity against pathogens, including bacteria, viruses, fungi, and parasites. The results of studies from the last decades revealed that some of the AMPs (particularly AMPs with net positive charge) have cytotoxic activity against cancer cells, known as anticancer peptides (ACPs). The electrostatic interaction between negatively charged phosphatidylserine on the surface of cancer cells and positively charged AMPs/ACPs is thought to play a fundamental role in the selectivity of the peptides toward tumors (Fig. 1). As an alternative chemotherapeutic agent, AMPs/ACPs display several extraordinary properties such as broad spectrum activity, high specificity, rapid mode of action, efficient tumor penetration due to

small size, good solubility, low toxicity, ability to bypass the multidrug-resistance mechanism induced by tumor cells against conventional chemotherapy drugs and finally capability to produce in commercially available scale and make AMPs/ACPs as suitable candidates for the development of novel anticancer agents. Furthermore, the ease of various chemical modifications allows AMP/ACPs to be utilized alone or combined with routinely used treatments (such as peptide drug conjugates) for tumor targeting during combination therapy (12-15). Interesting features of peptides and remarkable advances in the biotechnology industry led to an increase in approved peptide-based drugs that revolutionized the pharmaceutical market. The impact of biotechnology products on pharmaceutical industries and new therapeutics can be illustrated by the fact that a remarkable percentage of recent drug approvals by the FDA are in the biological category (recombinant proteins and peptides, monoclonal antibodies, etc.). For example, 3 peptide-based drugs, 2 antibody-drug conjugates, 10 monoclonal antibodies, and 2 oligonucleotides were approved in 2020. The high potential of peptide or protein-based pharmaceuticals provides a clear perspective for the pharmaceutical industry, biotechnology companies, and researchers to treat disease conditions (16).

In this review article, we presented an overview of the studies focusing on AMPs/ACPs classification, mechanisms of action, and selectivity factors, and then pointed out some of the ACPs produced for targeting different types of malignancies. Also, advanced strategies described for designing therapeutic peptides, AMPs/ACPs applied in targeted therapy approaches, as those peptides engaged in clinical trials were discussed. Briefly, we focused herein on the prospect of the anticancer activity of the mentioned peptides.

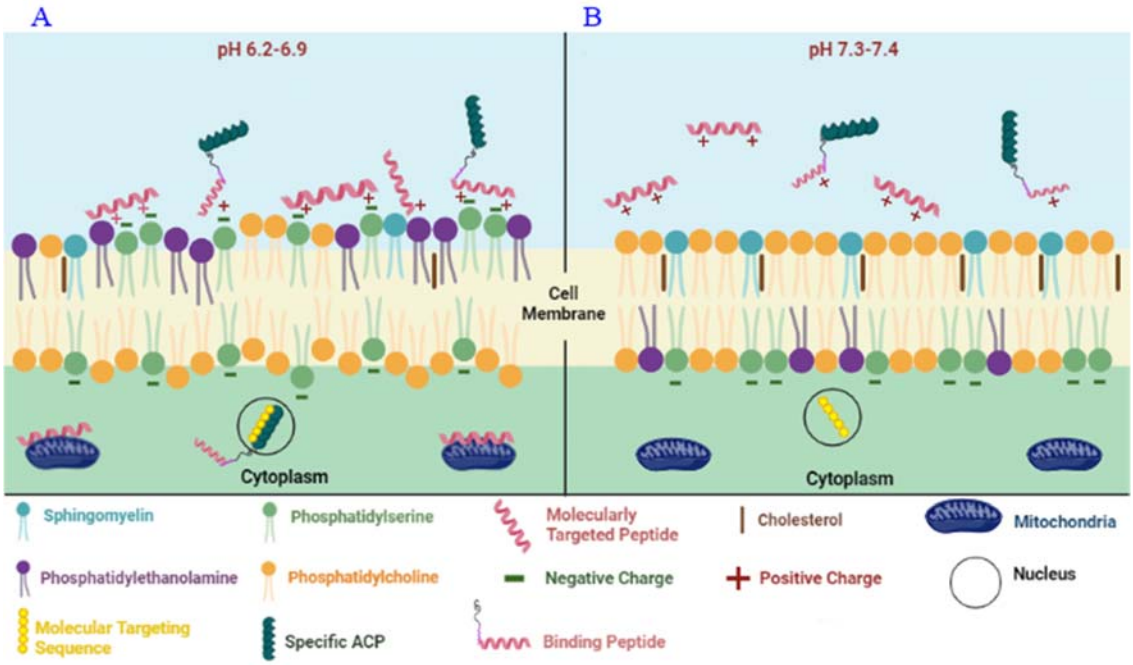

Fig. 1. Comparisons of healthy and cancerous membrane characteristics and selectivity of ACPs to bind to them. (A) Cancerous membranes and the actions of ACPs on them. Due to the negative net charge on the outer leaflet of membranes of cancer cells and the positive net charge of ACPs, ACPs can attach to the membranes and then penetrate to the cancer cell and target directly the membrane of a specific organ, causing apoptotic cell death and (B) healthy cells. The healthy cell membrane outer leaflet has a neutral net charge, which prevents ACPs from interacting. ACPs, anticancer peptides.

Classification of ACPs

Following the discovery of cecropins, several bioactive peptides with diverse bioactivities, such as immune system modulation and anti-tumor properties, were found (17). As previously stated, various types of ACPs are obtained from different organisms and categorized in numerous ways. Different models can be used for the classification of ACPs, i.e., based on their secondary structure (18), amphipathicity (19), or sources. ACPs are structurally classified into 4 different groups, including alpha (α), beta (β), alpha-beta (αβ), and non-alpha-beta (non-αβ). Amphipathicity classification is based on the hydrophobic and hydrophilic (cationic and non-cationic) features of a peptide. ACPs can be obtained from different sources, such as plants, microbes, animals, *etc*. (20) (Table 1).

Based on sources

Animal source

Although bioactive ACPs derived from mammal species have not yet been thoroughly studied, peptides with anti-cancer properties were found primarily in the central nervous system, digestive system, muscles, heart, immune system, bones, and skin of animals. For example, long-acting natriuretic peptides, vessel dilators, kaliuretic peptides, and atrial natriuretic peptides are natriuretic peptides secreted by the heart and have been shown to have significant anti-cancer properties in prostate (21), pancreatic adenocarcinoma (22), and breast cancer (23). A report described 4 beef-derived peptides with anti-proliferative activity that can be used for cancer treatment (24).

Peptides such as alpha-fetoprotein-derived growth inhibitory peptide, angiotensin 1-7 derived from the renin-angiotensin system, peptides obtained from anchovy protein, and an 11-amino acid peptide entitled KV11 in human apolipoprotein are samples obtained from animal proteins with potent anticancer activities (25). ACPB-3 isolated from goat liver was found to have *in vitro* anticancer activity against gastric cancer stem cells and also on a human gastric cancer cell line (BGC-823) (26). The peptide was previously found to suppress BGC-823 and CD44+ cell proliferation in a concentration-dependent manner, as well as suppress globular cell proliferation (27). ACBP-3, alone or in conjunction with cisplatin, inhibits xenograft tumor development *in vivo*, and enhances chemotherapy tolerance in a mouse model by decreasing toxicity during tests (28).

Plant source

Over 300 sequences of plant-derived peptides such as vincristine, paclitaxel, vinblastine, lentinan, camptothecin derivatives, and epipodophyllotoxin have been identified and significantly used in the development of cancer chemotherapy (25). Some plant AMPs have cytotoxic activity against mammalian cells and anticancer activity against cancer cells. Anti-cancer peptides derived from plant sources originate from both medicinal and non-medicinal herbs (29). In this respect, a study revealed that RA-V (deoxybouvardin), a natural cyclopeptide derived from the *Rubia yunnanensis* medicinal plant, has strong anti-tumor activity in breast cancer cells. In a preclinical study, it was found that Ganoderma lucidum poly-saccharide peptide possesses anti-tumor effects (30). Rapeseed peptide is another plant-derived bioactive peptide with anticancer properties induced by apoptosis (31). A 43-amino acid peptide from soy, barley, and wheat, called lunasin, has been shown to prevent the effect of chemical carcinogens in human cells (32).

Based on the secondary structure

ACPs with a β-pleated sheet structure

Most ACPs with β-pleated sheets found in animals and plants have 3 disulfide bonds to connect their antiparallel β-sheets (33). Bovine lactoferrin (LfcinB) an important component of the bovine immune system is a typical β-pleated sheet ACPs (34). The half-maximal inhibitory concentration (IC50) value of LfcinB in the gastric cancer cell line (MGC803) was 32 μM. MPLfcinB6

created by linking 7 arginines to LfcinB *via* glycine-glycine binding sites, effectively eliminates human T-leukaemia cells with an IC50 value of 25 μM, which is half of what it was before modification (35,36). Another peptide derived from LfcinB, known as LfcinB-P13, was discovered in another study. This peptide could improve apoptosis in the hepatocellular carcinoma cell line HepG2. Its IC50 value was 50 $\mu g.mL^{-1}$, which is better than that of LfcinB (IC50: 70 $\mu g.mL^{-1}$) (17). A human neutrophil peptide (HNP-1) is another frequent endogenous-pleated peptide. This peptide has a considerable inhibitory effect (IC50 value of 2.2 μM) on the prostate cancer cell line PC-3 (37).

ACPs with α-helical structure

A great number of α-helical ACPs have been discovered in recent years. Alpha-helical ACPs are the most widely studied kind of ACPs, but not all have potent anti-cancer effects. Alpha-helical ACPs are less complicated than pleated sheets and have a shorter length. This peptide type is abundant in the epidermis of amphibians (38). Magainin II, for example, was the first α-helical ACP discovered in African clawed frogs (39). Magainin II has anti-cancer properties. In lung cancer cells, its IC50 was 110 $g.mL^{-1}$ (A549) (39,40).

The glandular secretions of golden and green bell frogs and southern bell frogs were used to extract aurein as an α-helical peptide. Aurein has shown high inhibitory activity on T98G glioblastoma cells in various studies, with an IC50 value of 2 μM (41). As previously stated, some ACPs have only minor anti-cancer properties. L-K6 inhibits breast cancer cells (MCF-7) with IC50 values as high as 30.2 μM (42) and has an inhibitory effect on LL37 and FK-16 colorectal cancer cells (HCT116) with IC50 values of 40 μM and 30 μM, respectively (43). Notably, although these peptides have inhibitory effects on tumor cells, it has been suggested that some ACPs have side effects, such as cytotoxicity (44).

ACPs with cyclic structure

Cyclic ACPs are circled peptides with a head-to-tail cyclization foundation or cystine knots formed by disulfide bonds (35). Cyclic ACPs are more stable than linear ACPs, and the majority of them in clinical trials are cyclic ACPs because these peptides have a considerable inhibitory effect on cancer cells (45). Three new cyclic peptides observed in the roots and leaves of the white snake plant are Diffusa cytide 1-3.

The peptides at a concentration of 0.05 μM significantly inhibit prostate cancer cells and can prevent cancer cells from migrating *in vitro* (46). H-10 is a new cyclic pentapeptide that inhibits mouse malignant melanoma cells with an IC50 value of 39.68 μM while causing no cytotoxic activity in peripheral lymphocytes (47). A study found that RA-XII, derived from *Taxus yunnanensis*, could prevent the growth and metastasis of colorectal tumors at an IC50 value of 5 μM by affecting some cellular signaling pathways (48). In general, according to the results of various studies, it seems that cyclic ACPs have better anti-cancer and less toxicity than other ACPs. It is possible that modifying cyclic ACPs may achieve the desired results in ACP research faster.

ACPs with random coil structure

ACPs with random coils lack common secondary structures and have high concentrations of glycine and proline (49). Alloferon is an ACP with glycine-rich random coil, which is derived from insects. This ACP stimulates interferon and natural killer (NK) cell synthesis in the human and animal models (50). Alloferon has immunomodulatory and antiviral effects in people infected with human papillomavirus and herpes simplex virus, indicating that this peptide has therapeutic potential (51).

KW-WK is a peptide derivative of LFcinB18-28 created by adding the amino acids tryptophan and arginine, resulting in an irregular coil in an aqueous medium. Notably, even in high concentrations, KW-WK leads to little damage to kidney cells (20). Another peptide rich in proline arginine (PR-39) derived from neutrophils showed a strong inhibitory effect on normal embryonic kidney 293T cells. A PR-39 mutant variant, PR-35, displayed less cytotoxicity.

The data demonstrated that while cytotoxicity was reduced, biological activity was conserved. PR-39 and PR-35 showed an IC50 value of 16 $g.mL^{-1}$, but PR-35 had a higher cell survival rate than PR-39 (52). It seems that the impact of random coil ACPs on normal cells is much lower than that of other kinds of ACPs, but their inhibitory activity on tumor cells is also lower.

ACPs with alpha-beta (αβ) and non-alpha-beta (non-αβ) structures

ACPs with αβ structure are a class of peptides with combined α-helix and β-sheet structures. One well-known example of the αβ peptide is the human β-defensin-3, which contains 3 β-strands and a short helix in the N-terminal region (53). According to a recent report, the majority of the defensin family as well as β-defensin-3, had anticancer activity both *in vitro* and *in vivo* (54). Non-αβ ACPs are a class of peptides that do not adopt well-defined α or β secondary structures. Non-αβ peptides exhibiting high flexibility in aqueous solution are rich in tryptophan, proline, glycine, threonine, serine, and histidine amino acids (53). Indolicidin (ILPWKWPWWPWRR) extracted from bovine neutrophils is a peptide with a non-αβ structure. The existence of tryptophan in the structure of indolicidin not only plays an important role in the anti-cancer activity but also contributes to the interaction of the peptide with the cell membrane and, finally cell-penetrating ability of the indolicidin peptide (55).

Based on amphipathicity

Glycine, lysine, and leucine are the most common amino acid residues in ACPs (56). Peptides rich in arginine and lysine are hydrophobic, positively charged, and considered cationic peptides. These peptides interact with membranes by mechanisms of snorkeling. Snorkeling is proposed to increase the hydrophobic part of the protein allowing a deeper position in the membrane and thus a stronger binding. Disrupting cell membrane integrity, interaction with cancer cells with anionic membranes, and penetrating the membrane are examples of these mechanisms (57,58). Furthermore, due to the protonation of histidine under acidic pH, histidine-containing peptides can cause cancer cytotoxicity by increasing membrane permeability (59). Although cysteine in ACPs does not play a role in cancer cell selectivity or toxicity, domains that are rich in cysteine on a variety of receptors can preserve domain structures or extracellular motifs (60). Just like glycine residues, internal prolines in ACPs are important for conformational flexibility and interaction of the peptide with the membrane (61). According to some studies, glycine and serine residues slow tumor growth and have antiproliferative effects, which are beneficial in the treatment process (62). Although methionine is a moderately hydrophobic amino acid and plays a minimal role in ACPs, it can be taken in large quantities by cancer cells. A methionine-deficient diet also produces a metabolic deficit in cancer cells by halting cell proliferation (63). In early tumors, a highly hydrophobic residue, phenylalanine, is abundant and serves as a protective amino acid (64). ACPs containing phenylalanine can also improve the affinity of peptides for attacking the cancer cell membrane (65). As stated in the previous section, tryptophan is a mildly hydrophobic amino acid that may have a role in the toxicity of ACPs, such as trans-activator of transportation (TAT)-Ras GTPase-activating protein-326 peptides and indolicidin against cancer cells (66,67). Although tyrosine does not have a role in ACP toxicity, synthetic peptides including tyrosine, phenylalanine, or proline have been shown to increase cytotoxic activity (68). The tryptophan location on ACPs is critical for their entry into malignant cells, followed by an endocytic route (69). Overall, many investigations have shown that ACPs must have hydrophobic and cationic amino acid residues to form secondary structures that are deadly to malignant cells.

Table 1. Some effective ACPs and their characteristics such as sequence, structure, anticancer activity, and source.

Peptide	Sequence	Structure	Cancer type	Source	Reference
AAP-H (Anthopleura anjunae anti-tumor	YVPGP	Coil	Prostate cancer	Sea anemone (*Anthopleura anjunae*)	(70,71)
Bombinin-BO1	GIGSAILSAGKSIIKGLAKGLAEHF	Coil/α-helix	Hepatoma cell lines	*Bombina orientalis*	(72,73)
Pep27	MRKEFHNVLSSGQLLADKRPARDYNRK	α-helix	AML-2, HL-60, Jurkat, MCF-7 and SNU-601 cell lines	Streptococcus	(74,75)
Lactoferricin B	FKC1RRWQWRMKKLGAPSITC1VRRAF	β-sheet	Lung, tongue, esophagus, liver, and colorectal cancers	*Bos taurus*	(76,77)
Polybia-MP1	IDWKKLLDAAKQIL	α-helical	Bladder, prostate, and multi-resistant leukemic cancer cells	*Polybia paulista*	(78,79)
Pardaxin	GFFALIPKIISSPLFKTLLSAVGSALSSSGGQE	α-helical	Oral squamous cell carcinoma	Fish	(80,81)
P28	LSTAADMQGVVTDGMASGLDKDYLKPDD	Coil/α-helix	Breast cancer cell lines	Azurin from *Pseudomonas aeruginosa*	(82,83)
Bovine lactoferricin	FKC1RRWQWRMKKLGAPSITC1VRRAF	Coil/α-helix	Acute lymphoblastic T, leukemia	Bovine	(84,85)
Magainin 2	GIGKWLHSAKKFGKAFVGEIMNS	α-helix	Bladder cancer cell lines, MDA-MB-231 and M14K tumor cell lines	African clawed frog	(86,87)
Temporin-1CEa	FVDLKKIANIINSIF-NH(2)	α-helical	Breast cancer	*R. chensinensis*	(88)
Cecropin B	KWKVFKKIEKMGRNIRNGIVKAGPAIAVLGE AKAL	α-helix	Stomach carcinoma, acute lymphoblastic, T-leukemia cells, lung carcinoma	*Hyalophora cecropia*	(88,89)
R-lycosin-I	RNGIVKAGPAIAVLGE	α-helical	Lung cancer	Spider venom	(90)
NRC-03	GRRKRKWLRRIGKGVKIIGGAALDHL-NH2	Coil/α-helix	Breast cancer, multiple myeloma, leukemia	Winter flounder	(91,92)
Anoplin	GLLKRIKTLL-NH2	α-helix	Leukemia	Venom sac of the solitary wasp	(93,94)
Tachyplesin-1	KWC1FRVC2YRGIC2YRRC1R-Am	β-sheet	Melanoma cell lines	*Tachypleus gigas*	(95,96)
BMAP-28	GGLRSLGRKILRAWKKYGPIIVPIIRI	α-helix	U-937 lymphoma cell line, K562 leukemia cell line	*Bos taurus*	(97)
LL-37	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRT ES	α-helix	Ovarian and breast cancer	*Homo sapiens*	(98,99)
Magainin 2	GIGKFLHSAKKFGKAFVGEIMNS	α-helix	Leukemia, spontaneous ovarian tumor, breast cancer	*Xenopus laevis*	(87,100)
Melittin	GIGAVLKVLTTGLPALISWIKRKRQQ	α-helix	Breast cancer, lung cancer	Insects (honey bee)	(101-103)
Bombinin H-BO1	IIGPVLGLVGKALGGLL	Coil/α-helix	Hepatoma cell lines	*Bombina orientalis*	(72,104)
HNP-1 (β-defensin)	AC1YC2RIPAC3IAGERRYGTC2IYQGRLWAFC3C 1	β-sheet	Lung carcinoma	*Homo sapiens*	(37,106)
BR2	RAGLQFPVGRLLRRLLR	α-helix	Cervical carcinoma, breast cancer	Buforin	(106-108
Tachyplesin I	KWC1FRVC2YRGIC2YRRC1R	β-sheet	Prostate cancer	*Tachypleus tridentatus*	(109)
Moronecidin like peptide	FFRNLWKGAKAAFRAGHAAWRA	α-helix	Breast cancer	Hippocampus comes	(110,111)

Mode of action of ACPs

Although it is not yet known how AMPs kill tumor cells, one option is to categorize them depending on their mode of action (112). ACPs and AMPs have the same structures and physicochemical properties, but ACPs do not appear to have specific secondary structures if free in solution, they form β-plate or α-sheet structures following weak electrostatic interactions with negatively charged sites on tumor cell membranes (113). Many ACPs isolated from natural sources have been well studied and identified. For example, the HNP-1 (ACYCRIPACIAGERRYGTCIYQGALWAFC C) is an AMP with extensive activity against gram-negative and gram-positive bacteria that have been shown to have low anti-tumor activity against healthy cells (114). Aurein 1.2 is an attractive ACP, an AMP derived from the frog *Litoria aurea*, that has shown strong anti-tumor capabilities *in vitro* and has been found to fight against 55 distinct types of tumor cell lines while showing tiny cytotoxicity (115).

Attacking the structure of the cell membrane

The first hypothesis about the effect of ACPs was that they could break cell membranes and cause apoptosis *via* cell membrane depolarization (116). In general, multiple models of membrane permeation, such as the "barrel-stave", "carpet", and "toroidal pore" models, have been proposed to describe the mechanism action of the mentioned peptides (117). According to one study, ACPs could cause cell death after destroying cancer cells, resulting in cytoplasm discharges.

The carpet model is the name given to this proposal (118). The majority of ACPs operate directly through this process. It is worth emphasizing that ACPs are appealing since they can target only cancer cells, as opposed to chemotherapy, which destroys healthy cells as well (119). A hybrid peptide called HPRP-A1-TAT, for example, has strong anti-cancer behavior and can decimate the cancerous cell membrane with an IC50 value of 10 µM in liver, cervical, and gastric cancers (120). Another study showed an IC50 of Temporin-La in liver cancer cells of about 11.19 µM. This ACP is extracted from the skin of a bullfrog and selectively enters and kills tumor cells, leaving healthy cells intact (121). So far, most studies on ACPs have shown good anti-tumor activity using this mechanism. However, more specialized research is needed to design them accurately (Fig. 2).

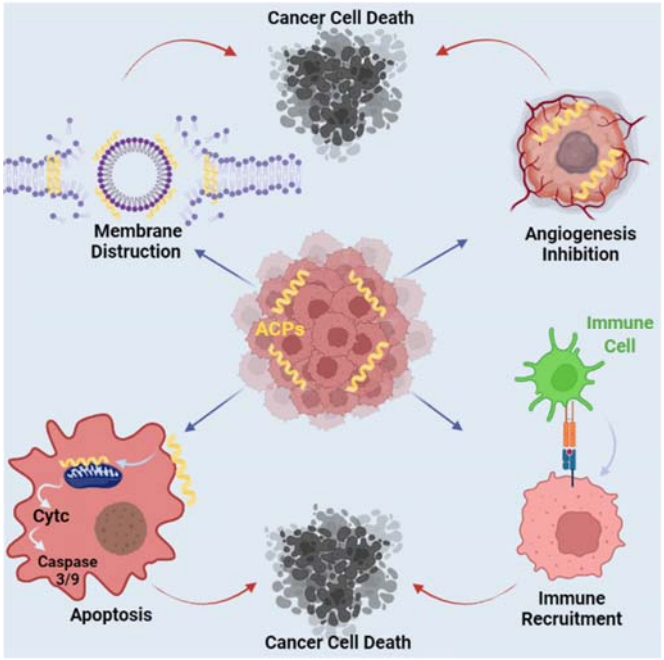

Fig. 2. Anti-tumor mechanism of ACPs. The mode of action of ACPs may include disruption of plasma/mitochondrial membranes, necrosis, apoptosis, mechanisms of mediated immunity, and angiogenesis inhibition. ACPs, anticancer peptides.

Tumor angiogenesis inhibition

Angiogenesis promotes the growth, invasion, and metastasis of solid tumors by supplying them with the nutrients and oxygen they require and removing metabolic abnormalities (122). The growth factors, including fibroblast growth factor, vascular endothelial growth factor (VEGF), epidermal growth factor, and tumor necrosis factor-alpha are involved in tumor angiogenesis. Placental growth factor, angiogenin, and platelet-derived growth factor are all examples of growth factors found in the body (123). Many peptides have been shown to decrease tumor anti-angiogenesis by interfering or interacting with growth factors and their receptors (25).

The high expression of VEGF in tumor cells could form new blood vessels. Tumor cells that have not undergone neovascularization grow slowly (124). KV11 peptide is an example of ACPs with anti-angiogenesis activity. This 11-amino-acid peptide inhibits angiogenesis by preventing microtubule formation and human umbilical vein epithelial cells (HUVEC) migration. Although the KV11 peptide did not have a considerable effect on breast cancer growth and proliferation in mice transplanted tumor models with an intense combined immune deficiency, it prevented the growth of the tumor by suppressing angiogenesis. This ACP has an IC50 of 15 μM and has no effect on HUVEC (125). Another example of ACPs with anti-angiogenesis activity is FN070315, which was isolated from the soil fungus *Penicillium* sp. It has been proven that this cyclic peptide inhibits VEGF-induced proliferation, invasion, HUVEC migration, tube formation, and neovascularization (126). The results of previous reports revealed that 2 cyclic peptides, PF1171A and PF1171C, inhibit angiogenesis by lowering the expression of the phosphorylation of VEGF receptor 2 and hypoxia-inducible factor-1α (126) (Fig. 2). ACPs work by inhibiting neovascularization rather than killing tumor cells, so they have few side effects on normal cells. As a result, ACPs of this type have a promising clinical future.

Regulation of the immune system

LfcinB, a cationic peptide produced from lactoferrin, can boost cytokine production, hence strengthening the fight of the host against malignancies. In fact, through immune regulation, the growth of cancer can be inhibited (127). Tumor immunohistochemistry examination demonstrated that after utilizing LfcinB in cancer animals, lymphocytes increased significantly compared to untreated animals, as did tumor-infiltrating lymphocytes. It's worth noting that tumor inhibition stopped when LfcinB-induced $CD3^+$ cells became tired in this study (128). A neuropeptide is MENK, which plays a role in response to tumor immune. MENK can intensify $CD4^+$ T cell functions and secretion of cytokines by inducing dendritic cell maturation and regulating $CD8^+$ T cells. Besides, forkhead box P3 transcription factor (FOXP3) expression is inhibited, followed by reducing levels of the regulatory T cell (Treg) *in vivo*. All these steps end up in tumor inhibition (129). MENK also plays a role in the immune and neuroendocrine systems. It works as an immune booster and anti-tumor agent by binding to opioid receptors (130). MENK can also stop human cancer cells from proliferating by blocking cyclin-dependent kinase pathways (131) (Fig. 2). More research is needed to determine the possible immunomodulatory function of ACPs and how they strengthen the body's immune system against tumors.

Apoptosis

Cancer cell apoptosis is another mechanism of action by induction of α-helical ACPs through disruption of the mitochondrial membrane (132). Within eukaryotic cells, α-helical ACPs can induce mitochondrial infiltration and swelling, releasing cytochrome c (Cytc), ultimately leading to cancer cell apoptosis. The release of Cytc from the damaged mitochondria causes oligomerization of Apaf-1, activation of caspase-9, and subsequent conversion of procaspase 3 to caspase-3, which is responsible for many of the apparent symptoms of apoptosis (133,134).

A peptide derived from Meretrix could induce apoptosis, increase reactive oxygen species in the K562 cell cycle, eliminate electrical potential on the membrane surface, and degrade microcracks (135). One study confirmed that paradox induces apoptosis in the HT-1080 cell line by inhibiting caspase and disrupting the mitochondrial membrane, releasing Cytc. In the mitochondrial pathway, the induction of apoptosis in cancer cells is also associated with the death receptor pathway (136). Furthermore, it has been shown that synthetic tachyplesin conjugated to the integrin homing domain induces apoptosis of cancer cells through the aforementioned pathways. ACPs have been shown in numerous studies to cause Cytc release and stimulate apoptosis in tumor cells by wrecking the mitochondrial membrane (36). Ra-V peptide, for example, provokes apoptosis of mitochondria, which causes human breast cancer cells to die by mediating caspase signaling pathway activation, the release of Cytc, and mitochondrial membrane potential loss (36). Dolastatin 10 ACP derived from the marine mollusk *Dolabella auricularia* has significant cytotoxicity against various human cancer cell lines. This peptide can induce apoptosis in tumor cell lines with downregulated anti-apoptotic molecule Bcl-2 (137) (Fig. 2).

Selectivity of ACPs and targeted therapy by ACPs

Regarding cell targets and selectivity of ACPs, ACPs can be classified into 2 main groups. The first group is peptides that are only active against cancer cells and microbes and do not harm healthy mammalian cells, while the second group of ACPs is peptides that do not have the ability to diagnose all 3 groups of cells (healthy, cancerous, and microbial cells) (29). Although various results have been published about experiments on the selective criteria of ACPs that kill cancer cells, their selectivity is still controversial. ACPs have been shown to generally exert their oncolytic effects by non-membrane or membrane mechanisms (138). The mechanism of each membranolytic peptide's activity is influenced by the characteristics of ACP and the target membrane, which impact the selectivity of ACPs. Cancer and normal cells appear to have many distinct differences, which contribute to the selectivity of some ACPs. The first difference is the net negative charge on the membrane, which characterizes malignant cells (139). There are several anionic molecules in the membrane of cancer cells, such as O-glycosylated mucins, heparin sulfate, phosphatidylserine, and sialylated gangliosides, which give them a net negative charge while normal mammalian cell membrane is zwitterionic (29) Increasing the content of sialic acid on the membrane leads to enhancing the surface concentration of acidic groups and thus changing the membrane charge (140). The glycosylation characteristics of cancerous tissues are linked to their phenotype. Another feature of most cancer cells is that their membranes are more fluid than normal cells, which ACPs can disrupt, leading to increased permeability and potential cell death (141). ACPs can also have more contact with the microvilli in malignant cells because the cell surface area of cancer cells is much larger than that of healthy cells, so this can also be a selectivity option for ACPs. The membrane of cancer cells has a negative charge, which is also the same in bacterial cells. Thus, it can be said that the enhanced anionicity of the cytoplasmic membrane of cancerous cells and the swelling of mitochondria with Cytc release may explain the selectivity and membranolytic activity of ACPs. Various approaches to tumor management focus on addressing the angiogenesis process. Peptides inhibit the action of receptors expressed on angiogenic endothelial cells and, as a result, disrupt the establishment of the vasculature associated with a tumor (142,143). Molecularly targeted ACPs can bind, penetrate, and inhibit or destroy cancer cells at any phase of carcinogenesis or growth. As previously stated, peptides are categorized into 2 types, including a. peptides that are only effective against cancer cells and do not affect healthy cells and b. peptides that are effective against both cancer and healthy cells (144). ACPs derived from lactoferricin B, chrysophsin-1, cecropins, and magainin-2 are peptides that have only selectivity for cancer cells and not healthy cells (145). The cancer PPD database (http://crdd.osdd.net/raghava/

cancerppd/) is used to predict the structure of peptides and recommend the appropriate ACP for further study (146). Furthermore, techniques that consider binary profiles, amino acid contents, and sequence-based methods are employed to target the desired cancer cells (147).

Membranolytic ACPs are synthesized from scratch utilizing designs based on helical cationic amphipathic peptide sequences (148). Anionic molecules in cancerous cells confer a net negative charge, whereas healthy cell membranes contain a neutral net charge (139). Healthy cells have high cholesterol levels in their membrane, which can prevent cationic peptides from entering through the cell fluid. Furthermore, healthy cells contain less fluid than cancer cells (149). Mastoparan-I is an α-helical structure peptide and plays a role in cell swelling, cell bursting, and necrosis by interacting on the negative charge of cell surfaces of liver and prostate cancer (150). Also, an SVS-1 that is a β-sheet structure peptide breaks cell membranes in lung and breast cancer by forming pores (151). The amino acid content of ACPs is crucial in the therapy of several forms of cancer. Cationic peptides, for example, can increase the specificity of ACPs, but increasing hydrophobic peptides can decrease the degree of specificity (152). Furthermore, polycationic peptides demonstrated selectivity for acute T-cell leukemia because they have a larger membrane potential than normal tissues (153). ACPs design strategies, such as hybridization, cyclization, modification, and fragmentation, can potentially improve the therapeutic efficacy by extending the half-life time of medications in plasma, boosting activity, and minimizing drug toxicity (154).

Targeted therapy by ACPs means ACPs can bind to receptors on the cancer cell surface, allowing cell internalization (155). Therapeutic peptides are further divided into 3 types based on their biological targets, which include i. cell cycle regulation, ii. signal transduction pathways; and iii. cell death pathways (156). KLA is a tumor-penetrating ACP that promotes apoptosis. In reality, by disrupting the mitochondrial membrane, KLA causes programmed cell death (157). One of the targeted therapy approaches by ACPs is their application in the structure of fusion proteins. Fusion proteins are chimeric proteins composed of targeting and toxic moieties (107).

Denileukin diftitox (Ontak), approved by the FDA in 1999 against recurrent cutaneous T-cell lymphoma, is one of the first recombinant engineered chimeric proteins that combined interleukin-2 and diphtheria toxin. In the structure of Ontak, IL-2 and diphtheria toxin are responsible for targeting and toxic activity, respectively (158). Due to the versatile features of ACPs, they could be applied not only as tumor-targeting moieties but also as toxic or effector moieties in the structure of fusion proteins. Previously, several research groups have demonstrated that ACPs, either as targeting or toxic moiety, play a crucial role in the targeted therapy of multiple cancers (91,106,159,160). Also, a recent study used IL-24 (a pro-apoptotic cytokine) combined with p28, a tumor-specific or cell-internalizing peptide against breast cancer. The anti-tumor effects of engineered p28-IL-24 recombinant protein were investigated *in vitro* and *in vivo*. This novel fusion protein induced apoptosis and suppressed the growth of MDA-MB-231 and MCF-7 cancer cells without affecting HUVEC normal cells (159).

Clinical trials and approved ACPs

The therapeutical utility of therapeutic peptides is straightforward because only in the USA were nearly 140 clinical trials registered to evaluate the eligibility of peptides for cancer treatment. Among these peptides, ACPs appear to comprise a notable proportion of all agents entering into clinical trials (161,162). Some of the well-known ACPs at the different phases of clinical trials have been summarized in Table 2 (see website https://clinicaltrials.gov).

Table 2. Some anticancer peptides in clinical trials, their phase, diseases, NCT number, and conditions.

Peptide name	Phase	Disease	NCT number	Condition
p-28	Phase 1	Recurrent or progressive central nervous system tumors	NCT01975116	Completed
	Phase 1	Refractory solid tumors	NCT00914914	Completed
Nerofe	Phase 1	Solid tumors	NCT01690741	Completed
G250	Phases 1	Renal cell carcinoma	NCT00520533	Completed
	Phases 1 and 2	Kidney cancer	NCT00003102	Completed
Aplidine (plitidepsin)	Phase 1	Multiple myeloma	NCT02100657	Completed
	Phase 1	Advanced solid tumors lymphomas	NCT00788099	Completed
	Phase 2	Myelofibrosis	NCT01149681	Completed
MUC1	Phase 1	Non-small cell lung cancer (NSCLC) Stage III	NCT01731587	Withdrawn
LL-37	Phases 1 and 2	Melanoma	NCT02225366	Completed
iRGD	Phase 1	Acinar cell adenocarcinoma of the pancreas Duct cell adenocarcinoma of the pancreas Liver metastases Lung metastases Recurrent breast cancer Recurrent pancreatic cancer Stage IV breast cancer Stage IV pancreatic cancer	NCT01741597	Withdrawn
ATN-161	Phases 1 and 2	Brain and central nervous system tumors	NCT00352313	Completed
	Phases 2	Renal cell carcinoma	NCT00131651	Completed
LTX-315	Phase 1	Melanoma Breast cancer Head and neck cancer Lymphoma	NCT01986426	Completed
		Cancer with transdermal accessible tumor	NCT01058616	Completed
		Carcinoma	NCT01223209	Completed
	Phase 2	Basal cell carcinoma Skin cancer Cancer of the skin, basal cell Cancer of the skin	NCT05188729	Recruiting
LTX-315 in combination with pembrolizumab	Phase 2	Advanced melanoma	NCT04796194	Recruiting
LTX-315 and TILs	Phase 2	Soft tissue sarcoma	NCT03725605	Active, not recruiting
ANG-1005	Phase 2	Breast cancer Brain metastases	NCT02048059	Completed
		Brain tumor Glioblastoma	NCT01967810	
	Phase 1	Advanced solid tumors with and without brain metastases	NCT00539383	Completed
		Recurrent or progressive malignant glioma	NCT00539344	Completed

Obstacles in clinical trials

A problem is the lack of selectivity of the available drugs and their consequent undesirable side effects for the patients (163). As a result, there is a need to design more selective medicines with fewer adverse effects for non-target cells. It is preferable for these novel chemicals to have distinct modes of action in relation to a specific molecule in the target cells (164). ACPs have captured the interest of several researchers due to their potential to kill or impede the growth of a wide range of bacteria and tumor cells. There are thousands of synthetic and natural peptides, many of which have anti-cancer action (165). However, only a few are now undergoing clinical testing. This is primarily owing to the numerous hurdles connected with producing these peptides into medicines, such as manufacturing costs. As a result, scientists are attempting to create new ACPs utilizing the initial restructuring of natural peptides so that the physicochemical features can be easily modified while also lowering production costs.

Because certain peptides have negative effects on other healthy cells, such as being highly toxic or altering the immunological response, there are still concerns about the use of ACPs (166,167). Another critical point is the sensitivity of peptides to proteolysis, while oral administration is the preferred method of drug delivery (168). As a result, these medicines are typically administered *via* intravenous or intramuscular injection because feeding leads to low resistance to proteases (169). The use of a synthesis method to substitute naturally occurring amino acids with synthetic amino acids can reduce vulnerability to proteolytic degradation (170). Furthermore, determining the time of circulation, which is critical for drug efficacy, is difficult (171). Various solutions to this challenge have been offered, including the use of medication vectors such as bacteriophages (172). The use of a bacteriophage on ACPs increases targeting and enables increased activity.

Another great technique for the improvement of target specificity is to bind the ACPs to cell-penetrating peptides (CPPs). Accordingly, one study used the TAT protein of HIV as CPP to increase ACP-selectivity in cancer cells (173). The conjugation of ACPs to polymers such as polyethylene glycol has also been found to improve dynamics/pharmacokinetics by boosting penetration into desired cancer cells and allowing for additional circulation time (174). As a result, these alterations could affect the amphipathicity characteristics of therapeutic ACPs and lower their cytotoxicity against healthy cells. It also makes ACPs resistant to proteolysis while maintaining anti-cancer effects. Thus, their design and medicinal action will be improved (175).

CONCLUSION

One of the most critical issues of cancer is heterogeneity, which is a considerable obstacle to the success of cancer therapy. Although the exact mechanism of action of ACPs is still controversial, some characteristics of malignant cells make them susceptible to peptides. ACPs bind to negatively charged structures (like cancer cells) in a non-specific fashion, which are both exclusively and homogenously displayed by cancer cells. Negatively charged targets are mainly represented by phospholipids, such as PS, which are secluded in the inner side of the plasmatic membrane in normal cells, but increasing the content of PS and accordingly increasing the cancer cell's negative charge allows for the specificity of ACPs (176-178).

For the *in-silico* design of a construct from ACPs (like fusion proteins), the apoptosis-inducing anticancer peptides database (ApInAPDB) could be used. ApInAPDB (http://bioinf.modares.ac.ir/software/ApInAPDB/) is a recently established database composed of about 850 apoptosis-inducing peptides and their analogues provided from previous literature, including peptides binding target or binding affinity, function, and their effectiveness reported as IC50. Other information like charge, hydrophobicity, amino acid composition, and also prediction of secondary structure using different algorithms are accessible in the mentioned database (179). I-TASSER and RAMPAGE are other well-known web servers that could be used to design ACPs and fusion proteins. To predict 3-dimensional structures and the evaluation of molecular dynamic behaviors, MODELLER and GROMACS software are accessible, respectively (180).

In recent years, peptide design has benefited tremendously from advancements in artificial intelligence algorithms. These algorithms have greatly facilitated and accelerated the process of peptide discovery and optimization. By leveraging complex computational models, machine learning techniques, and large datasets, artificial intelligence algorithms can efficiently analyze the vast space of peptide sequences and structures, predicting their potential anti-cancer activity and identifying optimal candidates for further experimental validation. Moreover, these algorithms can also take into account various physicochemical and structural properties of peptides, enabling the design of molecules with enhanced stability, selectivity, and bioavailability. The integration of artificial intelligence algorithms in peptide design has not only improved the efficiency of the discovery process but has also opened up new avenues for the rational design of novel peptide-based therapies with improved efficacy

and specificity. As such, the exploration and application of artificial intelligence algorithms for peptide design hold great promise for advancing the field of anti-cancer peptide therapeutics (181,182).

Although it was reported that the specificity of the ACPs is better than that of chemotherapy drugs, in some cases, especially in the case of synthetic ACPs, lower specificity toward cancer cells might be observed. The lower specificity of ACPs generally refers to their physicochemical properties, such as charge, hydrophobicity, and structure. Investigations have revealed that ACPs with high hydrophobicity and a positive net charge selectively kill cancer cells by interacting with anionic cell membrane components of cancer cells (183,184). So, rational design of ACPs as well as manipulation of physicochemical properties are 2 key parameters to enhance specificity. For example, in a study by Fu *et al*., the TAT-KLA peptide was conjugated to the BRBP1 peptide, which was previously identified for its affinity toward the MDA-MB-231 cell line, to enhance its specificity against tumor cells. (185). In another study, the specificity of the HPRP-A1 peptide compared with the HPRP-A1-TAT peptide was evaluated. Between HPRP-A1 alone and HPRP-A1-TAT, the latter has higher positive charges and may have more chances to interact with the anionic surface of cancer cells (173).

Besides cancer heterogenicity and specificity, some other issues still exist in cancer treatment by ACPs. The challenges for using ACPs in cancer therapy are the poor bioavailability, immune response to treatments, toxicity of the peptides, and the cost-inefficiency of the approaches. Due to the peptide nature of ACPs, proteolytic degradation is a major threat to the potency of peptide-based drugs, which decreases their bioavailability and limits the systemic delivery potential of ACPs. To overcome lower bioavailability as well as immune response issues, various delivery systems (encapsulation of ACPs in liposomes, polymer nanoparticles, or quantum dots) were used (186).

Since most existing anti-cancer medications attack all rapidly dividing cells, existing cancer therapies have numerous adverse side effects. Although more research on the specific mechanism of ACPs on cancer cells is needed, several studies have demonstrated that many ACPs are capable of targeting cancer cells while avoiding damage to healthy cells. As a result, ACP therapy has an impact on molecular targets by binding anticancer medications to the target cell and stimulating biological processes (143). The emergence of highly cationic anticancer peptides as potent anticancer agents has opened new doors in cancer therapeutics. These peptides exhibit selectivity towards cancer cells while sparing normal mammalian cells, making them ideal candidates for targeted and less-toxic cancer treatments. As research in this field progresses, it is expected that more AMPs will be identified and developed for targeting the different types of malignancies. One promising aspect is the combination of ACPs with conventional medications, which may lead to synergistic effects and improved treatment outcomes. The ability of ACPs to penetrate tumors effectively due to their strong tumor penetration and solubility further adds to their potential as successful cancer treatments. In addition to preclinical studies, the translation of promising ACPs into clinical trials is a crucial step toward their development as cancer therapeutics. Current clinical trials evaluating the safety and efficacy of these peptides will provide valuable insights into their potential use in clinical practice (187-189).

ACPs possess unique pharmacokinetic properties that make them an ideal option for cancer therapy. These peptides are small in size, allowing for easy penetration into tumor tissues and cellular membranes. They exhibit high selectivity towards cancer cells, minimizing off-target effects and reducing toxicity to healthy tissues. Additionally, anti-cancer peptides have a short plasma half-life, which ensures rapid clearance from the body and reduces the risk of accumulation and adverse reactions. Furthermore, their inherent biodegradability and low immunogenicity make them suitable for repeated administration. These pharmacokinetic properties of anti-cancer peptides enhance their therapeutic efficacy and hold promise for the development of targeted and personalized cancer treatments (190,191). One intriguing aspect of targeted therapy utilizing ACPs is their potential application in cancer imaging. ACPs have

gained attention for their potential in cancer imaging, a targeted therapy approach. ACPs can be labeled with imaging agents, such as fluorescent dyes, radioactive isotopes, or nanoparticles, which enable their visualization in real time through imaging techniques like fluorescence imaging, positron emission tomography, and magnetic resonance imaging. This opens up possibilities for early detection, precise diagnosis, and monitoring of tumors. ACPs selectively bind to cancer cells, making them useful molecular probes for tumor-specific imaging. This targeted imaging approach can assist in detecting small or hidden tumors, monitoring treatment response, and guiding surgical resection. Additionally, cancer imaging with ACPs is non-invasive, minimizing patient discomfort while providing valuable information for personalized cancer management (192,193).

The future of peptides in cancer treatment looks promising, thanks to the advancements in personalized medicine, peptide engineering, drug delivery systems, and combination therapies. Personalized approaches using omics data can identify specific molecular targets, allowing peptides to deliver therapeutic payloads directly to cancer cells. Peptide engineering techniques enhance stability and efficacy, while novel drug delivery systems enable efficient tumor targeting. Combining peptides with other therapies can lead to synergistic effects and improved outcomes. Artificial intelligence algorithms expedite peptide design, leading to the discovery of novel sequences with enhanced properties. Together, these advancements hold the potential for highly targeted, effective, and personalized peptide-based cancer therapies.

Overall, the rapid progress in the understanding and development of ACPs as anticancer agents brings hope for improved cancer treatments with enhanced selectivity, reduced toxicity, and increased efficacy. Continued research and clinical trials will pave the way for the integration of ACPs into standard cancer treatment regimens, ultimately improving patient outcomes and reducing the global burden of cancer (194).

To that purpose, natural and synthesized peptides are novel cancer-fighting agents. Many ACPs have anti-apoptotic and anti-proliferative properties in various types of cancer cells, both *in vitro* and *in vivo*, which is why they have been tested in clinical trials for cancer treatment. In addition, clinical research believes that ACPs will boost cancer medications to prevent new instances of cancer and its related death cases.

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Conflict of interest statement

All authors declared no conflict of interest in this study.

Authors' contributions

A. Jahanian-Najafabadi contributed the initial idea and provided supervision throughout the research process; E. Khodamoradi was responsible for preparing the references and collaborated on the preparation of figures and tables; R. Ghavimi and S. Mahmoudi took the lead in drafting the original manuscript; A. Jahanian-Najafabadi and M. Mohammadi reviewed and edited the manuscript; M. Mohammadi and E. Khodamoradi assisted in the preparation of figures and tables. All authors read and approved the finalized version of the manuscript.

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