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Unveiling anticancer peptides; from the mechanisms of action to their development through artificial intelligence

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ABSTRACT

Cancer is a leading cause of death worldwide and a major burden on the healthcare system. Current treatment methods are limited as they have low selectivity, unspecific targeting and increasing multidrug resistance. Therefore, newer modes of therapeutic strategies need to be developed. Anticancer peptides (ACP) are small bioactive peptides that have the ability to be selective and toxic to cancer, with a high efficiency in cell penetration and internalization and low risk of inducing multidrug resistance. ACPs have multitude of mechanisms giving them the ability to target multiple cancer types as well as both slow growing and metabolically active cancers. Recently, a large number of literature papers examine the structure, mechanisms of action, synthesis, modifications and other non-direct cancer treatment applications of ACPs. A growing aspect in all areas of research and development especially in peptide drug discovery is now Artificial Intelligence (AI). It enables large amounts of data to be processed quickly and allows for rapid predictions hence the increased discovery of new ACPs. In this review, we discuss the structure, mechanisms of action, synthesis of ACPs and the different types of AI models, their algorithms and the ACPs prediction models currently available.

1. Introduction

Cancer is a leading cause of death worldwide with an incidence of almost 20 million cases and nearly 10 million deaths in 2022 (Ferlay et al., 2024; Chinnadurai et al., 2023). The most frequent cancers currently are lung, breast and colorectal (Ferlay et al., 2024). Cancer has six distinct characteristics: proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing apoptosis, activating invasion, and metastasis (Hwang et al., 2022) and is caused by major molecular/genetic alterations that lead to uncontrolled growth and multiplication of cells (Chinnadurai et al., 2023). The abnormal regulation of apoptosis is an important factor in the development of cancer (Kordi et al., 2023). The main treatment methods are chemotherapy, radiotherapy, surgery, and immunotherapy or a combination (Tripathi and Vishwanatha, 2022; Xie et al., 2020). Currently, cancer is being treated ineffectively therapeutically (Chiangjong et al., 2020) as the current methods are limited in their selectivity and unspecific targeting of healthy cells with deleterious effects (Gaspar et al., 2013), with a significant challenge of the increasing development of drug resistance (Nhàn et al., 2023).

Surgical treatment has the benefit of quickly removing solid tumours, but it leads to trauma, bleeding, risk of infection, and other associated risks (Xie et al., 2020), and is not a treatment method for smaller microscopic tumours. Chemotherapy is the most established method, which involves administering chemical compounds to the body to eliminate cancer cells (Xie et al., 2020). These drugs have very poor cell selectivity, resulting in normal cell death alongside (Tripathi and Vishwanatha, 2022), as well as the development of serious side effects with protracted use (Xie et al., 2020) and drug resistance (Tripathi and Vishwanatha, 2022). Cancer cells have multiple ways in which they can resist chemotherapy drugs, including the export of chemotherapeutic agents out of the cell, enhanced DNA damage repair, increased tolerance to stress conditions and abnormal expression of drug-detoxifying enzymes (Gaspar et al., 2013). Radiotherapy uses high-energy beams to destroy cancer cells (Tripathi and Vishwanatha, 2022) and is often used in combination with chemotherapy (Chinnadurai et al., 2023) or in

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patients who haven't benefited from surgical treatment (Xie et al., 2020). This treatment option isn't specific for cancer cells causing normal tissue damage as well (Tripathi and Vishwanatha, 2022). Immunotherapy is another treatment option that primes the patient's immune system to cause an anticancer response (Tripathi and Vishwanatha, 2022; Xie et al., 2020). These treatments include cytokine therapy, immune checkpoint inhibitors, monoclonal antibody-based therapies, and chimeric antigen receptor (CAR) T cells (Abd-Aziz and Poh, 2022). The effects are longer lasting and have fewer side effects compared to chemotherapy and radiotherapy (Xie et al., 2020). However, Immunotherapy is limited as it uses antibodies specific to particular antigens present on cancer cells, which can be present on certain normal cells (Chinnadurai et al., 2023), it can also cause autoimmune diseases to arise, and the effects vary from patient to patient (Xie et al., 2020). Therefore, there is a need to find new therapeutic strategies that can be more selective and at the same time less harmful to patients (Gaspar et al., 2013).

Peptide-based therapeutic options are currently being reviewed (Wang et al., 2022) and have the potential to be the next cancer treatment method (Ghaly et al., 2023). These new peptide-based approaches have several advantages, such as enhanced specificity, reduced toxicity, versatility, low production cost, deeper tissue penetration, lower immunogenicity, easy modification, and lower risk of multi-drug resistance (Nhàn et al., 2023; Qiao et al., 2019). They do have some disadvantages in that they have a shorter half-life, are susceptible to protease degradation (Nhàn et al., 2023) low oral bioavailability (Liscano et al., 2020) as well as certain undesired effects such as haemolytic activity (Feder et al., 2000). Peptide-based therapeutic options are becoming available, but are currently limited, and many are still in the phases of Clinical Trials.

2. Anticancer peptides

Anticancer peptides (ACPs) are short bioactive peptides that range from 5 to 50 amino acids (Ghaly et al., 2023; Nhàn et al., 2023). They are considered a subclass of Antimicrobial Peptides (Shahid et al., 2025b) that have anti-tumour bioactivity (Jia et al., 2025). Some of these peptides have the ability to be selective and toxic to cancer, while not affecting healthy tissue (Chiangjong et al., 2020). It has been shown that the most effective ACPs are cationic and hydrophobic (Tripathi and Vishwanatha, 2022), and they can interact with cancer through electrostatic interactions (Kordi et al., 2023). The physicochemical composition of ACPs can play an important role in determining their bioactivity. ACPs are predominantly composed of the following amino acid residues: Glycine, Lysine, Leucine (Chiangjong et al., 2020), Alanine, Phenylalanine, and Tryptophan (Manavalan et al., 2017). It has been shown that predominantly the N-terminal of ACPs contains Leucine, Lysine, Alanine, and Phenylalanine while the C-terminal contains Valine, Cystine, Leucine, and Lysine (Tyagi et al., 2013). Cystine (C) being present in the ACP doesn't serve a role with regards to selectivity or toxicity, however, these stabilize and maintain the ACP structures (Chiangjong et al., 2020) and thus, increasing their extracellular stability, required for their bioactivity (Sevim and Günes Altuntas, 2024). Having Glycine and Proline present within the peptide sequence is crucial for membrane interactions and conformational flexibility (Chiangjong et al., 2020). ACPs containing Phenylalanine can enhance their affinity for targeting the cancer cell membrane (Chiangjong et al., 2020). Tryptophan has been shown to have a role in ACPs' toxicity against cancer cells (Chiangjong et al., 2020). Lysine can cause cancer cell cytotoxicity by its ability to penetrate the cell membrane and disrupts the membrane integrity (Chiangjong et al., 2020). Leucine and Valine play an important role in the hydrophobicity of the peptide (Huang et al., 2011; Chen et al., 2005). Alanine is an amino acid that aids in the formation of α-helix (Burdukiewicz et al., 2020).

Cancer cells have a negatively charged outer monolayer membrane (Kordi et al., 2023), leading to cancer cell membranes being anionic (Tripathi and Vishwanatha, 2022). There are a multitude of factors that contribute to this, these include but are not limited to the increase in the proportion of phosphatidylserine groups on the membrane surface, elevated levels of zwitterion phosphatidylethanolamine, and disrupted glycosylation of glycolipids (Marunganathan et al., 2024; Zhao et al., 2021). While cancer cell membranes are anionic due to the greater abundance of phosphatidylserine in the membrane, non-cancer cells are Zwitterionic as a result of the zwitterionic lipids in their membrane (Hilchie et al., 2011). The Zwitterionic nature of healthy cells is why ACPs are not able to interact with normal cells as they cannot form secondary structures in this charge, shown in Fig. 1 part a) by the lack of a secondary structure and in part b) by the presence of alpha-helical structures on the cancer membrane (Tripathi and Vishwanatha, 2022). The cationic nature of ACPs is why the cancer membrane can specifically absorb them and are more active against these cells (Kordi et al., 2023), as they are attracted to the negative charge surface molecules rather than a unique receptor (Hilchie et al., 2011). This gives ACPs the advantage of targeting both metabolically active and slow growing cancers (Xie et al., 2020).

There are additional factors that are specific to cancer cell membranes that increase the interaction and efficiency of ACPs. There is a reduced amount of cholesterol levels within cancer cell membranes that increases the fluidity of these cells (Chiangjong et al., 2020; Marunganathan et al., 2024; Nhàn et al., 2023). However, Prostate and breast cancers have a higher content of cholesterol within their membrane, which poses an obstacle for ACPs to lyse their membrane (Gaspar et al., 2013). Another characteristic is that cancer cells have microvilli on their surface, this increases ACP interaction as this expands the surface area available for ACPs to interact with cancer cells (Marunganathan et al., 2024).

The secondary structure of ACPs has been shown to be essential in their cell surface interactions (Hamdi et al., 2025) and, therefore, is the most common way to categorize ACPs (Xie et al., 2020). The four most common structures formed are alpha helixes, beta-pleated sheets, random coils, and cyclic structures (Xie et al., 2020). Alpha helixes are the most common type of ACPs, they are shorter in length and simpler in structure (Xie et al., 2020). Helicity has been shown to strongly correlate with anticancer activity (Tripathi and Vishwanatha, 2022). Peptides BR2, Gaegurin, NRC-3, and NRC-7 all form alpha-helical structures. Beta-pleated sheets are formed when there are two or more disulfide bonds present. These structures have a lower anti-tumor activity compared to alpha helixes however are less toxic to normal tissues (Xie et al., 2020). LfcinB and Tachyplesin I are peptides that form beta-pleated sheets. Random Coils are classified based on their lack of a typical secondary structure (Xie et al., 2020). These peptides form the large majority of ACPs (Tripathi and Vishwanatha, 2022). Even lacking a typical secondary structure, these ACPs still have a good anticancer activity (Tripathi and Vishwanatha, 2022) and tend to be proline and glycine-rich (Xie et al., 2020). As listed in Table 1, Alloferin is a peptide with a random coil secondary structure. Cyclic ACPs are peptides that either contain a head-to-tail cyclization backbone or disulfide bonds that form cystine knots (Xie et al., 2020). These are more stable than the linear structured ACPs (Xie et al., 2020). Due to the cyclic structure of these ACPs, they have a higher resistance to proteases compared to the other three structure types (Alamdari-palangi V et al., 2023). All Examples of ACPs used throughout this paper are listed in Table 1.

There are numerous advantages of ACPs, including low molecular mass, relatively simple structures, greater tumor selectivity, fewer adverse reactions, ease of absorption, low risk of inducing multi-drug resistance (Qiao et al., 2019) and low cost of production (Xie et al., 2020). Even though both antimicrobial peptides (Abdille et al., 2022) and specific-target antibodies have been shown to accumulate in liver tissue with possible toxic effects (Hoppenz et al., 2020), ACPs don't accumulate in organs such as the Kidney and Liver and therefore have a minimal toxicity (Gómez Hernández et al., 2024). ACPs exhibit advantages over antibodies, including the higher efficiency in tissue

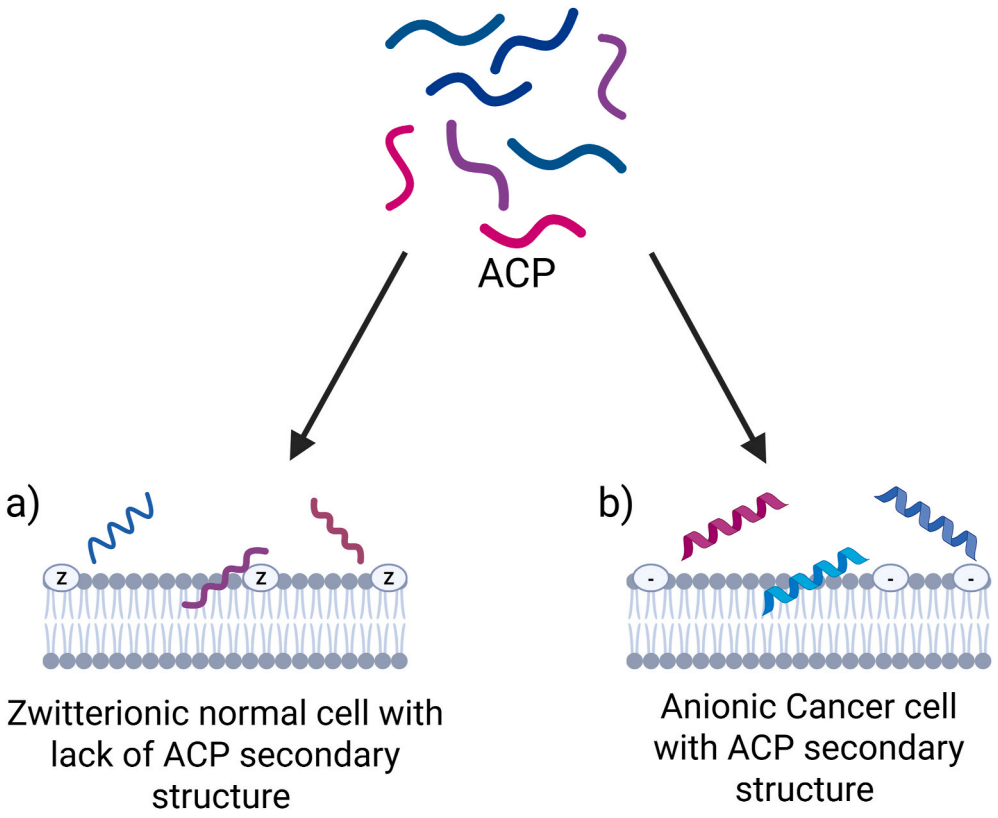

Fig. 1. ACPs electrostatic interactions with a) normal cell and b) cancer cell membranes and the resulting secondary structure or lack of.

penetration and cellular internalization (Sri et al., 2023), lower cost, lower immunogenicity, reduced toxicity, and can be easily modified and rapidly synthesized (Nhàn et al., 2023; Marqus et al., 2017). The disadvantages of ACPs are that they have a shorter half-life, resulting in limited blood circulation, preventing delivery of sufficient amounts to the cancer cells (Kordi et al., 2023), and are susceptible to protease degradation (Nhàn et al., 2023). The shorter half-life of ACPs can be considered an advantage as this reduces the time the peptide is in the blood, reducing the possible side effects and reducing the toxicity to the kidneys (Gómez Hernández et al., 2024; Kordi et al., 2023). This is especially advantageous with regard to radiolabelled peptides used for cancer diagnosis (Bojarska and Wolf, 2024).

The FDA and EMA had approved more than 20 Anticancer Peptides and currently, there are over 30 approved anticancer peptide drugs available, with 230 more still in clinical trials (Hamdi et al., 2025; KuicK Research, 2025). Table 2 lists some of the active peptide-based treatments for cancer currently in clinical trials. Some of the ACPs that are available include Buserelin, Goserelin, Histrelin, Leuprolide, Triporelin, Cetrorelix (Hamdi et al., 2025), Cosmegen, Zoladex, Octreoscan, and Kyprolis (Pan et al., 2020). However, some ACPs are discontinued during clinical trial phases. MAGE-A3 is a tumour-associated antigen peptide vaccine that was discontinued due to a lack of efficacy in Phase III against Non-small cell lung cancer (FDA, 2017). BMAP-28 is another anticancer peptide that failed clinical trials due to haemolytic activity against healthy neutrophils and erythrocytes (Hoskin and Ramamoorthy, 2008). Pluvicto is a peptide-drug conjugate that was discontinued after clinical trails as it had a higher incidence of severe adverse effects with normal treatment options with regards to prostate cancer (Lamb et al., 2024).

3. Synthesis

Bioactive peptides are commonly sourced naturally from a variety of animals, insects, plants, microorganisms (Chinnadurai et al., 2023), and food (Hamdi et al., 2025). From these many sources, peptides with anticancer activity were discovered (Hamdi et al., 2025), especially from those with already established antimicrobial activity. Anticancer peptides can be sourced naturally from many organisms, including mammals, amphibians, insects, microorganisms (Qiao et al., 2019), plants (Hamdi et al., 2025), many marine species (Hussein et al., 2025), and/or synthetically designed (Chiangjong et al., 2020). Currently, most ACPs are derived from extraction and purification from natural sources rather than being fully synthesized, with only a few being designed synthetically (Huang et al., 2025). ACPs can be synthesized via two processes, either chemosynthesis or biosynthesis (Chinnadurai et al., 2023), summarized in Table 4.

Chemosynthesis occurs through either solution-phase peptide synthesis (SuPPS) or solid-phase peptide synthesis (SPSS) (Chinnadurai et al., 2023). SuPPS has largely been replaced by SPSS but is still used in special cases (Chinnadurai et al., 2023) for example with Euryjanicin A (Anand et al., 2019). SuPPS synthesizes peptides in solutions that have different properties from the reagents and peptides being constructed (Ghaly et al., 2023). This process occurs in four steps: protection of amino groups, coupling of protected amino acids, deprotection, and purification and evaluation of efficacy through in vitro and in vivo assays (Chinnadurai et al., 2023). This method overall is efficient and flexible (Chinnadurai et al., 2023).

SPSS is the preferred method for peptides used in research and therapeutics (Petrou and Sarigiannis, 2018) and is the industry choice for the synthesis of ACPs (Chinnadurai et al., 2023). This method uses solid support materials to bind and immobilize the peptides, which allows for continuous synthesis (Chinnadurai et al., 2023). The first step is to load the protected amino acids onto the solid support. The addition of coupling reagents is to couple the protected amino acids. Once this occurs, the protecting group is removed to allow for the amino acid next in the sequence to be added. This process is repeated until the desired sequence is achieved, and then once that occurs, the peptide is cleaved. Lastly, the crude peptide is purified and evaluated for efficiency. This

Table 1
List of Anti-Cancer Peptides mentioned throughout this review, including their sequence, classification by structure, and mechanisms of action.

Peptide	Sequence	Classification by Structure	Mechanism of action	Cancer Types	Reference
BR2	RAGLQFPVGRLLRRLLR	α-helix	Drug carrier, cytotoxic to cancer cells	Colon cancer, Cervical carcinoma	(Kordi et al., 2023; Marqus et al., 2017; Yu et al., 2022)
Buforin IIb	RAGLQFPVG[RLLR]3	Helix-hinge-helix	Mitochondrial-dependent apoptosis of cancer cells	Lung cancer, Cervical carcinoma	(Kordi et al., 2023; Lee et al., 2008)
Gaegurins	FLGALFKVASKVLPSVKCAITKKC	α-helix	Barrel stave and carpet model	Neoplastic cells, Colon, Breast carcinoma cells	Kordi et al. (2023)
Citropin 1.1	GLFDVIKKVASVIGGL	α-helix	Carpet model	Haematopoietic and non haematopoietic tumour cell lines	Kordi et al. (2023)
Alloferon	HGVSGHGQHGVHG	Random coils	Stimulate NK cells and interferon synthesis	Pancreatic cancer, Colon cancer	(Appiah et al., 2024; Bae et al., 2013; Kordi et al., 2023; Xie et al., 2020)
NRC-3, NRC-7	GRRKRKWLRRIGKGVKIIGGAALDHL, RWGKWFKKATHVGKHVGKAALTAYL	α-helix	Cell membrane lysis by damaging the mitochondrial membrane	Breast cancer	(Gaspar et al., 2013; Hilchie et al., 2011; Hou et al., 2022; Kordi et al., 2023; Marunganathan et al., 2024)
LfcinB	FKCRRWQWRMKKLGAPSITCVRRAF	β-sheet	Induces apoptosis by disrupting the mitochondrial membrane, cell lysis	Leukaemia cells, Melanoma, Head and Neck squamous cells	(Gaspar et al., 2013; Guerra et al., 2019; Mader et al., 2005; Marunganathan et al., 2024; Eliassen et al., 2003; Xie et al., 2020)
Magainin II	GIGKFLHSAKKFGKAFVGEIMNS	α-helix	Inhibits proliferation and membrane perforation by pore formation	Bladder cancer cells	(Hirano et al., 2021; Kordi et al., 2023; Lehmann et al., 2006; Marqus et al., 2017)
(KLAKLAK)2	KLAKLAKKLAKLAK	α-helix	Apoptosis induction by membrane disruption	Breast cancer, Melanoma	(Jäkel et al., 2012; Marqus et al., 2017; Sri et al., 2023)
MENK	YGGFM	N.A	Regulates Immune function	Sarcoma, Pancreatic cancer	(Li et al., 2015; Xie et al., 2020; Zhao et al., 2016)
LL-37	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES	α-helix	Toroidal pore formation, apoptosis induction	Breast cancer, Ovarian cancer, Lung cancer, Gastric cancer	(Ghaly et al., 2023; Henzler Wildman et al., 2003; Ren et al., 2012; Tripathi and Vishwanatha, 2022)
Tachyplesin I	KWC1FRVC2YRGIC2YRRC1R	β-sheet	Lysis mediated complement pathways induce tumour cell differentiation	Melanoma, Cervical cancer	Ghaly et al. (2023)
Melittin	GIGAVLKVLTTGLPALISWIKRKRQQ	α-helix	Immunomodulatory, induce apoptosis, inhibit angiogenesis	Leukemic cells, Non Small cell lung cancer, Ovarian cancer	(Ceremuga et al., 2020; Marunganathan et al., 2024; Tripathi and Vishwanatha, 2022)
P18	KWKLFKKIPKFLHLAKKF	α-helix	Induce necrosis by membrane disruption	Haematopoietic cancers, Breast cancer	(Ghaly et al., 2023; Tang et al., 2010; Tripathi and Vishwanatha, 2022)
Dolastatin 10	dolavaline, dolaisoleucine, dolaproline, dolaphenine, valine	N.A	Apoptosis induction	Melanoma, Colorectal, Sarcoma and Ovarian cancer	(Beesoo et al., 2014; Marunganathan et al., 2024; Xie et al., 2020)
MP06	LAVISWKCQEWNSLWKKR	α-helix	Inhibit Angiogenesis	Non Small cell lung cancer	Kim et al. (2024)
Temporin-1 CEa	FVDLKKIANIINSIFGK	α-helix	Induces apoptosis by disrupting the mitochondrial membrane	Breast cancer	(Han et al., 2024)

method has the advantages of automation, high purity (Chinnadurai et al., 2023), the ability for simultaneous synthesis of different peptides (Ghaly et al., 2023), and the incorporation of chemical modifications (Chinnadurai et al., 2023). However, the disadvantages of this method are the use of hazardous substances and the high solvent consumption (Ghaly et al., 2023). To try and overcome these disadvantages, there is the development of green solvents, which are solvents with the same solubility and separability without the undesirable chemical properties (Wegner et al., 2021). They are still in evaluation and there is no one 'gold standard' solvent (Wegner et al., 2021).

Biosynthesis occurs through two methods: enzymatic hydrolysis or recombinant DNA technology (Chinnadurai et al., 2023). Enzymatic hydrolysis is when larger proteins are proteolytically cleaved into smaller proteins (Chinnadurai et al., 2023). This process is when a desired anticancer peptide sequence is found naturally in a larger peptide. The steps involved include the selection of protein, extraction of said proteins, enzymatic hydrolysis, separation and purification, and lastly characterization and evaluation (Chinnadurai et al., 2023). The advantages of enzymatic hydrolysis are high specificity, mild reaction conditions, and not using hazardous substances (Chinnadurai et al., 2023). Recombinant DNA technology is the other method of biosynthesis. This method uses genetic engineering to produce peptides (Chinnadurai et al., 2023). The selected peptide goes through gene cloning, and an expression vector is constructed and transformed. Then the peptide is extracted and purified, and lastly characterized and evaluated (Chinnadurai et al., 2023).

4. Mechanisms of action

ACPs work through a multitude of mechanisms to fight cancer cells within the body. These mechanisms include membrane disruption, apoptosis induction, angiogenesis inhibition, differentiation induction, and immunomodulation (Nhàn et al., 2023), with the main method being apoptosis and necrosis as a result of membrane disruption and lysis (Kordi et al., 2023). These mechanisms can be split into two categories, membranous interactions and non-membranous interactions.

Table 2
Active Peptide-based treatments for cancer currently in clinical trials.

Clinical Trials ID	Name	Type of Treatment	Cancer/Target	Phase	Reference
NCT05386550	Xevinapant	Peptide based drug combination with radiotherapy	Head and Neck squamous cell carcinoma	Phase III	Xiao et al. (2025); U.S. National Library of Medicine, 2025
ACTRN12619000769189	VG161-A101	Personalised Peptide Vaccine	Lung cancer	Pilot Study	Australian Clinical Trials, 2023
NCT04939610	177Lu-FAP-2286	Peptide targeted radionuclide therapy	Fibroblast Activation Protein expressing Solid tumours	Phase I, II	U.S. National Library of Medicine, 2025
NCT04733027	PEP-010	Cell Penetrating Peptide – Stand alone or combinational	Pancreatic ductal carcinoma	Phase I	U.S. National Library of Medicine, 2025
NCT03613181	ANG1005	Peptide drug conjugate	Breast Cancer with leptomeningeal metastases	Phase III	Xiao et al. (2025); U.S. National Library of Medicine, 2025
NCT04180371	BT5528	Peptide Drug conjugate	Ovarian cancer, Urothelial/Bladder cancer, Lung cancer, Breast cancer, Head and Neck cancer and Gastric/Upper Gastrointestinal cancer	Phase I, II	Xiao et al. (2025); U.S. National Library of Medicine, 2025
NCT04706962	TH1902	Peptide Drug conjugate	Breast cancer, Ovarian cancer, Endometrial cancer, Melanoma, Thyroid cancer, Prostate cancer	Phase I	Xiao et al. (2025); U.S. National Library of Medicine, 2025
NCT05691517	CBX-12	Peptide Drug conjugate	Metastatic Solid tumours	Phase I	Xiao et al. (2025); U.S. National Library of Medicine, 2025
NCT06220838	SC-101	Peptide Drug conjugate	Metastatic Solid tumours	Phase I	Xiao et al. (2025); U.S. National Library of Medicine, 2025
NCT04229979	Galinpepimut-S	Peptide Vaccine	Acute myeloid Leukaemia	Phase III	Xiao et al. (2025); U.S. National Library of Medicine, 2025
NCT05155254	IO102-IO103	Peptide Vaccine	Melanoma	Phase III	Xiao et al. (2025); U.S. National Library of Medicine, 2025
NCT05232916	GLSI-100	Peptide Vaccine	Breast Cancer	Phase III	Xiao et al. (2025); U.S. National Library of Medicine, 2025
NCT05188729	VP-315	Oncolytic peptide	Basal Cell Carcinoma	Phase II	U.S. National Library of Medicine, 2025); Ghavimi et al. (2025)
NCT04796194	LTX-315	Oncolytic peptide in combination	Melanoma	Phase II	U.S. National Library of Medicine, 2025); Ghavimi et al. (2025)

Table 3
The Anticancer peptides listed in this paper, sorted into their Mechanism of Action.

Mechanism of Action	Anticancer Peptides
Membrane Disruption	Gaegurins, Citropin 1.1, NRC-03, NRC-07, LfcinB, Magainin II, LL-37, P18
Apoptosis Induction	Buforin IIb, LfcinB, (KLAKLAK)2, LL-37, Melittin, Dolastatin 10, Temporin-1 CEa
Angiogenesis inhibition	Melittin, MP06
Differentiation Induction	Tachyplesin I
Immunomodulation	Alloferon, MENK, Melittin
Other Applications	BR2,

Table 4
Summary of the synthesis methods.

Process of Synthesis	Method	References
Chemosynthesis	- Solution-Phase Peptide Synthesis (SuPPS) - Solid-Phase Peptide Synthesis (SPPS)	(Chinnadurai et al., 2023; Ghaly et al., 2023; Inoue et al., 2002)
Biosynthesis	- Enzymatic hydrolysis - Recombinant DNA technology	Chinnadurai et al. (2023)

Table 3 summarizes the ACPs listed in this paper based on their mechanisms. The mechanism that ACPs use is dependent on their initial primary sequence and their amphipathic, hydrophobic, cationic secondary structure (Kordi et al., 2023). Hydrophobicity plays a critical role in how ACPs interact with the cancer cell cytoplasmic membrane (Huang et al., 2011). ACPs with higher hydrophobicity will penetrate deeper into the hydrophobic core, causing stronger activity in forming pores or channels in the cancer membrane (Huang et al., 2011). Higher penetration because of an increased hydrophobicity results in higher toxicity (Hadianamrei et al., 2022).

4.1. *Membrane interaction*

Membrane interaction and disruption mechanisms (Ghaly et al., 2023) are caused by ACPs resulting in membrane lysis and cytoplasmic leakage (Chiangjong et al., 2020; Xie et al., 2020). This is a result of the change in internal osmotic pressure (Alamdari-palangi V et al., 2023; Marunganathan et al., 2024). Lfcin B is an ACP that causes cancer cell lysis through the direct disruption of the cell membrane (Eliassen et al., 2003). There are a few different models in which the peptides form pores in the membrane; the most common models are the Barrel Stave model, Carpet model, and Toroidal pore model (Tripathi and Vishwanatha, 2022).

The Barrel Stave model is when the ACPs reach the cancer cell membrane and accumulate on the surface as monomers (Tripathi and Vishwanatha, 2022). They then form oligomeric aggregations along the membrane (Ehrenstein and Lecar, 1977), forming pores and ring-like patterns along the membrane exterior (Tripathi and Vishwanatha,

2022). Resulting in them aligning perpendicular to the membrane and inserting themselves into the lipid core of the membrane (Tripathi and Vishwanatha, 2022). This forms pores in the membrane that look like hollow barrels (Ehrenstein and Lecar, 1977), shown in Fig. 2 part a. Gaegurins form this model of pore to disrupt the integrity of the membrane and allow for entrance into the cell cytoplasmic compartments (Ghaly et al., 2023).

The Carpet model is when the ACPs aggregate in a parallel manner to the cancer cell surface (Ghaly et al., 2023; Tripathi and Vishwanatha, 2022). After reaching a certain concentration, the ACPs then cover the membrane in clusters (Zhang et al., 2021), leading them to rotate on themselves, causing the redirection of the membrane phospholipids (Ghaly et al., 2023). This is similar to a detergent-like manner and causes the membrane to form micelles and destroy (Ghaly et al., 2023; Zhang et al., 2021), demonstrated in Fig. 2 part b. This differs from the other methods in that there is no actual pore forming stage as the peptides never insert themselves into the membrane (Tripathi and Vishwanatha, 2022; Zhang et al., 2021). LL-37 is an ACP that uses the carpet model to cause lysis of the cancer cell membrane (Kordi et al., 2023).

The Toroidal pore model is when the ACPs bind with the cancer cell membrane, causing a positive curvature of the polar heads into the two phospholipid layers perpendicular to the membrane plate (Kordi et al., 2023). Resulting in the lipid heads being exposed to the membrane pore lumen (Kordi et al., 2023). This forms toroidal pores within the membrane, these pores have lipids interlaced with peptides in the transmembrane channel (Tripathi and Vishwanatha, 2022), Fig. 2 part c demonstrates this. Magainin II and LL-37 are ACPs that work through this model (Henzler Wildman et al., 2003; Kordi et al., 2023).

4.2. Apoptosis

Other mechanisms of action for ACPs are non-membranous interactions (Ghaly et al., 2023), these include but are not limited to apoptosis induction, angiogenesis inhibition, immune modulation (Xie et al., 2020), and induction of differentiation (Chinnadurai et al., 2023), shown in Fig. 2. Inhibition of protein-protein interactions is another mechanism of action of ACPs (Alhammadi et al., 2024). Many cellular processes involved in cancer progression, such as proliferation, angiogenesis, apoptosis evasion, and metastasis, are regulated by protein-protein interactions (Alhammadi et al., 2024). ACPs can exert therapeutic effects affecting these interactions (Fosgerau and Hoffmann, 2015; Alhammadi et al., 2024). ACPs can cause apoptosis induction through mitochondrial-mediated pathways or by modulating regulatory proteins. ACPs can induce apoptosis through the mitochondrial membrane breakdown, which releases Cytochrome C (Xie et al., 2020). Lfcin B is a peptide that works through this mechanism. This peptide induces apoptosis by penetrating the cancer cell membrane and permeabilizing the negatively charged mitochondrial membrane, which triggers the mitochondrial pathway of apoptosis (Mader et al., 2005). Melittin induces calcium to accumulate in the mitochondria, which leads to mitochondrial dysfunction, causing the induction of apoptosis (Ceremuga et al., 2020). Buforin IIb transverses the cell membrane without causing any damage and accumulates primarily on the nuclei, leading to mitochondrial-dependent apoptosis (Lee et al., 2008).

Another method of inducing apoptosis is modulating regulatory proteins like Bax or Bcl-2 expression (Marunganathan et al., 2024). Dolastatin 10, works through inducing apoptosis in this manner. This peptide does this through upregulating Bax, a pro-apoptotic protein, and downregulating Bcl-2, an anti-apoptotic protein (Xie et al., 2020). LL-37

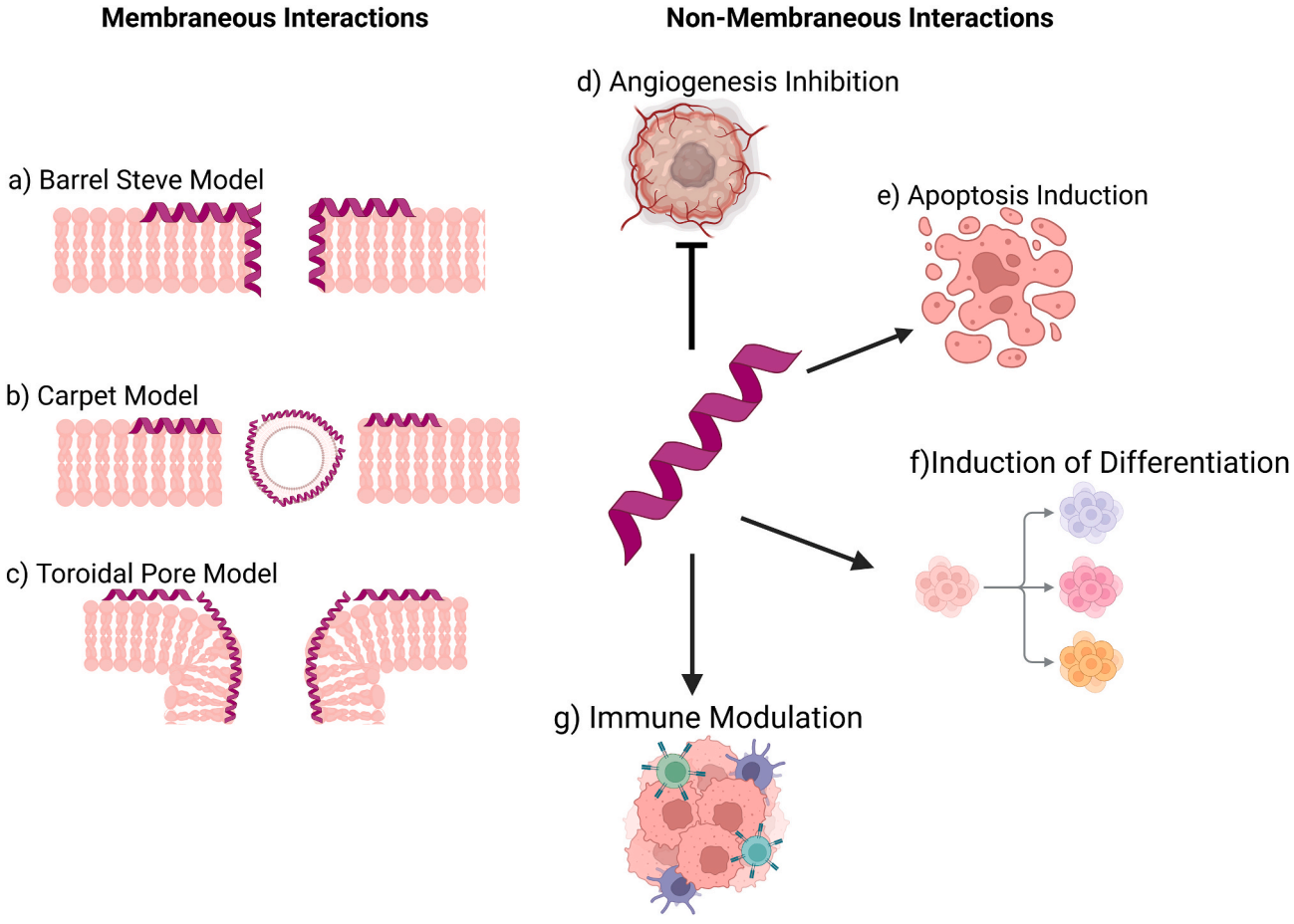

Fig. 2. Mechanisms of action for ACPs.

activates a P53-mediated apoptotic cascade that suppresses cancer (Ren et al., 2012). P53-mediated apoptotic pathway works through the upregulation of Bax and Bak and the downregulation of Bcl-2 (Ren et al., 2012). The mechanism of inducing the apoptotic process has been recognized as an important and effective mechanism, as it is a controlled method that causes minimal inflammation and damage (Nhàn et al., 2023) to surrounding tissue.

4.3. Angiogenesis inhibition

Angiogenesis is important for cancer cells as, without the growth of new blood vessels, they are unable to expand beyond normal size, invade, or metastasize (Inoue et al., 2002). Angiogenesis occurs as a result of an imbalance between pro- and anti-angiogenic factors (Inoue et al., 2002; Kim et al., 2024). Excessive angiogenesis contributes to cancer progression as it allows for the supply of nutrients and oxygen, which supports growth and metastasis (Kim et al., 2024). Inhibition occurs through the targeting and the inhibition of these specific signalling pathways involved (Nhàn et al., 2023), these include Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), Platelet-Derived Growth Factor (PDGF) (Alamdari-palangi V et al., 2023), Epidermal Growth Factor (EGF) and Tumor Necrosis Factor-alpha (TNFα) (Marunganathan et al., 2024). CXC chemokine-mediated angiogenesis has been shown to play a critical role in malignancies (Keeley et al., 2010). CXCR2 is considered a major angiogenic receptor in humans (Keeley et al., 2010), while CXCL1 promotes angiogenesis and secretes pro-angiogenic factors like VEGF (Yung-Taek et al., 2019). Melittin has an antiangiogenic effect, as this peptide downregulates the expression of VEGF (Pandey et al., 2023). MP06 also decreases the expression of VEGF, therefore resulting in an inhibition of angiogenesis (Kim et al., 2024). This method doesn't directly kill cancer cells but inhibits neovascularization, which reduces blood flow to cancer and impedes progression (Xie et al., 2020).

4.4. Immune modulation

Immune modulation occurs as the immune response against cancer can be modulated through a multitude of ways, ranging from cytokine production, dendritic cell maturation induction, upregulating $CD8^+$ T cells, to downregulating the regulatory T cells (Alamdari-palangi V et al., 2023). ACPs stimulate the activation and proliferation of immune cells, especially T cells, leading to enhanced recognition and elimination of cancer cells (Nhàn et al., 2023). LfcinB can enhance the immune system against the tumor by inducing the production of cytokines (Xie et al., 2020). MENK can regulate immune function and inhibit tumor growth through various mechanisms (Zhao et al., 2016). These include upregulating $CD8^+$ T cell activity, inducing dendritic cell maturation, increasing $CD4^+$ T cell functions (Xie et al., 2020), and inhibiting T_{reg} activity (Li et al., 2015). T_{regs} accumulate in tumor tissues and hinder the induction of effective anti-tumor immunity, thus, MENK directly inhibits or downregulates $T_{regs,}$ allowing for tumor development to reduce (Li et al., 2015). Alloferin can increase the killing activity of Natural Killer (NK) cells against cancer cells via the upregulation of the expression of NK activating receptors (2B4), thus causing an increase in the production of interferon gamma (IFN-γ), TNF-α, and granule exocytosis from NK cells (Bae et al., 2013).

4.5. Induction of differentiation

By inducing the differentiation of cancer cells, ACPs can reduce the proliferation and migratory abilities of the cells (Chinnadurai et al., 2023). This results in differentiated cancer cells that are less aggressive and less resistant (Chinnadurai et al., 2023) and reverses the malignant phenotype of cancers (Ghaly et al., 2023). Tachyplesin I induces cancer cell differentiation by decreasing the expression of tumor-associated antigens, modulating the expression of differentiation-associated enzymes, decreasing the expression of the c-myc oncogene, and increasing the expression of tumor suppression gene p21WAF1 (Ghaly et al., 2023).

5. Modifications

Peptides have the advantage of being able to be modified to help reduce the side effects while retaining the advantages (Xie et al., 2020) or to increase their therapeutic potential (Hamdi et al., 2025). Modifications of ACPs can be applied during the SPSS process (Ghaly et al., 2023), giving the benefit of having one reaction to synthesize and modify. Modifications can be divided into two categories, main chain or side chain modifications (Xie et al., 2020), as shown in Table 5.

5.1. Main chain modifications

5.1.1. Natural amino acid replacement

Main chain modifications are either natural amino acid replacement or non-natural amino acid replacement (Xie et al., 2020). Natural amino acid replacement is the most used and effective way to modify ACPs (Xie et al., 2020). Replacing natural amino acids with other amino acids causes the peptide to have changes in net charge, hydrophobicity, and helicity (Xie et al., 2020). This improves selectivity, potency as well as metabolic stability of ACPs (Hicks and Russell, 2011). Increasing an ACP's hydrophobicity enhances their biological activity, which increases their membrane interactions, stronger cytotoxicity, and greater selectivity (Hamdi et al., 2025). Non-natural amino acids contain unique physicochemical properties (Tripathi and Vishwanatha, 2022), allowing for the development of peptides with special properties (Xie et al., 2020). This approach uses D-amino acids to replace L-amino acids (Alamdari-palangi V et al., 2023). Substituting one or more L-amino acids with D-amino acids allows for ACPs to be resistant to proteolytic degradation while retaining their biological activities (Hilchie et al., 2015). These ACPs are less immunogenic as they can not be processed by Antigen Presenting Cells (Hilchie et al., 2015). This modification also allows for metabolic stability and greater control of overall conformation flexibility (Russell et al., 2011).

5.1.2. Chemical modifications

Chemical modification is another method of main chain modification. These modifications can facilitate entry, lower the concentration needed for activity (Tripathi and Vishwanatha, 2022), increase resistance to degradation, as well as increase the ACPs' half-life (Sri et al., 2023). By fusing a Fragment crystallizable region of an antibody with an ACP, the half-life of that ACP is increased (Sri et al., 2023). To increase the resistance to degradation, the modifications that can be applied to the ACP are N-term acetylation or C-term amidation (Sri et al., 2023). D-form amino acid modifications allow for ACPs with an enhanced average activity (Chen et al., 2005). The types of cyclization that can be applied are head-to-tail, head-to-side chain, side chain-to-side chain,

Table 5
Summary of possible Modifications.

Category of Modification	Modifications	References
Main chain	- Natural amino acid replacement - Chemical modifications - Cyclization	(Alamdari-palangi V et al., 2023; Chen et al., 2005; Gaspar et al., 2013; Hamdi et al., 2025; Hicks and Russell, 2011; Hilchie et al., 2015; Russell et al., 2011; Tørfoss et al., 2012; Tripathi and Vishwanatha, 2022; Sri et al., 2023; Xie et al., 2020)
Side chain	- Cholesterol modifications, - Phosphorylation - Polyethylene glycol - glycosylation	(Alamdari-palangi V et al., 2023; Bednarska et al., 2017; Ghaly et al., 2023; Han et al., 2013; Milla et al., 2012; Xie et al., 2020)

and tail-to-side chain (Alamdari-palangi V et al., 2023). Cyclization has the advantage of increasing the rigidity and amphipathicity of ACPs (Tørfoss et al., 2012), which causes stabilization of the secondary structures and increases proteolytic stability (Gaspar et al., 2013). This modification also increases cell permeability (Gaspar et al., 2013) which allows ACPs to penetrate the cell membrane deeper (Tørfoss et al., 2012).

5.2. Side chain modifications

5.2.1. Cholesterol modifications

The other category of modification is side chain modifications, which include but are not limited to cholesterol modifications, phosphorylation, Polyethylene glycol, and glycosylation (Xie et al., 2020). Cholesterol modification is the process of incorporating cholesterol into the side chains, which drives self-assembly, which facilitates penetration into cancer cells (Ghaly et al., 2023; Xie et al., 2020). Phosphorylation modification can occur at several different amino acid sites (Xie et al., 2020). This modification is not as good at enhancing anticancer effects, but significantly reduces the toxicity and side effects (Xie et al., 2020).

5.2.2. Polymer conjugation

Polymer conjugation is another side-chain modification, the most common of which is Polyethylene glycol (PEG) (Alamdari-palangi V et al., 2023; Xie et al., 2020). This is the coupling of PEG groups with free-side chain groups (Xie et al., 2020). PEG is a macromolecule that is hydrophobic, non-antigenic, non-immunogenic, highly soluble in water, low toxic, and a linear polyether of ethylene glycol (Alamdari-palangi V et al., 2023). The molecular weight, shape, reactivity, specificity, and type of bond of PEG are crucial in determining the effect on ACPs (Milla et al., 2012). Coupling a PEG molecule onto an ACP increases the size and weight of the peptide, which results in increased water solubility, protection from enzymatic degradation, reduction in renal clearance, and limitation of immunogenic reactions (Milla et al., 2012). PEGylated ACPs have an increased half-life and a decreased plasma clearance (Milla et al., 2012). The higher stability and lower immunogenicity as a result of PEG coupling allow for a sustained clinical response with minimal dosage required (Milla et al., 2012).

5.2.3. Glycosylation modifications

Glycosylation is the process that links sugars to specific amino acids, causing glycosidic bonds to form (Xie et al., 2020). This is one of the most frequently occurring co- or post-translational modifications (Han et al., 2013). There are four types of glycosylation, N-, O-, C-, and S-linked (Bednarska et al., 2017). N-linked glycosylation is when the glycan covalently attaches via a nitrogen atom, while O-linked glycosylation is the covalent attachment of the glycan through an oxygen atom (Bednarska et al., 2017). C-linked is a type of glycosylation that is characterized by a carbohydrate being linked to a protein via a carbon atom (Bednarska et al., 2017). S-linked is the type of glycosylation when a hexose residue is linked to the thiol group of the amino acid cysteine (Bednarska et al., 2017). Glycosylation is very dependent on the peptide as to the effectiveness, sometimes with the smaller peptides it can result in loss of function or activity (Xie et al., 2020). It can increase the rigidity of peptides, which protects them from rapid renal clearance and N-linked glycosylation has been shown to increase the peptides' serum half-life.

6. Other applications of ACP in cancer management

ACPs, whilst having the ability to directly treat cancer, can also have indirect applications that help manage and treat cancer. Other indirect applications include, but are not limited to, guided/target delivery, diagnostic tools, and cancer vaccines. ACPs can be used as delivery carriers to carry poorly stable, non-soluble drugs to the sites of cancer while also controlling drug release at these sites (Chiangjong et al., 2020). They can enhance drug delivery efficiency and target specific cells and tissues (Cho et al., 2025). ACPs that have this ability are classified as cell-penetrating peptides, tumor-homing peptides, or Peptide Proteolysis Targeting Chimera (PROTACs) (Chinnadurai et al., 2023). Guiding and targeted delivery ACPs require specificity, affinity, and dose effectiveness (Chiangjong et al., 2020). These peptides can retain drug concentrations during transport and include the release of drugs at target areas (Chiangjong et al., 2020). Cell-penetrating peptides (CPP) act as secondary agents and can guide molecules through the lipophilic barrier of the cell membrane (Chinnadurai et al., 2023). CPPs are used to deliver proteins, DNA, nanoparticles, and drugs (Chinnadurai et al., 2023), they can transport these various cargoes while maintaining functional integrity (Nhàn et al., 2023). CPPs are amphipathic, helical, and highly basic in their nature, and this gives them the ability to easily translocate into the nucleus or cytoplasm of the cancer cell (Chinnadurai et al., 2023). They are considered important delivery agents as they have excellent tissue penetration and are easily synthesized (Shadidi and Sioud, 2002). Peptide PROTACs are that are designed by coupling ACPS that target proteins of interest with E3 ligase inhibitors (Chinnadurai et al., 2023). These peptides have the advantage of simple design and synthesis, targeting undruggable proteins with high specificity, resistance to mutation/drug resistance, and low toxicity (Chinnadurai et al., 2023).

Tumor-homing peptides (THP) specifically target tumor-related receptors (Chinnadurai et al., 2023). Most THPs are amphiphilic, cationic lipopeptides that can overcome non-specific distribution and inadequate accumulation of chemo drugs at the site of interest (Chinnadurai et al., 2023). They are designed to be tumor-specific to enhance the internalization of small molecule drugs or chemo agents (Nhàn et al., 2023). THPs can be used in conjunction with nanoparticles, exosomes, radionuclides, or as peptide drug conjugates (Sri et al., 2023). Nanoparticles can be modified to have THPs attached which are used to guide the nanoparticle to cancer cells (Sri et al., 2023). THPs are specific to tumor cells and can enhance the internalization of the nanoparticles, so chemo agents can be delivered into the cancer cells (Nhàn et al., 2023; Sri et al., 2023). Conjugating THPs with nanoparticles also protects the peptide from protease degradation (Sri et al., 2023). THPs can label exosomes that are loaded with therapeutic agents and deliver them to the cancer cell (Sri et al., 2023). This can reduce major adverse side effects as the agents are contained within the exosome until reaching the intended target (Sri et al., 2023). THPs can be used in radionuclide therapy (Nhàn et al., 2023) by combining THPs with a radionuclide or radioactive isotope (Sri et al., 2023). Lastly, THPs can be used in peptide drug conjugates (PDCs). The components of PDCs are a THP, a linker, and a cytotoxic agent (Sri et al., 2023). PDCs reduce the cytotoxic effects on normal tissues while increasing therapeutic efficacy (Sri et al., 2023). PDCs have the advantage of exhibiting better tumor penetration, lower systemic exposure, low risk of immunogenicity and liver damage, and easier and cheaper production methods and lower molecular weights (Han et al., 2024; Sri et al., 2023).

ACPs can be used as diagnostic tools as well as treatment or delivery agents. ACPs can be radiolabelled and used for detecting specific cancer markers (Ghaly et al., 2023) such as somatostain receptors and prostate-specific membrane antigen (Nhàn et al., 2023). These radiolabelled ACPs lead to stronger binding affinity and are selectively compared to current diagnostic radiolabelled agents (Nhàn et al., 2023). Octreoscan is an ACP currently available that is used for this purpose (Pan et al., 2020). The advantages of using radiolabelled ACPs are rapid uptake, good sensitivity, low bone marrow uptake, rapid plasma renal clearance, and require a relatively low pharmacological dose (Ghaly et al., 2023).

Another anticancer application of ACPs is their use in cancer vaccines. Cancer vaccines are based on anticancer peptides that are 20–30 amino acids that contain specific epitopes for antigens known to be highly immunogenic to elicit the desired immune response (Abd-Aziz and Poh, 2022). They can either be ACPs alone or combined with

adjuvants or drugs (Hamdi et al., 2025). To be the most effective, ideally, these peptides must have $CD8^+$ T cell epitopes as well as $CD4^+$ T cell epitopes (Abd-Aziz and Poh, 2022). This allows for the peptide to activate cytotoxic T cells' anti-tumor immunity via the antigen cross presentation pathway as well as activate helper T cells to sustain the CTL effector functions (Abd-Aziz and Poh, 2022), resulting in an enhanced immune system's capability to recognize and effectively target cancer cells (Nhàn et al., 2023). Therefore, it is of the utmost importance that the right tumor antigen is selected (Abd-Aziz and Poh, 2022). Tumor-associated antigens (TAA) are self-antigens that are exclusively expressed in tumor cells but have low expression in normal cells (Abd-Aziz and Poh, 2022). When choosing the right TAA, there are three factors to consider. Firstly, the tumor-specific expression pattern; the expression must be specifically and exclusively in tumor tissue (Hirayama and Nishimura, 2016), secondly, the immunogenic characteristic of the TAA; capacity to be recognized as foregin antigen to elicit a T cell mediated response (Hirayama and Nishimura, 2016), and thirdly, the oncogenic characteristics of TAAs; as these are rarely lost in the process of tumor progression (Hirayama and Nishimura, 2016). TAAs do have the disadvantage that there is a risk of inducing autoimmunity, as these antigens can be expressed in normal tissue as well (Abd-Aziz and Poh, 2022). Another type of tumor antigen used in cancer vaccines is specific antigens (TSA) or neoantigens (Abd-Aziz and Poh, 2022). These antigens are highly immunogenic as they harbor genetic mutations that can escape immune tolerance and are recognized as non-self by the immune system (Abd-Aziz and Poh, 2022).

New types of cancer vaccine, which are still in development, are the personal neoantigen vaccine and Multiple Antigenic peptides (Abd-Aziz and Poh, 2022). Personal neoantigen vaccines use the personal neoantigens from the tumor itself and therefore has been shown to be safe and efficacious (Abd-Aziz and Poh, 2022). Multiple Antigenic peptides are a type of branched peptide with excellent stability and boosted immunogenicity (Abd-Aziz and Poh, 2022). These peptides are made of four or eight copies of an ACP attached to a core lysine residue (Abd-Aziz and Poh, 2022). The advantages of ACPs in the use of cancer vaccines are better tolerance, safety (Liu et al., 2021), and minimal side effects caused, compared to other treatment methods, which include the lack of significant toxicity that is often associated with chemotherapy (Abd-Aziz and Poh, 2022). The current disadvantages of ACPs in cancer vaccines are the immunoevasion of tumor cells, the loss of tumor antigens (Liu et al., 2021), quick degradation at the injection site, lack of costimulatory ability, and the absence of signals required for Antigen Presenting Cell activation (Abd-Aziz and Poh, 2022). To overcome these disadvantages, research is currently developing cancer vaccines that have ACPs conjugated to a carrier protein, this allows for them to be able to activate Antigen Presenting Cells as well as protect the peptide from degradation (Abd-Aziz and Poh, 2022).

7. Artificial intelligence modelling

Currently, the development and identification of ACPs have been performed using in vitro assays, computational-aided designs, and Mass Spectroscopy identification (Hwang et al., 2022). This method of identification is expensive and often time consuming, therefore, developing efficient computational methods is essential to identifying potential candidates before in vitro experimentation (Manavalan et al., 2017). This remains challenging due to the vastness of the chemical space and complexity of their interaction with biological targets (Huang et al., 2025). Artificial intelligence (AI) is growing and can be used to identify new potential ACPs (Hwang et al., 2022). The advantage of AI is that it is cheaper, more effective, and quicker than the traditional methods of identification (Hwang et al., 2022). AI allows for rapid prediction and enables large amounts of data to be processed quickly and easily (Hwang et al., 2022). AI makes the process faster and more targeted as it occurs before starting in vitro evaluations, which saves time, minimizes cost, and maximizes outputs (Ghaly et al., 2023). The predicted ACPs still go through complex biological evaluation processes, including biological functional validation, optimization, preclinical studies, and clinical trials (Hwang et al., 2022). Currently, AI is being used to predict peptide sequences with high anticancer activities (Ghaly et al., 2023) and to determine potential interactions with different proteins (Hwang et al., 2022). This modelling relies on using amino acid sequences and selecting proper features to capture the ACP sequences, which remains difficult for standard machine learning methods (Ghaly et al., 2023). The accuracy of the model relies on the specific input of features and depends on the algorithm chosen (Chen et al., 2024). Table 6 lists some of the current ACP AI models that are available on the market, including information about the algorithms they use and their predicted accuracy. There are three learning models that AI can use, which are deep learning, machine learning, or hybrid learning (Hwang et al., 2022), and each of these has specific algorithms (Chen et al., 2024).

Machine learning (ML) is a model of AI that has the following steps: feature extraction, classification, prediction, and lastly validation (Hwang et al., 2022). The advantage of ML is the capacity to consider multiple features simultaneously, which allows for hidden relationships to be captured (Manavalan et al., 2017). Feature extraction in this model is completed by a researcher (Hwang et al., 2022). Feature extraction is performed by extracting relevant features, measuring the important values of those features, and reducing the dimensions (Hwang et al.,

Table 6
Current AI models used for ACP identification, their algorithms, and predicted accuracy.

Model	Algorithm	Predicted	Reference
AntiCP	SVM	72.81 %	(Hwang et al., 2022; Kordi et al., 2023)
AntiCP2.0	SVM, KNN, RF, Etree	83 %	(Abbas et al., 2025; ? Agrawal et al., 2020)
ACPP	SVM	96 %	(Charoenkwan et al., 2021; Hwang et al., 2022)
iACP	RF, KNN, SVM, Probabilistic neural network	92.67 %	(Hwang et al., 2022; Kordi et al., 2023)
MLACP	SVM, RF	88.72 %	(Hwang et al., 2022; Kordi et al., 2023)
MLACP2.0	CNN	91.5 %	(Le Thi et al., 2022; Yue et al., 2024)
ACPred	SVM	92.87 %	(Charoenkwan et al., 2021; Hwang et al., 2022; Kordi et al., 2023)
ACPred-FL	SVM	90.4 %	(Abbas et al., 2025; Wei et al., 2018)
ACPred-Fuse	RF	88.7 %	(Abbas et al., 2025; Rao et al., 2019)
PEPred-Suite	RF	95.0 %	(Abbas et al., 2025; Wei et al., 2019)
ACP-DL	LSTM	90.6 %	(Abbas et al., 2025; Yi et al., 2019)
CNBT-ACPred	CNN, Bi-LSTM	96.8 %	Yue et al. (2024)
ACPred-BMF	Bi-LSTM	96.5 %	(Han et al., 2022; Yue et al., 2024)
xDEEP-AcPEP	Hybrid Learning model	84.9 %	(Ghaly et al., 2023; Kordi et al., 2023)
ACP-DA	Hybrid Learning Model	82.03 %	Hwang et al. (2022)
pACP-HybDeep	CNN + RNN hybrid	95.33 %	(Abbas et al., 2025; Shahid et al., 2025a)
pACPs-DNN	sADNN (self-attention Deep Neural network)	96.91 %	(Shahid et al., 2025b))
ACP-CLB	CNN, Bi-LSTM	94.74 %	Geng et al. (2025)
DeepACP	RNN + amino acid embedding	89.5 %	Yu et al. (2020)
iACP-SEI	ESM2, LR, SVM, LGBM	93 %	Zheng et al. (2025)
GCNCPR-ACPs	Graph Convolution Network	90 %	Wu et al. (2022)
MA-PEP	Multimodal fusion	94 %	Liang et al. (2024)

2022). This stage improves the prediction accuracy by removing unnecessary and irrelevant features (Hwang et al., 2022). To train the algorithm for this model, the data consists of amino acid sequences that are experimentally proven to be ACPs and non-ACPs (Ghaly et al., 2023). The validation step identifies the accuracy, sensitivity, specificity, and correlation coefficient of every studied case with a final suggested most accurate prediction model (Ghaly et al., 2023). There is a multitude of algorithms that can be used by ML these include Support Vector Machine (SVM), Random Forest (RF), K-Nearest Neighbor (KNN), Extreme Gradient Enhancement (XGBoost), Gradient Boosted tree (GBM), Discriminant analysis (DA), Plain Bayes (PB) and Hidden Markov Model (HMM) (Paul et al., 2020). KNN is one of the simplest ML algorithms, and its predictive performance and low computational cost make it one of the most used algorithms (Paul et al., 2020). However, because of its simplicity, sometimes the algorithm cannot achieve an appropriate classification in complex data cases (Manavalan et al., 2017). The application of ML algorithms in ACP research and development greatly speeds up the process (Zhao et al., 2021), allowing for rapid identification of potential candidates before experimental validation (Hwang et al., 2022). It reduces the time needed for the selection of optimal sequences from previously analyzed peptides and can provide rapid prediction of how the ACPs affect target cells or diseases without physical and biological analysis (Hwang et al., 2022).

Deep learning (DL) models are similar to ML however, the AI carries out the feature extraction stage instead of a researcher (Hwang et al., 2022). In DL models, the data is split and embedded (Hwang et al., 2022). Embedding quantizes peptide data into a matrix, which is then used to perform feature extraction (Hwang et al., 2022). After feature extraction, classification is performed through dense and sigmoid layers (Hwang et al., 2022). This model of AI is utilized to further increase the prediction accuracy and robustness (Hwang et al., 2022). Current DL algorithms include Convolutional Neural Networks (CNN), Recurrent Neural Networks (RNN), Long- and Short-Term Memory Recurrent Neural Networks (LSTM), Bidirectional Long and Short-Term Memory Recurrent Neural Networks (BiLSTM), Generating Adversarial Networks (GAN), and Variable Self Encoder (VAE) (Chen et al., 2024). RNN is bearing a lot of promise as a solid de novo design tool, as it has been developed for processing sequential data (Grisoni et al., 2018). The AI model DeepACP uses an RNN model combined with amino acid character embedding to predict ACPs (Yu et al., 2020). DL has gained popularity in ACP prediction (Huang et al., 2025), due to the efficiency with which these models handle large datasets and the autonomous representation of features (Shahid et al., 2025a). These models pose a significant challenge in their demand for substantial computational resources (Huang et al., 2025). DL models are better at processing longer sequences and therefore sometimes have difficulty with ACP sequences as they are shorter (Yu et al., 2020).

The hybrid learning model combines both deep learning and machine learning models (Hwang et al., 2022). In some hybrid models, the data split, embedding, and feature extraction are done by DL methods, and classification is performed by ML methods (Hwang et al., 2022). Another hybrid model has the data split and feature extraction completed by ML methods and classification completed by DL methods (Hwang et al., 2022). The AI model, iACP-SEI, uses multiple algorithms, including Evolutionary Scale Modelling 2 (ESM2), Logistic Regression (LR), SVM and LGBM (Zheng et al., 2025). This model characterises the peptide sequence using ESM2, optimises the feature vectors with LGBM and has a stacked ensemble learning model with SVM and LGBM (Zheng et al., 2025). The use of ensemble learning effectively captures diverse data features and patterns (Zheng et al., 2025). However, this model may struggle to predict some ACPs with cyclic structures or unconventional amino acid compositions as they may not align with the main patterns the model has learned (Zheng et al., 2025).

ACPs predicted by AI models are subjected to a complex evaluation process including biological functional validation, optimization, preclinical studies and clinical trials before they can be on the market and given to patients (Hwang et al., 2022). So, even though AI models can reduce the time and cost of wet lab experimentation, there is still a component of testing that is required in the wet lab to ensure the safety and validity of these peptides. Currently, most models are entirely based on peptide sequence information (Zhao et al., 2021), as sequence composition currently provides the best performance across most classifiers (Abbas et al., 2025). This causes some limitations as there is an inability to discriminate peptides having a similar composition but different bioactivity (?Agrawal et al., 2020). The AI model, MA-PEP is trying to overcome this by using a multi-head self-attention mechanism to combine learned sequence embedding and chemical representation to get a comprehensive representation of the peptide (Liang et al., 2024). The 3D structure of an ACP plays a critical role in inhibiting tumor cell proliferation (Zhao et al., 2021) and, therefore, should be taken into consideration when creating an AI model (Zhao et al., 2021). A major limitation of AI models is the selection of the dataset (?Agrawal et al., 2020). Both the quality and quantity of the dataset should be considered when developing a model (?Agrawal et al., 2020). Unfortunately, because of the limited data available, a lot of the AI models available are all using similar datasets (Zhao et al., 2021). Existing models still have the disadvantage of high computational costs (Shahid et al., 2025a), so even with lower wet lab costs, this is still a costly procedure. Another limitation of AI models is the 'black box' problem. This problem arises as a result of lack of an explanation in the decision making process (Hassija et al., 2023). This problem is specifically in DL models, as the internal works are undisclosed only input and output are known (Xu and Michael, 2023). This is an issue in transparency, as an explicit and interpretable explanation for the decision is missing (Hassija et al., 2023). AI models used to predict ACPs still need further development to be able to overcome the challenges of differentiating bioactivity of peptides, lack of datasets, 'black box' problems, and substantial computational costs. Currently, there is an increasing number of AI prediction models available, however, there isn't a corresponding increase in the ACPS available on the market (Yue et al., 2024). They should be constantly updated and developed to reflect the new data that is being discovered to ensure that the predictions are as accurate as they can be.

8. Conclusion

Cancer is a leading cause of death worldwide, and even with numerous treatment options, millions are still dying because of it. Chemotherapy, surgery, radiotherapy, and immunotherapy are the treatment options currently available, and while these treatments are working, they have serious disadvantages. Mostly, they have deleterious side effects and are causing an increase in drug-resistance. A new therapeutic option to overcome this is anticancer peptides.

ACPs are small bioactive peptides of 5–50 amino acids. They have the advantage of low molecular mass, simple structures, fewer adverse reactions, easy absorption, rapid synthesis, and a very low risk of multidrug resistance. They do, however, have the limitation of a shorter half-life, susceptibility to protease destruction, low oral bioavailability as well as undesired haemolytic activity. There are multiple mechanisms in which ACPs can work.

They can target the cell membrane and cause lysis or pores to form, induce apoptosis, regulate the immune system, inhibit angiogenesis, and induce differentiation. ACPs are not only used to directly treat cancer, they can be used in assisting other methods of cancer treatment, such as guided/targeted drug delivery, diagnostic tools, and cancer vaccines. Through the synthesis of these peptides, modifications can be applied to enhance their advantages and reduce the limitations. These modifications include replacing natural amino acids with non-natural substitutes, chemical modifications, cyclization, glycosylation, phosphorylation, and PEG coupling.

AI modelling is being used in many aspects of drug discovery, including the identification of potential ACPs. This streamlines the

identification process, reducing costs, time, and is more effective. Three different model types can be used: machine learning, deep learning, or a hybrid. Each of these model types have multiple algorithms they use to predict potential ACPs. These models are mainly developed on datasets composed of peptide sequence information and most models available are using similar or the same datasets.

Even with a streamlined prediction process, AI models still require an extensive wet lab evaluation. AI has reduced the identification stage, but the rest of the development is still a costly and time-consuming process. The limitations of AI models are the lack of datasets, the struggle to differentiate bioactivity, 'black box' problems, and the substantial computational costs. This requires the need to continuously update and develop the models to ensure accurate predictions.

CRediT authorship contribution statement

Alexandra R. Collins: Writing – review & editing, Writing – original draft. **Vasilis Paspaliaris:** Writing – review & editing. **Varun Pandey:** Writing – review & editing. **Muhammad Ikhtear Uddin:** Writing – review & editing. **Michail Spathakis:** Writing – review & editing. **George Kolios:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

Alexandra R Collins and Vasilis Paspaliaris are employed by Paspa Pharmaceuticals Pty Ltd and Black Arrow Biotech Inc. Varun Pandey and Muhammad Ikhtear Uddin are employees of Paspa Pharmaceuticals Pty Ltd. George Kolios is Emeritus Professor of Pharmacology in the Department of Medicine, Democritus University of Greece.

Data availability

No data was used for the research described in the article.

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