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Almeida, J. R. ORCID: https://orcid.org/0000-0002-4637-4468, Pinos-Tamayo, E. A., Mendes, B., Robles-Loaiza, A. A., Syahputra, R. A., Oliveira, A. G. S. and Ribeiro, R. I. M. d. A. (2025) Snake venom-derived peptides as anticancer candidates: pioneering next-generation therapies. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 1880 (6). 189479. ISSN 1879-2561 doi: 10.1016/j.bbcan.2025.189479 Available at https://centaur.reading.ac.uk/125298/

BBA - Reviews on Cancer 1880 (2025) 189479

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review Article

Snake venom-derived peptides as anticancer candidates: Pioneering next-generation therapies

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ARTICLE INFO

Keywords:
Anticancer therapy
Computational intelligence
Natural product drug discovery
Synthetic peptides

ABSTRACT

Cancer treatment has come a long way, but not all cancers can be completely cured. The current therapeutic landscape has significantly reduced mortality rates; however, it remains associated with side effects, limited accessibility, financial burden, drug shortages, and emotional as well as mental health consequences for patients. Hence, despite significant advances, the development of novel therapies remains a focal point of research. In this review, we explore the current state of snake venom-inspired peptides as templates for the design of much-needed innovative anticancer agents. Initially, we examine conventional cancer treatments, their main challenges, and the niche filled by newly approved peptide-based therapies. Then, we present a high-level overview of the potential of snake venoms as broad-spectrum libraries of bioactive components and discuss a roadmap for mining these rich and complex mixtures to pioneer the next generation of cancer drugs, leading to the emergence of "oncovenomics". Harnessing the potential of modern *in silico* approaches, we delve into the structure, biochemical parameters, and bioactivity of venom-inspired peptides. Our research identified more than 30 snake venom-derived peptides with micromolar lytic action against different cancer cells, including solid and liquid tumours. Transitioning from *in vitro* monolayer analyses to clinical settings remains an unfulfilled goal, with the majority of studies failing to progress to more advanced stages, including the preclinical phase involving *in vivo* experiments. Here, we also describe how artificial intelligence, and the integration of other cutting-edge technologies can provide an expandable framework for translating the high *in vitro* potential of venom-derived peptides into clinically useful therapies. Lastly, we examined the translational challenges and the strategies proposed to overcome them. In summary, snake venom-derived peptides are attractive scaffolds for drug discovery programs, demonstrating historical benefits. However, overcoming the existing barriers in their development requires further multidisciplinary efforts. On the horizon, advances in high-throughput research tools and peptide engineering strategies offer opportunities for introducing next-generation venom peptide-based therapeutics to address cancer in clinical practice.

1. Introduction

Cancer is one of the greatest global health challenges that humanity has faced in the 21st century [1]. This term refers to a heterogeneous and highly complex group of diseases where cell proliferation and growth cannot be efficiently controlled [2]. Its serious effects extend beyond affected individuals, influencing their families, public health systems, and the economy [3,4]. The global impact of this life-threatening issue is evident in estimates indicating that cancer accounts for 1 in 6 total deaths and 1 in 4 deaths from noncommunicable diseases worldwide [5]. Cancer is a major factor in reduced life expectancy, leading to more deaths than the well-documented burden of cardiovascular disease in

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https://doi.org/10.1016/j.bbcan.2025.189479
Received 2 August 2025; Received in revised form 11 October 2025; Accepted 14 October 2025
Available online 17 October 2025

certain countries [6,7]. To illustrate this point, cancer ranks among the top three causes of death in individuals aged 30 to 69, according to data from the International Agency for Research on Cancer, accounting for 30% of deaths [5].

From a global perspective, population-based cancer registries have clearly highlighted an alarming trend [8,9]. The latest snapshot of the global cancer burden in 2022 revealed 20 million new cases and approximately 10 million cancer-related deaths [5]. To emphasise the scale, this equates to approximately 55,000 new cancer diagnoses and 27,500 cancer-related deaths occurring each day. Over the long term, this upward trajectory is expected to persist, with demographic-based projections estimating more than 135 million new cancer cases, a 77% increase compared to 2022. Cancer epidemiology varies across global regions, with notable differences in cancer types and prevalence [10]. In 2022, Asia accounted for approximately half of all cancer cases and recorded the highest number of cancer-related deaths worldwide [5]. This represents a complex challenge that demands a multifaceted approach, including significant investment in the research and development of innovative control and prevention mechanisms. Additionally, there is a pressing need to rethink therapeutic strategies, as current oncology approaches have not comprehensively addressed this issue [11,12].

For many decades, conventional cancer therapy has rested on three main pillars: chemotherapy, surgery and radiotherapy, which apply to a wide range of tumours [13–15]. However, successful clinical trials have broadened these therapeutic pillars, introducing alternative pathways for tackling cancer [16,17]. Fundamentally, the field of oncology has been transformed with modern and molecular options, including immunotherapy, hormone therapy, stem cell transplant and targeted therapy [18,19]. Although the range of cancer treatments has expanded, many patients require combinatorial approaches, as some strategies alone do not suffice as standalone therapies, nor do they consistently lead to a cure or favourable outcomes [20,21]. In clinical settings, treatment regimens are guided by multiple factors, including the type and stage of cancer, the patient's overall health, condition history, lifestyle, molecular profiling, healthcare infrastructure, and personal preferences [22,23]. Currently, there is no universal solution for cancer, and its management is complex and challenging [24]. Despite advancements in broad-spectrum therapeutic strategies, the inherent complexity and variability of this diverse collection of over 200 distinct tumour types create additional barriers to effective cancer treatment [25,26]. In this scenario, cancer cells' resistance to conventional drugs further exacerbates the complexities of cancer management [27]. Cells have evolved multiple strategies to evade and minimise the killing action of drugs [28]. These include altering the tumour microenvironment, enhancing efflux systems, reprogramming DNA repair, suppressing apoptosis, modulating drug targets, and modifying metabolic, genetic, and epigenetic events [29,30]. As a result, the number of available treatments decreases, further complicating therapeutic options and leading to poor survival in cancer patients [27,30].

Fig. 1 illustrates both conventional and modern FDA-approved cancer therapies that are currently used in the ongoing fight against cancer. Some of the challenges and limitations associated with cancer treatment modalities are also outlined and further examined in the discussion below. The pillars of treatment form an intricate network that is extensively explored in various combinatorial therapeutic approaches.

The primary oncological treatment typically involves traditional modalities, either individually or in combination, to strategically maximise their potential benefits [31]. Surgery is a well-established procedure for the physical removal of solid tumours, providing

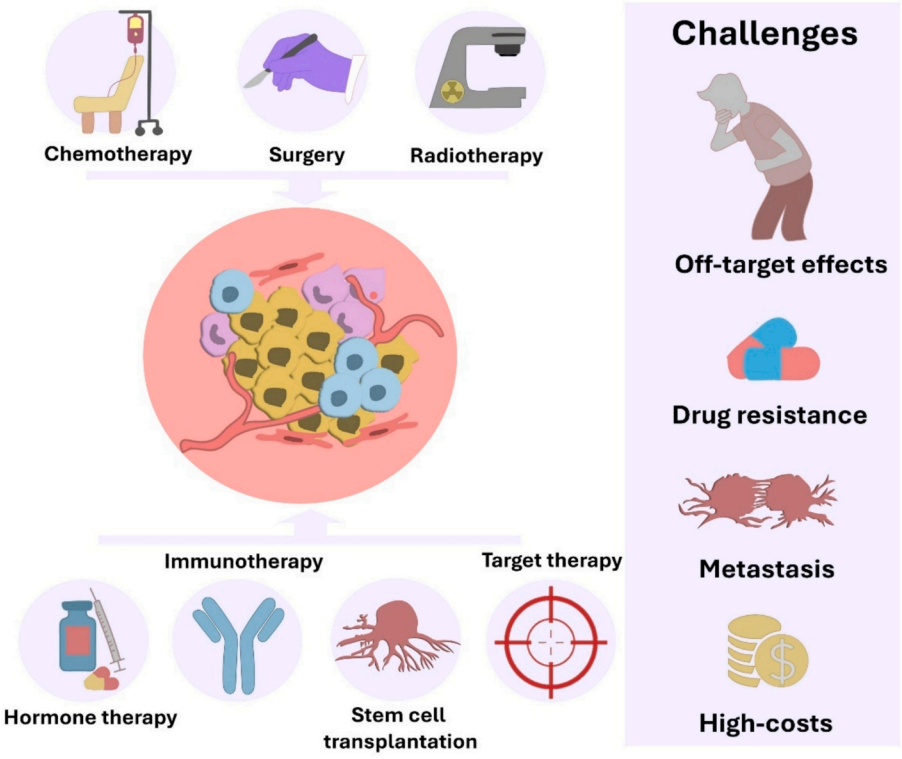

Fig. 1. The pillars of the oncology armamentarium and their challenges. The current landscape of licensed therapeutic options for cancer consists of a set of traditional and modern pillars. Historically, chemotherapy, surgery, and radiation therapy have constituted the traditional core of cancer care (indicated at the uppermost part of the figure). Novel pillars have been added to this arsenal, expanding the clinically useful strategies available to oncologists (highlighted at the bottom of the figure). Nowadays, immunotherapy, hormone therapy, stem cell transplantation, and targeted therapy are reshaping cancer treatment. Despite advances and expansion, cancer therapy is far from ideal, and many challenges remain, such as high costs, therapeutic index limitations, and off-target effects (marked on the right side of the figure). Combinatory approaches explore the possibility of harnessing the unique actions of each treatment type for enhanced therapeutic efficacy. The combination of therapies forms a promising network to combat cancer.

localised action. The direct removal can offer a cure and immediate results; however, remaining tissues with high proliferative rates can lead to recurrence [32]. Its effectiveness is limited, as it is ineffective for blood cancers and is associated with long recovery times and surgery-related risks, such as infection, bleeding, and damage to healthy tissues [33]. Radiation therapy, which utilises the properties of high-energy waves, represents a non-invasive option for localised cancers [34]. However, its application requires multiple sessions and has limited effectiveness in managing metastatic cancer. Several side effects, including skin irritation, long-term tissue damage, and fatigue, have also been reported [35,36]. On the other hand, chemotherapy relies on the ability of chemical compounds to kill or interact with fast-growing cells [37]. It is usually the first-line regimen for systemic cancers. However, due to its non-specific mechanisms, chemotherapy does not distinguish between healthy and cancerous cells, leading to toxicity and severe side effects [38]. Additionally, the regimen is characterised by a long duration, with many cases of cancer cells developing resistance leading to therapeutic failures [39].

A range of advanced treatment modalities is redefining the conventional cancer drug market, facilitating a more specialised and adaptable approach. The current therapeutic catalogue includes immunotherapy, hormone therapy, targeted therapy and stem cell transplant [40]. Immunotherapy is based on strengthening the patient's immune system through various pathways, including the activation of T cells, NK cells, and immunological memory [41]. It also involves the use of laboratory-engineered therapeutic antibodies and the engineering of innate immune cells [41]. Despite its beneficial effects, immunotherapy is associated with high costs, limited response rates, and immune-related side effects [42]. Hormone-based therapies work by employing blockers or modulators to disrupt the growth of tumour cells that rely on specific biological signals for proliferation. Fundamentally, this approach focuses on inhibiting hormone production, targeting hormone receptors, or eliminating the source of secretion [43]. It has become very common for the treatment of cancers using hormone signalling pathways to grow and/or survive, such as prostate and breast cancer. However, its use would be limited to these specific hormone-sensitive tumours [44]. The primary concerns relate to hormonal imbalances and the potential development of resistance [45]. On the other hand, targeted therapies, as their name suggests, employ selective compounds designed to interact with molecular targets that play vital roles in the key biological processes driving tumour proliferation and progression. However, similar to other drugs, their effectiveness can be greatly compromised due to mutations and acquired resistance, which in turn is a product of genomic plasticity and heterogeneity of different types of cancer [46]. Lastly, stem cell-based therapies have emerged following FDA approval in 2023 for patients with blood cancer [47]. In broad terms, the principle relies on introducing healthy stem cells into the patient's body to restore the production and functionality of blood cells. Positive outcomes have been observed; however, both short- and long-term health complications remain a concern. Intensive recovery requirements and the risk of rejection present significant challenges in clinical practice [48].

Given the challenges associated with cancer therapies and the complexity of this multifaceted disease, it is evident that we are still far from effectively treating all cancer types. Many patients continue to await life-saving therapeutic options [49]. Encouragingly, peptide-based strategies have matured into safe and useful therapeutic agents, ushering in an era of clinically viable cancer modalities [50].

2. Anticancer peptides are part of the list of clinically available oncology therapies

The global peptide therapeutic industry has experienced remarkable growth and sustained expansion in the last years [51]. The inclusion of peptides in the clinical treatment catalogue for various diseases, including cancer, along with numerous ongoing clinical trials in multiple therapeutic areas, is creating a promising outlook [52]. A market analysis report assessing the 2024 estimated valuation exceeding 100 billion. Strong projections and significant commercial success are also anticipated in the coming years [53]. Technological advancements in peptide synthesis and computer science are fostering a robust ecosystem that continues to drive this growth [54,55].

Peptides are small and versatile chemical molecules with simple and customizable structures [56]. Built from an amino acid alphabet, they are well-known for their high specificity, target engagement, safety profile, good tissue penetration properties, fast clearance and easy chemical obtention [57]. Their flexible biochemical nature and inherent ability to selectively interact with molecular and cellular targets make them unique templates for developing different useful drugs [58]. Cancer represents a specialised pharmaceutical niche for short synthetic peptides, which employs a range of efficient direct and indirect mechanisms to regulate the survival of cancer cells [59].

Peptides have a rich history in cancer research and development, contributing at every stage, from discovery and screening to preclinical and clinical trials [60]. Anticancer peptides have been discovered in a wide range of natural sources and designed through both human-driven and computer-assisted rational strategies [61]. These peptides or their analogues can be reproduced in laboratory settings via chemical synthesis or recombinant technologies [56]. Large-scale production of therapeutic peptides has been successfully implemented to meet high demand and is continually optimised to enhance yield and reduce costs [62]. Several factors, including oral bioavailability, protease-mediated degradation, scalability, and toxicity, have hindered the development and hampered the translation of some peptide-based candidates [63]. However, innovative approaches have driven significant progress in drug delivery, peptide engineering, selectivity, and emergent manufacturing technologies, paving the way for a promising translational process [64].

Anticancer peptides integrate the list of FDA-approved therapeutic modalities for combating cancer [59]. Some of the licensed peptide-inspired anticancer drugs are Tebentafusp (uveal melanoma, FDA), Buserelin (breast cancer, EU), Plitidepsin (multiple myeloma, EU), Triptorelin (prostate cancer, FDA), Bortezomib and Carfilzomib (multiple myeloma and mantle cell lymphoma, FDA), Lanreotide (neuroendocrine tumours, FDA), Degarelix (prostate cancer, FDA), Lutathera (gastroenteropancreatic neuroendocrine tumours, FDA), Octreotide (neuroendocrine tumours, FDA), Leuprolide (prostate cancer, FDA) and Abarelix (prostate cancer, FDA). Interestingly, a significant portion of peptide-based drugs target prostate cancer and neuroendocrine tumours. Table 1 provides a snapshot of anticancer peptide-based drugs and clearly evidences the pivotal role of peptide engineering in successful cases. A high number of peptide-based drugs are chemically modified. Cyclisation, conjugation, and peptidomimetics are important chemical tools for addressing challenges associated with the amino acid nature of peptides, such as protease-induced degradation, toxicity and stability [65].

Considering both the mechanistic perspective and practical applications, peptide-based anticancer drugs are described as multifunctional players [88]. In the first dimension, they work on specific targets associated with key biological processes, such as inflammatory response, programmed cell death, cell cycle regulation and hormonal balance. Typically, at a mechanistic level, anticancer peptides exert inhibitory effects, modulate protein-protein and ligand-receptor interactions, or damage membrane components [89]. From a functional and applied standpoint, they exhibit diverse actions, including immunomodulatory properties, antibacterial effects, and roles as drugs, vaccines, delivery of carriers, or cargoes [90]. The multifunctionality and multimodal mechanisms of anticancer peptides make them compelling candidates for therapeutic development and further commercialisation.

Building on the success of anticancer peptide-based drugs in the pharmaceutical industry, discovering novel lead sequences remains a promising initiative. The chemical space for peptide discovery is vast, and complex biological secretions have been an important drug

Table 1
Repertoire of FDA-approved anticancer peptide-based agents. Since 1985, anticancer peptides have been introduced in clinical settings, mainly for hormone-related cancers. By interacting with specific proteins or receptors, they regulate cellular processes and can induce cell death.

Peptide-based drug	Cancer type	Molecular target	Mechanistic view	Year of approval	Reference
Buserelin	Prostate and breast	Gonadotropin-releasing hormone (GnRH) receptor	Alter the hormonal axis and the growth of hormone-dependent tumours	1985	[66]
Leuprolide (Leuprorelin)	Prostate	GnRH receptor	Regulates sex hormones	1985	[67]
Goserelin (Zoladex)	Prostate and breast	GnRH receptor	Regulates sex hormones	1997	[68]
Octreotide	Neuroendocrine tumours	Somatostatin receptors (SSTR2, SSTR5)	Inhibition of hormone secretion	1998	[69]
Depreotide (Neotect)	Lung	Somatostatin receptors	Labeled with the radioisotope technetium-99m (Tc-99m), which allows tumours to be visualized by scintigraphy or SPECT	1999	[70]
Triptorelin (Decapeptyl)	Prostate and breast	GnRH receptor	Regulates sex hormones	2000	[71]
Bortezomib	Multiple myeloma	Proteasome 26S	Accumulation of misfolded proteins and induction of apoptosis	2003	[72]
Abarelix	Prostate	GnRH receptor	Suppress the production of sex hormones	2003	[73]
Degarelix	Prostate	GnRH receptor	Inhibition of the production of sex hormones	2008	[74]
Carfilzomib	Multiple myeloma	Proteasome 20S	Accumulation of misfolded proteins and induction of apoptosis	2012	[75]
Lanreotide	Metastatic enteropancreatic neuroendocrine tumours	Somatostatin receptors (SSTR2, SSTR5)	Inhibition of hormone secretion	2014	[76]
Netspot, ^{68}Ga DOTATATE	Neuroendocrine tumours	Somatostatin receptors	Diagnostics of neuroendocrine tumour by positron emission tomography (PET)	2016	[77]
Lutathera, 177Lu-DOTATATE	Gastroenteropancreatic neuroendocrine tumours	Somatostatin receptors (SSTR2)	Peptide conjugated with DOTA (chelator for the radioisotope lutetium-177), which emits beta radiation, destroying tumour cells (peptide receptor radionuclide therapy (PRRT))	2018	[78]
Edotreotide gallium, ^{68}Ga-DOTATOC	Neuroendocrine tumours	Somatostatin receptors	Diagnostics of neuroendocrine tumour by PET	2019	[79]
Detectnet, ^{64}Cu-DOTATATE	Neuroendocrine tumours	Somatostatin receptors	Diagnostics of neuroendocrine tumour by PET	2020	[80]
Gallium gozetotide, ^{68}Ga-PSMA-11	Prostate	Prostate-specific membrane antigen (PSMA)	Diagnostics of recurrent prostate cancer by PET	2020	[81]
Piflufolastat F 18 (Pylarify)	Prostate	PSMA	Detection of PSMA-positive lesions by PET	2021	[82]
Pluvicto, ^{177}Lu-PSMA-617	Prostate	PSMA	PRRT for metastatic castration-resistant prostate cancer	2022	[83]
Tebentafusp	Uveal and malignant melanoma	T cell receptor (TCR) CD3	Activation of polyclonal T cells, to release inflammatory cytokines and cytolytic proteins, resulting in the direct lysis of tumour cells	2022	[84]
Flotufolastat F 18 (Posluma)	Prostate	PSMA	Detection of PSMA-positive lesions by PET	2023	[85]
Motixafortide (APHEXDA^{TM})	Multiple myeloma and pancreatic	CXCR4 receptor	Inhibition of mobilisation and migration of tumour cells	2023	[86]
Pegulicianine (Lumisight^{TM})	Breast	Cancerous tissue	Cleaved by enzymes abundant around tumours, resulting in the generation of fluorescence for detection	2024	[87]

screening platform for identifying novel anticancer scaffolds [91]. For instance, snake venoms are dynamic chemical libraries of tissue-targeting and membrane-active peptides and proteins with inherent cytotoxicity and high therapeutic potential [92,93]. With this in mind, after reviewing the current use of peptides in cancer therapies, we explore snake venom as a screening system for identifying peptide candidates. We begin with a compositional perspective, outlining strategies to gain insights into their biochemical composition, followed by a detailed analysis of snake venom-derived peptides. Finally, we examine emerging frontiers in peptide discovery, applying insights from existing peptide-based drugs to illuminate novel avenues for developing next-generation anticancer therapeutics inspired by venom molecules.

3. Snake venoms: a biochemical puzzle of bioactive toxins and peptides

Snake venoms are chemically and functionally diverse biological matrices [94]. By combining short peptides, non-enzymatic toxins, and enzymes, these potent toxic cocktails disrupt molecular events and cellular processes [95]. The fast localised action and systemic effects induced by venom components serve as strategic mechanisms for snakes to defend, immobilise, kill and digest prey [96]. Ranging from low molecular weight peptides to large proteases, venom toxins interact with cells, proteins, and receptors, leading to tissue alterations [97]. Due to the snake-human conflicts and their associated health and social implications, venom research has largely focused on venom composition characterisation, venom-induced toxicity and the development of anti-venom strategies [97,98]. However, leveraging the effects of venom molecules on cellular targets is an established approach for discovering therapeutic agents [99,100]. The multicomponent nature confirms its status as an underexplored source.

Snake venoms are not static samples with a standard compositional profile [101]. Rich and diverse biochemical patterns have been discovered, constituting a puzzle of different toxin families and isoforms [102]. Interspecific and intraspecific variability are common phenomena [103,104]. The structural and functional richness of snake venoms is intriguing, as they express multiple isoforms of the same toxin family, each with varying abilities to recognise natural and synthetic substrates or induce biological effects [105]. For example, *Agkistrodon piscivorus leucostoma* venom is rich in phospholipid-disrupting enzymes and contains a diverse range of isoforms [106]. Researchers have explored this source and isolated both basic and acidic isoforms, which exhibit

differences in catalytic and functional properties [107,108].

Viper and elapid venoms are the most studied due to their medical relevance; however, a significant portion of snake venom samples remain uncharacterized [98]. Generally, elapid venoms are simpler than viper venoms, with a predominance of low molecular weight toxins, mainly phospholipase A_2 and three-finger toxins, alongside other less abundant proteins [109]. A representative proteome of this group is found in coral snake venoms, which primarily consist of these two protein families, typically comprising more than 80% of the proteome [110]. Similarly, cobra venoms are also dominated by these two toxin classes. In contrast, viper venoms lack three-finger toxins but contain high concentrations of proteases, phospholipases, and other biomolecules [111]. This differential toxin expression drives variations in the clinical profile signatures of viper and elapid envenomation [101]. Consequently, the large-scale identification of venom constituents has been an active research area. For more details on venom compositional trends, we refer readers to reviews on snake venom proteomes [110–113].

Snake venoms represent a rich source of scaffolds for onco-peptide development due to their evolutionary refinement as biochemical libraries that target physiological systems and molecular processes [114]. Over millions of years, snake venom molecules have evolved to modulate biological events such as angiogenesis, apoptosis, migration, and cell adhesion, processes that are also critical for cancer cell survival and progression [91]. Hence, snake venom components are capable of targeting mechanisms underlying the hallmarks of tumour development. The peptides and proteins within snake venoms exhibit high potency, and structural diversity, making them attractive candidates for the development of next-generation anticancer drugs [115]. Their inherent ability to interact with receptors and influence biochemical signalling pathways further supports their potential in designing therapeutics that can target tumour growth and metastasis [116].

In addition to their functional specificity, venoms are complex cocktails of biomolecules with unique physicochemical properties [99]. Many exhibits stability (due, for example, to a high content of disulfide bridges) [117], high binding affinity for cellular targets (such as membrane bilayer [118], integrin receptors [119] and ECM-based substrates [120]), and membrane-active capabilities that enable the fast recognition and lysis of cancer cells [121]. The combination of these biochemical properties with advances in peptide engineering and synthetic modification facilitates the optimisation of venom-derived peptides for improved translational outcomes. Collectively, snake venoms constitute natural puzzles of molecular templates for the rational design of novel anticancer therapeutics.

3.1. *Traditional composition profiling and cytotoxic screening of snake venoms*

While the great complexity of snake venoms has allowed them to be classified as a fertile ground for bioprospecting, a valuable source of bioactive molecules, it has also made their study and in-depth analysis challenging [122]. Currently, analytical tools, bioinformatics, *in vitro* techniques, and omics approaches have led to the identification of the main venom components, their structures and biological functions. To date, more than 230 snake venoms have been biochemically catalogued, revealing the presence of over 60 distinct toxin families [111,123]. In this section, we briefly discussed the approaches commonly employed to enable the integrative capture of venom composition, as well as the *in vitro* systems to screen the cytotoxic potential of individual venom proteins/peptides.

Our understanding of snake venom complexity has undergone substantial evolution, with mass spectrometry-centred approaches refining key details [124]. In general, there are two strategic analytical routes in proteomics used to decipher the molecular phenotype of venom libraries: the top-down or bottom-up approaches [125]. These primary methods differ in their handling approaches, each with distinct advantages and disadvantages. In brief, top-down proteomics involves the analysis of intact venom proteins without proteolytic digestion or chemical treatment [126]. Proteoform-level identification, combined with high sequence coverage and reduced database dependency, makes it an attractive option [127]. However, its scalability is limited due to the low identification efficiency of large molecules commonly found in snake venoms, particularly in viper species [128]. In contrast, bottom-up analysis of snake venoms relies on the study of proteolytically digested toxin fragments, with tryptic digestion being the most common approach [129]. This method is recognised for its high-throughput nature and ability to detect even less abundant venom components. However, its main challenge lies in the low resolution of isoforms [130].

Although both strategies have significantly advanced our understanding of the nature of venoms, no single approach can capture the full inventory of venom toxins [96]. In summary, they can be applied to address different questions in toxinology, in addition to the assessment of global protein content. In practical terms, the most widely applied framework combines sequential analytical steps based on the bottom-up principle [131]. This robust experimental design for venom analysis, developed by the Calvete team, integrates biochemical separation and quantification via liquid chromatography and electrophoresis, along with mass spectrometric analysis of digested snake venom-derived peptides [131]. This combinatorial approach provides a bidimensional perspective, encompassing the identification of toxins present in snake venoms and their relative abundance [132]. Since venomics is not the primary focus of this review, readers requiring a more detailed exploration of venom profiling methodologies can consult several comprehensive reviews for valuable insights [96,129,130,133–135]. Fig. 2 illustrates the roadmap for deconstructing the molecular composition of snake venoms, highlighting the most successful workflow.

Interestingly, to gain deeper insights, proteomic-based strategies have been integrated with complementary techniques, broadening our understanding of venom toxicity and immune recognition. In fact, antivenomics and toxicovenomics emerged from the fusion of venomics with immunological approaches and toxicological assays, respectively [136,137]. Antivenomics is a crucial tool for the design, evaluation, and development of antivenom strategies aimed at counteracting venom toxins [138]. On the other hand, toxicovenomics remains in its infancy, requiring optimization and the refinement of ideal models since its establishment in 2015 [131]. This approach aims to elucidate the role and contribution of toxins to venom-induced toxicity and the clinical profile of envenoming, strengthening its connection to medical relevance [139]. With this in mind, integrating cell-based assays using both cancer and healthy cells can create new frontiers and enhance the dimensionality of snake venomics.

Traditionally, snake venoms are screened against healthy and cancer cells to assess their therapeutic potential [140]. Subsequently, they are fractionated, and individual fractions are tested. The most common strategy involves colourimetric absorbance-based assays, which detect mitochondrial activity or cell membrane integrity or microscopic views. However, this process is expensive and time-consuming, as multiple chromatographic separations and lyophilisation steps must be performed to obtain a detectable amount of all snake venom toxins, especially those present in low quantities. Potential bioactive candidates are then identified [141]. Typically, fraction collection and digestion for mass spectrometry analysis require manual handling, which presents challenges for scaling up the workflow. Commercially available established cancer cell lines, together with fibroblast and red blood cells, are the most common models employed to assess both cancer potential and toxicity of snake venom fractions. Future screening studies should incorporate primary cell cultures, as they provide more physiologically relevant models for drug testing. Overall, these cultures more accurately reflect the genetic and phenotypic traits, as well as the heterogeneity, of patient-derived tissues. However, most studies have tested only a limited number of cancer cell lines. Given tumour heterogeneity and the distinct characteristics of healthy cells, this approach does not offer a full view of

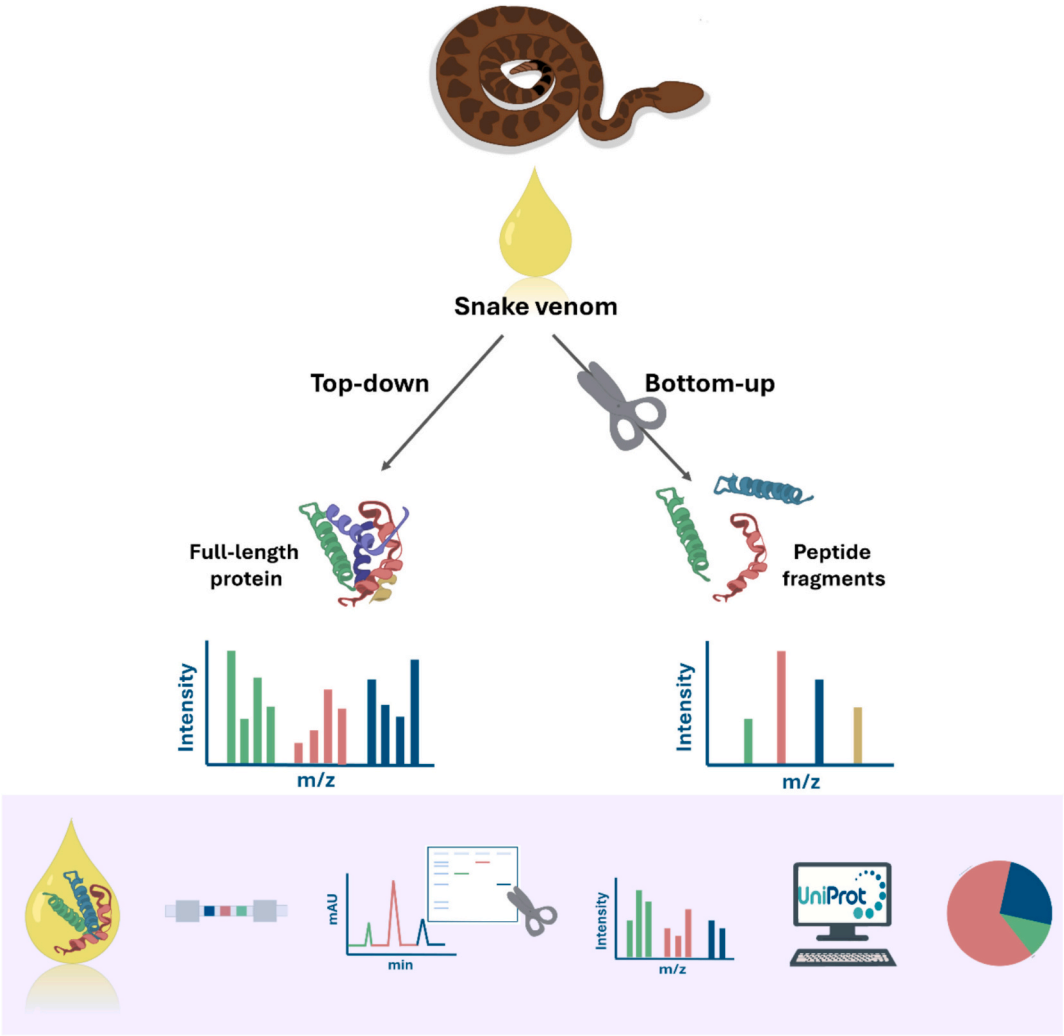

Fig. 2. Key analytical workflow tools for miniming snake venom composition. The heterogeneous combination of toxins in snake venoms can be studied using bottom-up and top-down proteomic strategies. Their differences extend beyond the use of intact venom proteins or digested fragments, with important implications for method selection based on the research question. However, both approaches have significantly broadened our understanding of these natural toxin libraries. The venomics workflow, developed by Calvete and collaborators, remains a cornerstone in venom proteome studies. The key steps are emphasised within the blue rectangle.

the selectivity of venom components.

A high-throughput screening approach that directly integrates venomics and cytotoxicity assessment or omics approaches could lay the foundation for a novel field known as "oncovenomics". This represents a potentially new branch of venomics. In this innovative analytical workflow, venom fractions can be collected in multiwell plates, enabling simultaneous analysis by mass spectrometry and cell-based assays. Some researchers have automated sample digestion to enhance the scalability of venom component sequence characterisation [142]. The adoption of this high-throughput technology is the core of oncovenomics. However, standardising scoring systems such as selectivity index or therapeutic score, which incorporate toxin abundance and cellular toxicity in both cancerous and healthy cells remains a task. This concept is empirical, grounded in the potential to integrate multidisciplinary approaches already employed in the field. From a methodological standpoint, a similar approach has been developed to identify key coagulopathic toxins in snake venoms. A high-throughput screening system integrating a miniaturised plasma coagulation assay, venom nanofractionation, and mass spectrometry successfully characterised pro- and anti-coagulant proteins across a wide range of snake venoms [143]. Along the same lines, a high-throughput screening approach integrating various cell-based assays with proteomics data was developed to investigate the *in vitro* cell-damaging properties of snake venom components [144]. However, this method utilised only a single immortalised epithelial cell line, aiming to establish a platform for future assessments of antivenom strategies. A similar approach, integrating traditional cytotoxicity assays using both cancer and healthy cell lines, could enhance our understanding of the value of venom-derived compounds in anticancer drug discovery. Another beneficial route could involve combining venomics with omics analyses of peptide-exposed cells or integrating these methods with pathway-centric high-throughput assays in microplates. Additionally, employing a diverse range of cell types or three-dimensional models could enhance the translational relevance of the findings. AI-based technologies can be employed to screen the venom proteome, significantly reducing the number of fractions requiring testing. Given its critical role in refining the screening process, the application of AI in snake venom peptide drug discovery will be explored in Section 5. The advancement and implementation of this workflow require further experimental optimisations and theoretical analysis to achieve resolutions and parameters compatible with available technologies while minimising experimental bias, particularly due to the differential abundance of venom toxins in the proteome. As diagrammed in Fig. 3 we can compare the traditional workflow with the future of anticancer drug discovery in the snake venom field.

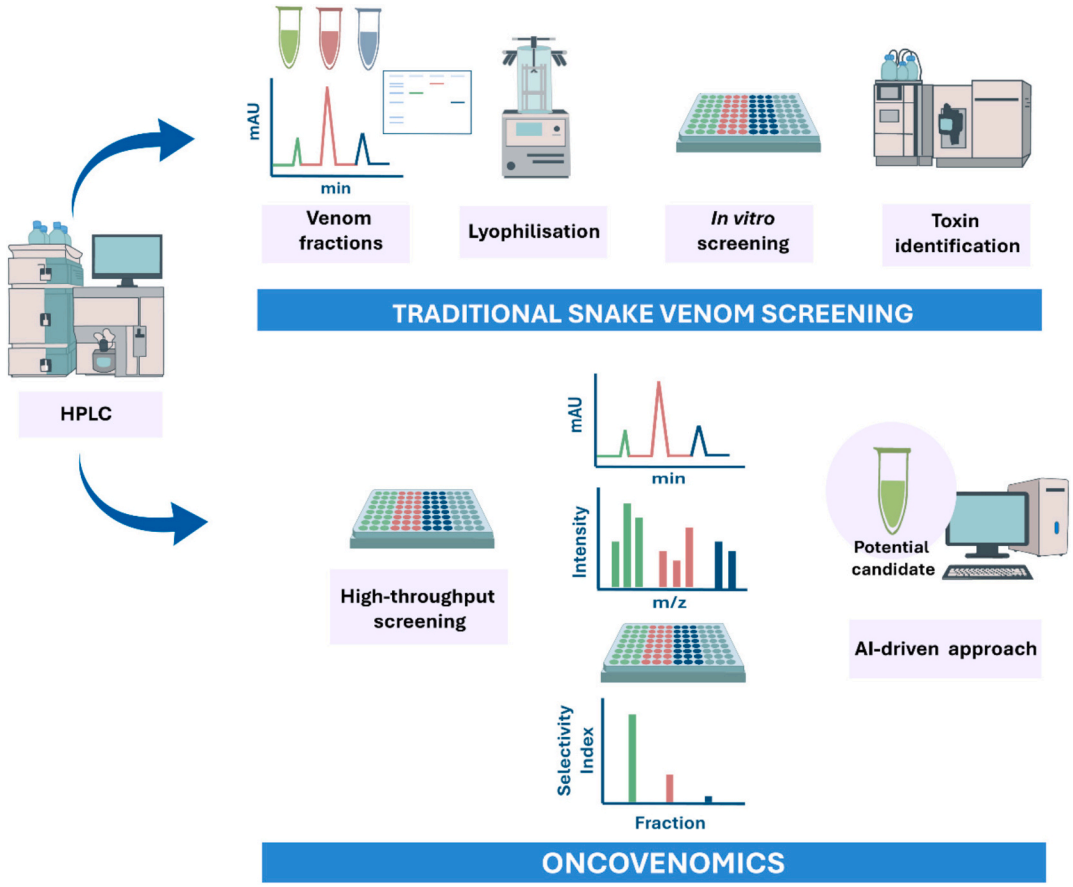

Fig. 3. Current approach in snake venom-based anticancer drug discovery and future large-scale experimental strategies. The early discovery of anticancer agents in venom has remained largely dependent on traditional biochemical and cell biology experiments, which have limited automation and scalability. Integrating recent high-throughput screening methods with venomics could give rise to 'oncovenomics', a specialised branch of venomics that expands the exploration of venom components across a broader cellular landscape and physiologically relevant models. While significant work remains, the foundational strategies are already in place and demonstrating potential in multiple areas of drug screening. Our proposal involves the simultaneous analysis of automatically collected and digested venom fractions using mass spectrometry, alongside the determination of safety profiles through toxicity assays in microplates. These assays incorporate assessments of cell health and cancer cell viability. Additionally, we consider the integration of AI, which will be discussed later, helping to reduce the number of potential candidates to be screened. Another option includes omics analyses of cells incubated with venom fractions to gain a comprehensive view of molecular regulatory mechanisms, potential targets and pathways.

Oncovenomics redefines the workflow by integrating simultaneous proteomic analysis and selectivity profiling. Rather than sequentially analysing individual toxins, it employs a comprehensive assessment approach. One key challenge is evaluating the toxicity of solvents used for toxin fractionation. Since gradient elution is commonly employed, its impact on both healthy and cancerous cells must be carefully considered. Pilot experiments and proof-of-concept studies are necessary to establish baseline parameters for its advancement.

3.2. *Snake venom proteins in the anticancer drug discovery agenda*

The shift in focus from toxicity to therapeutics in snake venom research has driven significant advancements in hypertension management [95,145]. Captopril is the first venom-derived peptide drug to enter the pharmaceutical market, demonstrating the therapeutic potential of these previously called toxic structures [146]. This was not an isolated case, as other snake venom toxin-inspired drugs, such as Eptifibatide and Tirofiban, have also successfully gained approval for clinical use [147]. This accumulated knowledge has broadened the understanding of the value of venom-derived components and is now being explored in the context of anticancer drug discovery agenda. The anticancer application of snake venoms dates back over 30 years, with Calmette pioneering investigations into the *in vivo* effects of cobra venom [148]. The anticancer activity of crude snake venom has been frequently reported in the literature [93]. For instance, *Vipera lebetina turanica* venom targets ovarian cancer cells under *in vitro* conditions. A closer analysis revealed inhibition of p65 and p50, as well as modulation of Bax and Caspase-3 gene expression [149]. Another study has reported the effects of *Ophiophagus hanna* snake venom on pancreatic cancer cells [150]. These findings further support the cytotoxic potential of venoms against cancer cells. However, direct application of snake venoms poses high risks, as it can trigger life-threatening manifestations similar to those observed in clinical signatures of snakebites. In this context, screening crude venoms in the early stages of drug discovery can help identify promising novel sources of anticancer compounds, though their translational potential remains limited. Another key limitation is the low abundance of certain components, which may be overlooked in such assessments. Hence, the analytical decomplexation of snake venoms represents an important step toward gaining deeper insight into the anticancer potential of their components.

The longstanding interest in the anticancer properties of venom components has led to the identification and characterization of several toxins [151]. Table 2 provides clear examples of the cytotoxic effects of specific snake venom-derived toxins. More specifically, proteins from snake venoms across different regions of the globe have been characterised, though their study is largely influenced by the medical relevance of the species. Interestingly, most research has focused on viper venoms rather than elapid venoms. At the genus level, *Agkistrodon*, *Bothrops*,

Table 2
Snake venom-derived toxins target cancer cells. Purified toxins from viper and elapid venoms compromise the viability of both liquid and solid cancer cell lines, exerting their effects within the μg/mL or μM range. Different toxin families and commercial cell lines have been used in small-scale screenings, with PLA_2s being the predominant evaluated group.

Identification	Toxin family	Species	Cancer cell line (Type)	Concentration or dose (Approach)	References
Nigexine	PLA_2	*N. nigricollis nigricollis*	C13-T (neuroblastoma) HL60 (Leukemia)	2.9 μM (In vitro) 3.1 μM (In vitro)	[152]
BthA-I	PLA_2	*B. jararacussu*	Jurkat (Leukemia) Erlich ascitic tumour (breast)	100 μg (In vitro; both cell lines)	[153]
Drs-PLA_2	PLA_2	*D. russelii siamensis*	SK-MEL-28 (melanoma) B16F10 (Melanoma)	25.6 nM (In vitro; SK-MEL-28)* 100 μg/kg (In vivo; B16F10)	[154]
BF-CT1	PLA_2	*B. fasciatus*	U937 (Lymphoma) Ehrlich ascites carcinoma (EAC) (Mammary adenocarcinoma) B16F10 (Melanoma)	610 μg/mL (In vitro; U937) 470 μg/kg (In vivo; EAC)	[155]
BPB-BthTX-I	PLA_2	*B. jararacussu*	SKBR3 (Breast) Jurkat (Leukemia) S180 (Sarcoma)	1 μg/mL (In vitro; all cell lines) 50 μg (In vivo; S180)	[156]
BthTX-II	PLA_2	*B. jararacussu*	MDA-MB-231 (Breast)	100 μg/mL (In vitro)	[157]
Ser49PLA_2s	PLA_2	*E. ocellatus, E. pyramidum leakeyi, E. carinatus sochureki* and *E. coloratus*	A549 (Lung)	2.9 – 8.5 μM (In vitro; range of concentrations of Ser49PLA_2s isolated from the different snake venoms)	[158]
MTX-I and MTX-II	PLA_2	*B. brazili*	Jurkat (Leukemia)	100 μg/mL (In vitro; both toxins)	[159]
BnSP-6	PLA_2	*B. pauloensis*	MDA-MB-231 (Breast)	52.24 μg/mL (In vitro)	[160]
CC-PLA_2-1 and CC-PLA_2–2	PLA_2	*C. cerastes*	HT1080 (Fibrosarcoma)	0.8 μM (In vitro; CC-PLA_2-1)* 0.7 μM (In vitro; CC-PLA_2-2)*	[161]
$BmPLA_2$	PLA_2	*B. moojeni*	Caco-2 (Colon)	0.6 μM (In vitro)	[141]
ACP-TX-I	PLA_2	*A. contortrix pictigaster*	A549 (Lung)	≥20 μg/mL (In vitro)	[162]
B-Bgt	PLA_2	*B. multicinctus*	SK-NSH (Neuroblastoma) HT1080 (Fibrosarcoma)	10 μM (In vitro)	[163]
MVL-PLA_2	PLA_2	*M. lebetina transmediterranea*	IGR39(Melanoma cell) HT29-D4 (Colon) HT29-D4/β3 (Colon) K562(Leukemia)	35 nM (In vitro; IGR39)* 10 nM (In vitro; HT1080)*	[164]
Mlx-9	PLA_2	*M. lemniscatus*	U138 (Glioblastoma) U251 (Glioblastoma)	0.2, 20 and 200 nM (In vitro; both cell lines)	[165]
NN-I2c, NN-I2d and NN-I2e	PLA_2	*N. naja naja*	EAC (Mammary adenocarcinoma)	10 μM (In vitro; all toxins)	[166]
Crotoxin	PLA_2	*C. durissus terrificus*	SCC-9 (Head and neck) SCC-4 (Head and neck) MCF-7 (Breast)	100 μg/mL (In vitro; SCC-9) 10 μg/kg (In vivo; SCC-9 and SCC-4) 100 μg/mL (In vitro; MCF-7)	[167,168]
PLA_2	PLA_2	*N. naja atra*	SK-N-SH (Neuroblastoma)	10 μM (In vitro)	[169]
BaMtx	PLA_2	*B. atrox*	MDA-MB-231 (Breast) MCF-7 (Breast)	20 μg/mL (In vitro, MCF-7) 20 and 40 μg/mL (In vitro, MDS-MB-231)*	[170]
BPII	PLA_2	*P. flavoviridis*	Jurkat (Leukemia)	200 μg/mL (In vitro; both cell lines)	[171]
$VBBPLA_2$	PLA_2	*V. berus berus*	K562(Leukemia)	7.23 μM (In vitro)	[172]
Rusvinoxidase	LAAO	*D. russelii*	MCF-7 (Breast) Colo-205 (Colon) C6 (Glioma)	55 μg/mL (In vitro; MCF-7) 9.8 μg/mL (In vitro, Colo-205) 1.9 μg/mL (In vitro; C6)	[173,174]
OHAP-1	LAAO	*T. flavoviridis*	RBR17T (Glioma) U251 (Glioma)	2.48 μg/mL (In vitro; RBR17T) 2.1 μg/mL (In vitro; U251)	[175]
ACTX-8	LAAO	*A. acutus*	HeLa (Cervical)	40 μg/mL (In vitro)	[176]
BjarLAAO-I	LAAO	*B. jararaca*	EAC (Mammary adenocarcinoma)	0.1 mg/kg (In vivo)	[177]
OH-LAAO	LAAO	*O. hannah*	MCF-7 (Breast) PC3 (Prostate) A549 (Lung)	0.04 μg/mL (In vitro; MCF-7) 0.05 μg/mL (In vitro; PC3 and A549) 1 μg/g (In vivo; PC3)	[178,179]
BM-Apotxin	LAAO	*B. multicintus*	MCF-7 (Breast) BT474 (Breast) MDA-MB-231 (Breast) MGC-803 (Gastric adenocarcinoma) SMMC-7721 (Liver) HepG2 (Liver) PC3 (Prostate) HL60 (Leukemia)	20 nM (In vitro; MCF-7) 5.8 nM (In vitro; BT474) 12 nM (In vitro; MDA-MB-231) 4.8 nM (In vitro; MGC-803) 60 nM (In vitro; SMMC-7721) 54 nM (In vitro; HepG2) 113.1 nM (In vitro; PC3)	[180]
Apoxin I	LAAO	*C. atrox*	A2780 (Ovary) KN-3 (Larynx)	10 μg/mL (In vitro; all cell lines)*	[181]
BjussuLAAO-II	LAAO	*B. jararacussu*	MCF-7 (Breast) HepG2 (Liver) HL60 (Leukemia)	1.80 μg/mL (In vitro) 0.25 – 5 μg/mL (In vitro)	[182,183]
BmooLAAO-I	LAAO	*B. moojeni*	HL60.Bcr-Abl (Leukemia) K562-R (Myelogenous leukemia) K562-S (Myelogenous leukemia)	0.038 μg/mL (In vitro; HL60) 0.192 μg/mL (In vitro; HL60.Bcr-Abl) 0.116 μg/mL (In vitro; K562-R) 0.148 μg/mL (In vitro; K562-S)	[184]

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Table 2 (*continued*)

Identification	Toxin family	Species	Cancer cell line (Type)	Concentration or dose (Approach)	References
Bl-LAAO	LAAO	*B. leucurus*	MKN-45 (Gastric adenocarcinoma) RKO (Colon)	0.41 μM (In vitro) 0.04 μM (In vitro)	[185]
CR-LAAO	LAAO	*C. rhodostoma*	HL60 (Leukemia) HepG2 (Liver)	1.7 μg/mL (In vitro) 10.78 μg/mL (In vitro)	[186]
BatroxLAAO	LAAO	*B. atrox*	HL60 (Leukemia) Jurkat (Leukemia) B16F10 (Melanoma) PC12 (Rat adrenal gland pheochromocytoma)	50 μg/mL (In vitro; HL60 and Jurkat) 25 μg/mL (In vitro; B16F10 and PC12)	[187]
Cv-LAAOI	LAAO	*C. vipera*	MCF-7 (Breast) HepG2 (Liver) A549 (Lung) HCT116 (Colon) PC-3 Prostat	2.75 μg/mL (In vitro) 23.11 μg/mL (In vitro; HepG2) 61 μg/mL (In vitro; A549) 39.11 μg/mL (In vitro; HCT116) 47.19 μg/mL (In vitro; PC-3)	[188]
Disintegrin	Disintegrin	*N. naja*	MCF-7 (Breast) A549 (Lung) HepG2 (Liver)	2.5 μg/mL (In vitro) 3.5 μg/mL (In vitro) 3 μg/mL (In vitro)	[189]
Leucurogin	Disintegrin	*B. leucurus*	Ehrlich tumour (Mammary adenocarcinoma)	10 μg/day (In vivo)	[190]
Contortrostatin	Disintegrin	*A. contortrix contortrix*	MDA-MB-435 (Breast)	10 and 30 μg/mouse/day (In vivo)	[191]
Jarastatin	Disintegrin	*B. jararaca*	B16F10 (Melanoma)	1 μM (In vivo)	[192]
Flavoridin	Disintegrin	*T. flavoviridis*	B16F10 (Melanoma)	1 μM (In vitro) 1 μM (In vivo)	[192]
Kistrin	Disintegrin	*C. rhodostoma*	B16F10 (Melanoma)	1 μM (In vivo)	[192]
Colombistatin	Disintegrin	*B. colombiensis*	T24 (Bladder) SK-MEL-28 (Melanoma)	4.4 μM (In vitro)* 33 nM (In vitro)*	[193]
Lebein	Disintegrin	*M. lebetina*	SK-MEL-28 (Melanoma) LU-1205 (Melanoma) HCT116 (Colon) LS174 (Colon) HT29 (Colon)	10 nM (In vitro; SK-MEL-28) 1 nM (In vitro; LU-1205) 0.2 μM (In vitro; HCT116, LS174 and HT29) 1.25 mg/kg (In vivo; LS174)	[194,195]
Triflavin	Disintegrin	*T. flavoviridis*	B16F10 (Melanoma) 1205Lu (Melanoma) WM164 (Melanoma)	1-30 μg/mouse (In vivo; B16F10)	[196]
Eristostatin	Disintegrin	*E. macmahoni*	SBcl2 (Melanoma) C8161 (Melanoma) MV3 (Melanoma) M24met (Melanoma)	3 μM (In vitro, all cell lines)* 20, 66 and 166 μg/mL (In vivo)	[197]
Acurhagin-C	Disintegrin	*A. acutus*	B16F10 (Melanoma)	0.8 μM (In vitro)	[198]
Leberagin-C	Disintegrin	*M. lebetina transmediterranea*	IGR39 (Melanoma)	5 and 25 μg/mL (In vitro)*	[199]
Obustatin	Disintegrin	*V. lebetina obtusa*	K562 (Leukemia) Lewis lung carcinoma cells	2 nM (In vitro; K562)* 5 mg/kg (In vivo; Lewis)	[200]
Viperistatin	Disintegrin	*V. palestinae*	B16F10 (Melanoma)	5 mg/kg (In vivo)	[201]
Alternagin-C	Disintegrin	*B. alternatus*	MDA-MB-231 (Breast)	1000 nM (In vitro)	[202]
r-rub	Disintegrin	*C. ruber ruber*	SK-MEL-28 (Melanoma)	2.5, 3 and 3.5 μM (In vitro)*	[203]
r-Mojastin1 and r-Mojastin-GST	Disintegrin	*C. scutulatus*	T24 (Bladder carcinoma) SK-MEL-28 (Melanoma) B16F10 (Melanoma)	5.3 μM (In vitro; T24 and SK-MEL-28; both r-Mojastins)* 1000 μg/kg (In vivo; B16F10; both r-Mojastins)	[204]
Salmosin	Disintegrin	*A. halys brevicaudus*	SK-MEL-2 (Skin melanoma)	267 nM (In vitro)	[205]
Vicrostatin	Disintegrin	*A. contortrix contortrix*	MDA-MB-435 (Breast)	100 μg (In vivo)	[206]
DisBa-01	Disintegrin	*B. alternatus*	MDA-MB-231 (Breast)	225, 100 and 1000 nM (In vitro)*	[207]
BJcuL	C-type lectin (Hemagglutinin)	*B. jararacussu*	MKN45 (Gastric adenocarcinoma) AGS (Gastric adenocarcinoma)	2.5 μg/mL (In vitro; both cell lines)*	[208]
Vixapatin	C-type lectin	*V. xantina palestinae*	K562 (Myelogenous leukemia) HT1080 (Fibrosarcoma) Rat C6 (Glioma) MDA-MB-231 (Breast)	3 nM (In vitro; K562)* 25 nM (In vitro; HT1080)* 50 nM (In vitro; Rat C6 and MDA-MB-231)*	[209]
Daboialectin	C-type lectin	*D. russelii*	A549 (Lung)	50 and 100 nM (In vitro)	[210]
Lebectin	C-type lectin	*M. lebetina*	IGR39 (Melanoma) HT1080 (Fibrosarcoma) HT29-D4 (Colon) K562 (Myelogenous leukemia)	25 μg/mL (In vitro; IGR39, HT1080 and HT29-D4)* 10 μg/mL (In vitro; IGR39, HT1080 and K562)	[211]
Macrovipectin	C-type lectin	*M. lebetina*	SK-MEL-28 (Melanoma)	0.1 μM (In vitro)*	[212]
Cytotoxin 1 (NKCT1)	S-type cytotoxin	*N. kaouthia*	K562 (Myelogenous leukemia) U937 (Lymphoma)	1.1 μg/mL (In vitro) 3.5 μg/mL (In vitro)	[213]
GNP-NKCT1	S-type cytotoxin	*N. kaouthia*	K562 (Myelogenous leukemia) U937 (Lymphoma)	0.75 μg/mL (In vitro) 1.2 μg/mL (In vitro)	[214]
drCT-I	Three-finger cytotoxin	*D. russelli russelli*	U937 (Lymphoma) K562 (Myelogenous leukemia) EAC (Mammary adenocarcinoma)	8.9 μg/mL (In vitro; U937) 6.7 μg/mL (In vitro; K562) 125 μg/kg (In vivo; EAC)	[215]
Nubein6.8	Three-finger cytotoxin	*N. nubiae*	A375 (Melanoma) A2780 (Ovary)	0.54 μM (In vitro) 1.25 μM (In vitro)	[216]

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Table 2 (*continued*)

Identification	Toxin family	Species	Cancer cell line (Type)	Concentration or dose (Approach)	References
CT1, CT2 and CT3	Three-finger cytotoxin	*N. oxiana, N. haje* and *N. kaouthia*	A549 (Lung) HL60 (Leukemia) MCF-7 (Breast)	16.6 μM (In vitro; A549; CT1; *N. oxiana*) 1.7 μM (In vitro; A549; CT2; *N. oxiana*) 2.6 μM (In vitro; A549; CT3; *N. kaouthia*) 132 μM (In vitro; A549; CT1; *N. haje*) 116 μM (In vitro; A549; CT2; *N. haje*) 0.58 μM (In vitro; HL60; CT1; *N. oxiana*) 0.33 μM (In vitro; HL60; CT2; *N. oxiana*) 0.18 μM (In vitro; HL60; CT3; *N. kaouthia*) 2.6 μM (In vitro; HL60; CT1; *N. haje*) 1.9 μM (In vitro; HL60; CT2; *N. haje*) 4.18 μg/mL (In vitro; MCF-7; CT2; *N. oxiana*)	[217,218]
rCT3	Three-finger cytotoxin	*N. naja oxina*	MCF-7 (Breast)	3.66 μg/mL (In vitro)	[219]
Cytotoxin P4	Three-finger cytotoxin	*N. nigricollis nigricollis*	B16 (Melanoma) WEHI 3B (Leukemia) Rat chondrosarcoma	0.8 μg/mL (In vitro; B16) 1 μg/mL (In vitro; WEHI 3B) 1.2 μg/mL (In vitro; Rat chondrosarcoma) (In vivo; B16 and Rat chondrosarcoma)	[220]
NN-32	Three-finger cytotoxin	*N. naja*	MCF-7 (Breast) MDA-MB-231 (Breast) A549 (Lung) EAC (Mammary adenocarcinoma)	2.5 μg/mL (In vitro; MCF-7) 6.7 μg/mL (In vitro; MDA-MB-231) 4 mg/ kg (In vivo; EAC)	[221]
CTX3 and CTX4	Three-finger cytotoxin	*N. naja atra*	MDA-MB-231 (Breast) SK-N-SH (Neuroblastoma)	0.8 μM (In vitro; SK-NSH; CTX3) 1.2 μM (In vitro; SK-NSH; CTX4) 0.15 μM (In vitro; MDA-MB-231; CTX3) 8.71 (24 h) and 6.50 μg/mL (48 h) (In vitro; MCF-7)	[222]
Cytotoxin 10	Three-finger cytotoxin	*N. kaouthia*	MCF-7 (Breast) MDA-MB-231 (Breast) A549 (Lung) NCI–H522 (Lung)	6.04 (24 h) and 5.39 μg/mL (48 h) (In vitro; MDA-MB-231) 6.44 (24 h) and 4.83 μg/mL (48 h) (In vitro; A549) 6.60 (24 h) and 5.19 μg/mL (48 h) (In vitro; NCI–H522)	[223]
Leucurolysin-B	SVMP	*B. leucurus*	T98 (Glioblastoma) U87 (Glioblastoma) RT2 (Mice kidney) MCF-7 (Breast) EAC (Mammary adenocarcinoma) UACC (Melanoma)	0.54 μM (In vitro; T98) 0.62 μM (In vitro; U87) 0.22 μM (In vitro; RT2) 0.45 μM (In vitro; MCF-7) 0.20 μM (In vitro; EAC) 0.57 μM (In vitro; UACC)	[224]
Nasulysin-1	SVMP	*P. nasutum*	Jurkat (Leukemia) K562 (Myelogenous leukemia)	20 μg/mL (In vitro; both cell lines)	[225]
GST-acocostatin	SVMP	*A. contortrix contortrix*	HeLa (Cervical) SK-MEL-28 (Melanoma)	5 μM (In vitro; HeLa)* 220 μg/ML (In vitro, SK-MEL-28)*	[226]
Bothropoidin	SVMP	*B. pauloensis*	MDA-MB-231 (Breast)	10 and 40 μg/mL (In vitro)*	[227]
VaH4	SVMP	*V. ammodytes ammodytes*	HeLa (Cervical)	375 nM (In vitro)	[228]
Jararhagin	SVMP	*B. jararaca*	SK-MEL-28 (Melanoma)	>0.4 μM (In vitro)	[229]
VLAIP	SVMP	*V. lebetina*	PC3 (Prostate)	50 μg/mL (In vitro)	[230]
Jerdonitin	SVMP	*P. jerdonii*	Bel7402 (Liver) K562 (Leukemia) BGC823 (Gastric carcinoma)	0.99 μM (In vitro; Bel7402) 0.82 μM (In vitro; K562) 0.60 μM (In vitro; BGC823)	[231]
Batroxase	SVSP	*B. atrox*	K562 (Leukemia)	2 μg/mL (In vitro)*	[232]
Vipegrin	SVSP	*V. russelii russelii*	MCF-7 (Breast)	1.68 μM (In vitro)	[233]
Collinein-1	SVSP	*C. durissus collilineatus*	MCF-7 (Breast)	4.2 μM (In vitro)	[234]
PIVL and rPIVL	SVSP	*M. lebetina transmediterranea*	U87 (Glioblastoma)	10 – 100 nM (In vitro)* 2 μg (In vivo)	[235]
sv-cystatin	Cystatin	*N. naja atra*	MHCC97H (Liver) B16F10 (Melanoma)	50, 100 or 200 μg/mL (In vitro; both cell lines) 25, 50 and 100 mg/kg (In vivo; B16F10)	[236]
Crotalase	Thrombin like enzyme	*C. adamanteus*	B16 (Melanoma)	32.5 U/mL (In vivo)	[237]

* Concentrations associated with anticancer properties, assessed using assays other than cytotoxicity, such as migration or cell adhesion.

Crotalus, Daboia, Echis, Naja, Trimeresurus and *Vipera* are among the most extensively studied. A variety of cell lines, including those derived from solid and liquid tumours, have been employed in screening experiments. However, no large-scale assessments have been documented, with most studies utilising only 1 to 7 cell lines. The evaluation of potential anticancer effects is typically based on toxicity analysis, with results expressed in concentrations of μg/mL or μM. However, comparison and standardisation in data presentation remain challenging, as the primary structure or molecular weight of some toxins is not available.

In vitro screening has been the predominant approach, with only a limited number of studies incorporating preclinical assessments using animal models. An analysis of 20 *in vivo* anticancer assessments of venom toxins found in the literature revealed a variety of evaluated toxins, including PLA_2s, thrombin-like enzymes, LAAO and predominantly disintegrins. Four different mouse strains were employed: Swiss albino, old nude, C57BL/6, and BALB/c, the two last animal models being the most frequently used. The toxins were administered via intramuscular, intravenous or intraperitoneal injections; however, a significant number studies utilised a pre-incubation model, in which venom toxins and cells were initially incubated before implantation in the animal, a method that does not accurately replicate clinical and pathological conditions. Melanoma and Ehrlich ascites carcinoma have

been among the most extensively studied models in murine oncology employing snake venoms toxins.

Decades of research on snake venom toxins support their anticancer activity and future application [114]. However, our primary focus is on short peptides, as harnessing the potential of larger toxins presents greater challenges and has already been extensively covered. Detailed information on anticancer proteins in snake venoms is available in previous reviews [93,116,238,239] and the Snake Venom Database (https://www.snakevenomdb.org/polypeptides).

4. Snake venom-derived peptides as attractive templates for anticancer drug development

In contrast to large toxins, venom-inspired peptides are more attractive and chemically versatile for large-scale production and integration into the pharmaceutical industry. Peptides have paved the way for innovations across various therapeutic fields [240], with snake venom-derived peptides having a well-documented and rich history, beginning with the development of captopril [146]. Peptides from the Brazilian viper (*B. jararaca*) served as the inspiration for the creation of the first oral angiotensin-converting enzyme inhibitor [92]. In line with this perspective, we identified 31 snake venom-derived peptides in literature with anticancer properties, in agreement with the growing trend in anticancer drug discovery toward exploring smaller molecules. Their dominance and preference in pharmaceutical companies arise from a combination of favourable properties, including lower structural complexity, ease of large-scale production and optimization, reduced immunogenicity, and a diverse biological space.

Table 3 provides clear evidence that peptides are leading a new way in venom bioprospecting. The studies have focused on purified peptides or synthetic peptides that replicate the natural amino acid sequences of identified peptides. In some cases, these peptides are present in snake venoms at low abundance. Chromatographic techniques, including size exclusion, ion exchange, and high-performance liquid chromatography, are the primary separation tools used for this purpose [241]. Advances in peptide chemistry have enabled the production of higher peptide yields compared to those obtained through biochemical fractionation of crude venoms, facilitating the screening of these components in smaller quantities [58]. Our literature analysis, confirmed that more synthetic peptides have been used in the screening than isolated peptides. Interestingly, peptides have been screened against a broader panel of cancer cells than toxins, likely due to the easier obtention and consequently greater availability of material for assessment. These peptides have been tested in several cancer cell lines, including the following types of cancer: breast, colon, lung, lymphoma, melanoma, sarcoma, cervical, glioblastoma, cervical, leukemia, colon, osteosarcoma, ovary, prostate, neuroblastoma and medulloblastoma.

Snake venom-derived synthetic peptides have been obtained using the solid-phase Fmoc strategy, which has been instrumental in ensuring scalability and rapid production [242]. Its compatibility with automated systems and ability to achieve reasonable yields have significantly contributed to peptide science and its pharmaceutical applications [243]. However, challenges such as difficulties in post-translational modifications, limitations in synthesising long peptides, reliance on hazardous reagents, and the high cost of purification remain significant hurdles [244]. Thus, the drug discovery process for venom-based peptides could be enhanced by incorporating alternative synthetic approaches, including cell-free biosynthesis, DNA-based strategies, and microfluidic-based peptide synthesis. These methods have already been adopted in various therapeutic peptide research areas, particularly for high-throughput applications, addressing some of the limitations of chemical synthesis [245–247].

Another route that has expanded the classical toolbox for snake venom drug discovery is the chemical synthesis of molecular fragments of toxins [248]. This strategy explores the possibility of generating short mimetic peptides from larger toxin sequences. The rational design of anticancer toxin-inspired peptides has been guided by either human expertise or computational tools [121,249,250]. For example, Araya and Lomonte (2007) have explored the anticancer properties of cationic short peptides mimicking the C-terminal of naturally occurring membranolytic PLA_2s. In contrast, some researchers have begun harnessing the power of freely available *in silico* tools to dissect venom toxin sequences and identify potential anticancer peptides. Notable examples of this approach include the studies by Almeida et al. (2021) et al. and Peña-Carrillo et al. (2021), which utilised predictive models to select small peptides for synthesis and characterisation. Although still at a small scale, as far as we know, these studies mark the initial integration of AI-based tools into venom-derived anticancer drug discovery. Previously, Falcao and collaborators employed *in silico* proteolysis analysis to guide the design of anticancer peptides based on the primary structure of crotalicidin [251].

PLA_2 toxins have been the primary source of anticancer peptides obtained through this approach. The literature is rich with examples of PLA_2-inspired peptides exhibiting anticancer activity. Due to the ability of these toxins to bind and destabilise membranes, the derived peptides are typically membrane-active, enabling them to disrupt cancer cell membranes [252]. Peptides reproducing short amino acid fragments from PLA_2 isolated from *A. piscivorus piscivorus*, *B. asper*, *B. jararacussu*, *B. marajoensis*, *A. contortrix laticinctus* and *B. brazili* snake venoms have been reported. This aligns with our previous analysis, which highlights the dominance of PLA_2s *in vitro* studies. The extensive availability of anticancer PLA_2 sequences has positioned them among the most explored toxin classes for the design of anticancer peptides.

However, other toxins or polypeptides have also been used as structural templates for the design of short anticancer peptides, for example, C-type lectin, crotoxin and crotalicidin. Collectively, these findings suggest that toxin-inspired peptides represent a promising avenue for harnessing venom components while mitigating the challenges associated with large molecular-weight toxins. The greater number of anticancer venom toxins (Table 2) compared to peptides (Table 3) highlights the abundance of overlooked primary structures of toxins that could be rationally employed to guide the design of potential anticancer peptides.

A similar trend observed for toxins is also evident in snake venom-derived peptides, with viper venoms being more extensively studied than elapid venoms. Peptides from various genera within the Viperidae family have been investigated, including *Agkistrodon, Bothrops*, *Bungarus*, *Calloselasma*, *Crotalus*, *Daboia* and Vipera. In contrast, only a few species from the Elapidae family, specifically those belonging to the *Naja* and *Dendroaspis* genus, have been explored. Interestingly, no peptides from *Micrurus* have been reported, despite documented anticancer activity in crude venom, suggesting the presence of potential candidates [268]. Given the richness of *Micrurus* venoms in low molecular-weight components, this genus remains an important yet underexplored source for future studies. One possible reason for this gap is the limited availability of venom and the challenges associated with obtaining sufficient material using traditional biochemical fractionation workflows [110]. However, advancements in molecular biology techniques and synthetic chemistry may offer alternative production methods, enabling further exploration of these peptides from *Micrurus* venoms. These biases may also result from the greater availability of proteomic data from the Viperidae family and its higher medical relevance, as previously documented [110].

Snake venom peptides exhibit high toxicity to cancer cells, with effects in the range of μM or μg/mL. On the molarity scale, Cbf-K16 exhibited the highest cytotoxic activity against the B16 melanoma cell line. However, when results expressed in μg/mL were analysed, Batroxin I stood out, demonstrating activity at 0.72 μg/mL. No conversions were performed for uniform comparison, as both the sequence and the synthetic strategy for detecting alterations at the C-terminal or N-terminal are available for all peptides. The anticancer activity of snake venom-inspired peptides has been monitored using the gold-standard

Table 3
Snake venom-derived peptides as selective anticancer templates. Peptides have been isolated from snake venoms and also synthetically or recombinantly produced in laboratory settings. Some synthetic peptides are designed based on the sequences of venom toxins, either through human expertise or computational guidance. A selective action has been reported, with preference of cancer cells and minimal impact on the integrity and survival of healthy and red blood cells.

Name	Sequence	Snake precursor	Cancer cell line (Type)	Concentration or dose (Approach)	Normal cell line (Type)	Concentration or dose (Approach)	Reference
Natural peptides							
Oxineur	TCSEGQCYKKTWRDHR	*N. naja oxiana*	HT29 (Colon)	1.1 μg/mL (In vitro) 23 μg/mL (In vitro; EMT6/AR1)	HEK-293 (Kidney)	No effect	[253]
Ruviprase*	EVXWWWAQLS	*D. russelii russeli*	EMT6/AR1 (Breast) U87MG (Glioblastoma) HeLa (Cervical) MCF-7 (Breast)	8.8 μg/mL (In vitro; U87MG) 5.8 μg/mL (In vitro; HeLa) 4 μg/mL (In vitro; MCF-7) 2.5 μg/mL (In vitro)	HEK-293 (Kidney)	No effect	[254]
NN-32	LKCNKLVPLF (first 10 aa)	*N. naja*	MCF-7 (Breast) MDA-MB-231 (Breast)	6.7 μg/mL (In vitro) 10 μg/mL (In vitro)**	MCF-10A (Breast)	25 μg/mL (In vitro)	[255]
			A549 (Lung)	10 μg/mL (In vitro) 5 and 10 μg/mL(In vitro)**	3T3L1 (Mouse fibroblast)	125 μg/mL (In vitro)	[256]
Batroxin I	EKWPRPDAPIPP (E=pyroglutamic acid)	*B. atrox*	HepG2 (Liver)	0.72 μg/mL (In vitro)	Peripheral blood monoculear	No effect	[257]
Crotalicidin (Ctn)	KRFKKFFKKVKKSVKKRLKKIFKKPMVIGVTIPF	*C. durissus terrificus*	U937 (Lymphoma) THP-1 (Leukemia) MM6 (Leukemia) HL60 (Leukemia) Jurkat E6.1 (Leukemia) HeLa S3 (Cervical)	<1 μM (In vitro; HeLa S3 and U937) 1.56 μM (In vitro; THP-1) 3.12 μM (In vitro; MM6) >12.5 μM (In vitro; HL60 and Jurkat E6.1)	Red blood cells (RBC) 1BR3G (Human fibroblasts)	100 and 400 μM (In vitro; RBC). 6.25 μM (In vitro; 1BR3G)	[251]
Crotamine	KQCHKKGGHCFPKEKICLPPSSDFGKMDCRWRWKCCKKGSG	*C. durissus terrificus*	B16F10 (Melanoma)	10 μg/animal/day (In vivo)	Not reported	-	[258]
Dabmaurin–1*	NSGNPXXDPVTXKPRRGEHXVSGPXXRNXKFLNAGTIX	*D. mauritanica*	PC12 (rat adrenal gland pheochromocytoma) K562 (Leukemia) U87 (Glioblastoma) HT29–D4 (Colon)	0.7-51.1 nM (In vitro, HT29-D4 and K562)	HMEC (Breast)	0.2 – 2 μg/mL (In vitro)	[259]
CTNsen1	LKCHQLVPPFWKTCPEGKNLCYKMYMVSSSTVPVKRGCIDVCPKNSALVKYVCCNTDKCN	*N. senegalensis*	U87 (Glioblastoma) U251 (Glioblastoma) T98G (Glioblastoma)	54.69 μg/mL (In vitro; U87) 462.18 μg/mL (In vitro; T98G)	HUVEC (Umbilical endothelial)	225.65 μg/mL (In vitro) No effect	[260]
CTNsen2	LKCHKLVPPFWKTCPEGKNLCYKMYMVATPMIPVKRGCIDVCPKNSALVKYVCCNTNKCN						
CTNsen3	LKCHQLVPPFWKTCPEGKNLCYKMYMVATPMIPVKRGCIDVCPKNSALVKYMCCNTDKCN			45.38 μg/mL (In vitro; U87)		No effect	
CTNanc1	LKCHKLVPPVWKTCPEGKNLCYKMFMVSTSTVPVKRGCIDVCPKDSALVKYVCCSTDKCN	*N. anchietae*	U87 (Glioblastoma) U251 (Glioblastoma) T98G (Glioblastoma)	36.41 μg/mL (In vitro; U87) 38.34 μg/mL (In vitro; U87) 475.8 μg/mL (In vitro; U251)		No effect 467.21 μg/mL (In vitro)	
CTNanc2	LKCHKLVPPFWKTCPEGKNLCYKMYMVATPMLPVKRGCIDVCPKDSALVKYMCCNTDK						

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Table 3 (*continued*)

Name	Sequence	Snake precursor	Cancer cell line (Type)	Concentration or dose (Approach)	Normal cell line (Type)	Concentration or dose (Approach)	Reference
CTNanc3	LKCHKLIPPFWKTCPEGKNLCYKMYMVATPMIPVKRGCIDVCPKDSALVKYMCCNTDKCN			389.59 μg/mL (In vitro; T98G) 5.33 μg/mL (In vitro; U87) 416.37 μg/mL (In vitro; U251) 420.01 μg/mL (In vitro; T98G)		3.58 μg/mL (In vitro)	
Toxin F-VIII	MICYSHKTPQPSATITCEEKTCYKKSVRKLPAIVAGR	*D. angusticeps*	A549 (Lung) MDA-MB-231 (Breast) HT29 (Colon)	106 μg/mL (In vitro; A549) >300 μg/mL (In vitro; MDA-MB-231 and HT29)	HUVEC (Umbilical endothelial) RBC	>300 μg/mL (In vitro; HUVEC) >1000 μg/mL (In vitro; RBC)	[261]
Toxin C13S1C1	RICYSHKLLQAKTTKTCEENSCYKRSLPKIPLIIIGR			56 μg/mL (In vitro; A549) 62 μg/mL (In vitro; MDA-MB-231) 110 μg/mL (In vitro; HT29)		57 μg/mL (In vitro; HUVEC) >600 μg/mL (In vitro; RBC)	
Synthetic peptides							
p-AppK	KKYKAYFKLKCKK-NH_2	*A. piscivorus piscivorus*	B16 (Melanoma) EMT6 (Breast) S180 (Sarcoma) P3X (Myeloma)	139 μM (In vitro; B16) 56 μM (In vitro; EMT6) 172 μM (In vitro; S180) 84 μM (In vitro; P3X)	C2C12 (Skeletal muscle) tEnd (Endotelial)	156 μM (In vitro; C2C12) 139 μM (In vitro; tEnd)	
pEM-2	KKWRWWLKALAKK-NH_2	*B. asper*	B16 (Melanoma) EMT6 (Breast) S180 (Sarcoma) P3X (Myeloma)	161 μM (In vitro; B16) 178 μM (In vitro; EMT6) 317 μM (In vitro; S180) 78 μM (In vitro; P3X)	C2C12 (Skeletal muscle) tEnd (Endotelial)	184 μM (In vitro; C2C12) 162 μM (In vitro; tEnd)	[249]
pepBthTX-I	KKYRYHLKPFCKK	*B. jararacussu*	Jurkat (Leukemia) S180 (Sarcoma) B16F10 (Melanoma)	12 mg/kg (In vivo; EMT6) 10 μg/mL (In vitro; all cell lines) 250 μg (In vivo; S180)	Not reported	-	[156]
pBmje	YNKKYRYHLKSCKKADK-NH_2	*B. marajoensis*	MCF-7 (Breast)	464.85 μM (In vitro)	RBC	No effect	[121]
p-AppK	KKYKAYFKLKCKK-NH_2	*A. piscivorus piscivorus*	Jurkat (Leukemia) TALL (Leukemia) HL60 (Leukemia) HOS (Osteosarcoma) MG63 (Osteosarcoma) OVCAR (Ovary) MACL1 (Breast) MCF-7 (Breast) VW473 (Medulloblastoma)	100 μM (In vitro; all cell lines)	RBC	No effect	[250]
p-Acl	KKYKAYFKFKCKK-NH_2	*A. contortrix laticinctus*		100 μM (In vitro; all cell lines)			

(*continued on next page*)

Table 3 (*continued*)

Name	Sequence	Snake precursor	Cancer cell line (Type)	Concentration or dose (Approach)	Normal cell line (Type)	Concentration or dose (Approach)	Reference
			SHSY5S (Neuroblastoma) NCI (Lung) U138 (Glioblastoma) U87 (Glioblastoma) PC3 (Prostate) H1299 (Lung)				
pepMTX-I pepMTX-II	RKYMAYLRVLCKK KKYRYHLKPLCKK	*B. brazili*	Jurkat (Leukemia)	120 μg/mL (In vitro; both peptides)	Not reported	-	[159]
AACT	CGALEKLTGFRKWVNYYCEQMHAFVCKLLPY	*C. rhodostoma*	HepG2 (Liver) Huh-7 (Liver)	100 μg/mL (In vitro; HepG2)** 10 μg/g (In vivo; Huh-7)	Not reported	-	[262]
3-NAntC	MFYPDSRCRGPSET	*C. durissus terrificus*	MDA-MB-231 (Breast)	2.95 μg/mL (24 h) (In vitro; MDA-MB-231)	HMEC (Breast) MCF10A (Breast) Zebrafish embryos (In vivo)	No effect	[263]
BF-30	KFFRKLKKSVKKRAKEFFKKPRVIGVSIPF	*B. fasciatus*	HepG2 (Liver) MCF-7 (Breast) H460 (Lung) HeLa (Cervical) PC3 (Prostate) A375 (Melanoma) Lewis (Lung) YAC-1 (Lymphoma) B16F10 (Melanoma) B16 (Melanoma)	102.4 μM (In vitro; HepG2) 97.1 μM (In vitro; MCF-7) 45 μM (In vitro; H460) 22.8 μM (In vitro; HeLa) 19.3 μM (In vitro; PC3) 71.2 μM (In vitro; A375) 40.3 μM (In vitro; Lewis) 20.3 μM (In vitro; YAC-1) 7.3 μM (In vitro; B16F10) 13.9 μM (In vitro; B16) 3 mg/kg (In vivo; B16F10)	MDCK (Kidney)	No effect	[264]
Cbf-K_{16}	KFFRKLKKSVKKRAKKFFKKPRVIGVSIPF	*B. fasciatus*	HepG2 (Liver) MCF-7 (Breast) H460 (Lung) PC3 (Prostate) A375 (Melanoma) Lewis (Lung) B16F10 (Melanoma) B16 (Melanoma)	35.7 μM (In vitro, HepG2) 50.8 μM (In vitro, MCF-7) 16.5 μM (In vitro, H460) 12.5 μM (In vitro, PC3) 70.3 μM (In vitro, A375) 10.5 μM (In vitro, Lewis) 7.3 μM (In vitro,	MDCK (Kidney) RBC	0 – 40 μM (In vitro; Low effect in both cells)	[265]

(*continued on next page*)

Table 3 (*continued*)

Name	Sequence	Snake precursor	Cancer cell line (Type)	Concentration or dose (Approach)	Normal cell line (Type)	Concentration or dose (Approach)	Reference
				B16F10) 0.4 μM (In vitro, B16) >10 μM (In vitro; HeLa S3)		No effect	
Ctn [1–14]	KRFKKFFKKVKKSV						[251]{Pérez-Peinado, 2019 #300, [266]}
		C. durissus terrificus	HeLa S3 (Cervical) U937 (Lymphoma) THP-1 (Leukemia)	1 μM (In vitro; HeLa S3) 6.25 μM (In vitro; U937) 25 μM (In vitro; THP-1)	RBC 1BR3G (Human fibroblasts) PK15 (Kidney) HaCat (Keratinocytes) HEK-293 (Kidney)	No effect	
Ctn [15–34]	KKRLKKIFKKPMVIGVTIPF						
ΔPb-CATH4	TRSRWRRFIRGAGRFARRYGWRIA	*P. bivittatus*	MCF-7 (Breast)	>30 μg/mL (In vitro)		>30 μg/mL (In vitro; all cell lines)	[267]
Obtustatin peptide	CWKTSLTSHYS	*V. lebetina obtusa*	K562 (Leukemia)	600 μM (In vitro)**	Not reported	-	[200]

* Peptides with sequences containing the letter X, indicating that the full sequence remains unknown.
** Concentrations associated with anticancer properties, assessed using assays other than cytotoxicity.

technique for cell viability quantification, known as the MTT assay. This colourimetric absorbance-based method provides an indirect measurement, as it assesses mitochondrial activity rather than direct cell viability. An important caveat is the assumption that increased metabolic activity directly correlates with a higher number of cells [269]. However, this approach remains widely accepted in early-stage anticancer drug screening [270]. A key limitation of this assay is that the viability assay focuses on cultured cells, rather than the broader tumour network and microenvironment. This method does not capture specific cellular contexts and may overlook potential therapies that specifically target the tumour microenvironment [270]. Another barrier is the lack of insight into the underlying mechanisms driving cancer cell death. This restricts understanding of the targets and potential pathways.

The anticancer mechanisms of snake venom-derived peptides are diverse, involving a range of cellular and molecular events [271]. These include modulation of gene expression, DNA fragmentation, disruptions in redox homeostasis, apoptosis, necrosis, cell cycle arrest, alterations in cell migration, and interactions with membrane components that compromise permeability and osmotic balance [272]. Ultimately, these effects can lead to intracellular content release, contributing to cancer cell death. From a methodological point of view, a combination of many approaches has been used to capture these events. The most common are: LDH assay, PCR, western blot, microscopic-based approaches, fluorescence and absorbance-based assays, scratch assay and flow cytometry.

Interestingly, most snake venom-inspired peptides exhibit selective activity, affecting cancer cells significantly more than healthy cells. This dual analysis is essential in cancer therapy development [273] and was incorporated into most studies. In general lines, many assessments of toxicity relied on a single cell type, with erythrocytes being the most frequently used. Some studies also employed myoblasts, an epithelial cell line, embryonic kidney tissue, mammary epithelial cells, and fibroblasts. While red blood cells are widely accepted for toxicity evaluation in peptide drug screening, their use does not fully represent all human cells due to significant phenotypic and molecular differences, for instance, their anucleated nature. Few studies have utilised canine or murine cell lines to assess off-target effects; however, human-derived cell lines remained the preferred choice due to their relevance in predicting human drug responses. Therefore, future studies in this field should prioritise healthy human cells that closely resemble the cancer cells used in screening to better assess selectivity.

An important takeaway from the current list of licensed anticancer peptides is the crucial role of peptide engineering. While this dynamic field has benefited from various strategies to enhance activity, stability, and selectivity [274], only two approaches have been employed to anticancer snake venom-derived peptides. We identified the use of amino acid substitution, mirror-image and truncation peptide strategies. The first two approaches were used to design pEM-2, a synthetic peptide inspired by the C-terminal region of a bothropic membranolytic toxin [249]. Some residues from the natural sequence were substituted, with tryptophan and all amino acids synthesised in the D-form. In drug discovery, this approach produces more stable and less immunogenic peptides, reducing enzyme-induced degradation in *in vivo* systems [275]. In fact, pEM-2 demonstrated anticancer activity in animal models when administered intraperitoneally. From another perspective, some venom-derived peptide sequences have been shortened to identify the minimal molecular functional regions essential for anticancer activity [251]. The use of truncation brings several benefits, such as reduced complexity, lower synthesis costs, and optimized biological activity, making it a common and useful approach in peptide-based drug design steps [276]. This principle was employed to dissect crotalicidin, crotamine and crotoxin. In the first case, a more selective 20-mer peptide, designated as Ctn[15–34], was derived from the parent 34-residue peptide while preserving its anticancer properties [251]. In the second case, the screen and fragmentation of crotamine led to the discovery of nucleolar-targeting peptides that, while non-cytotoxic, exhibit excellent

cell-penetrating properties [277]. Their accumulation in intracellular compartments has inspired their development for drug delivery, imaging diagnostics, and research applications in cancer biology [278]. This exemplifies another dimension of the application of venom-derived peptides. The third example involved the design of a short 14-m34 peptide with action on triple-negative breast cancer based on the sequence of crotoxin B [263]. On the practical side, advances in snake venom-derived peptides require a more extensive exploration of strategies to create safer and more effective peptides, such as lipidation, cyclisation, backbone modification, PEGylation, stapling, and cross-linking. The use of these viable options will create a wider library of robust anticancer snake venom peptide-based candidates for pre-clinical experimentation.

The *in vivo* validation of the anticancer potential of five snake venom-inspired peptides has been reported. With the exception of crotamine, which was isolated from venom, the remaining peptides were chemically synthesized for evaluation. One peptide reproduced the natural sequence of a cathelicidin (BF-30), while two mimicked functional regions of PLA_2 (pEM-2 and pepBthTX-I) and one reproduces a fragment of a C-type lectin (AACT). Peptides of varying lengths, ranging from 13 to 42 amino acid residues, were evaluated. BALB/c and C57Bl/6 mice were equally employed, while one study used SCID (severe combined immunodeficient) mice. The peptides were inspired by sequences obtained from various venoms, including *B. asper, C. rhodostoma, B.fasciatus, C. durissus terrificus,* and *B. jararacussu.* The skin cancer model (B16-F10) was investigated in two studies, while others explored mammary carcinoma (EMT6), hepatoma (Huh-7), and sarcoma (S18). No uniform route of administration was observed; although intraperitoneal injection was the most common, intravenous, intratumoural, and intramuscular routes were also employed. Variable doses and treatment regimens (duration) were observed, but peptides were consistently administered at the μg/animal scale.

From another angle, one study employed *in vivo* models to evaluate toxicity and gain insights into potential off-target effects [263]. Interestingly, the authors utilised zebrafish, a well-established model in toxicology research. A crotoxin B-derived peptide, 3-NAntC, was subcutaneously injected into zebrafish embryos, and survival as well as malformations were monitored at three different time points (24, 48, and 72 hours). The results confirmed a favourable safety profile for this synthetic anticancer snake venom-derived peptide. This recent study highlights the ongoing pursuit of novel toxicity screening methods that align with the 3Rs principle while incorporating high-throughput design strategies.

The structure and biochemical properties associated with the sequence of anticancer peptides hold significant value for their functionality. In turn, they can aid in understanding peptide action and serve as a guide for designing optimal molecules. Many novel AI-based tools, which we will discuss in the following section, have examined these parameters to enhance peptide bioactivity prediction. With this in mind, we highlight key physicochemical characteristics determined using the PepDraw tool (https://pepdraw.com/). Table 4 summarises the main findings.

Peptide length influences not only stability and biological activity but also manufacturing complexity and cost. Snake venom-derived peptides ranging from 10 to 60 amino acid residues have been screened. However, short peptides (fewer than 20 amino acids) with a lower molecular weight (< 2,400 Da) have drawn significant attention. This meets the growing demand and increasing interest of pharmaceutical companies in smaller molecules. A global analysis of peptides entering clinical development has shown that those ranging from 2 to 20 amino acids dominate the process. Interestingly, the presence and contribution of longer peptides (20–40 amino acids) are also becoming more significant [279]. Advances and optimisations in peptide synthesis methods are likely to influence this trend. Collectively, these findings reinforce the feasibility of obtaining sufficient quantities of anticancer snake venom-inspired peptides to meet demand.

As detailed in Table 4, snake venom-derived peptides typically exhibit cationic and hydrophobic characteristics, with high isoelectric points and pronounced hydrophobicity. Their charges range from -1 to +15, with the majority falling between +6 and +8. This amphiphilic nature aligns with the properties of other oncolytic and antimicrobial peptides identified and characterised from natural products. Cationicity and affinity for non-aqueous environments are considered the mechanistic basis of their action, primarily targeting the cell membrane. Many

Table 4
Overview of sequence-associated properties of snake venom-derived peptides. *In silico* characterisation of physicochemical properties using PepDraw tool (https://pepdraw.com/). Short cationic-hydrophobic peptides appear with greater frequency in the list of anticancer snake venom-derived candidates.

	Peptides	Length	Net charge	Isoelectric point	Mass (Da)	Hydrophobicity (Kcal*mol^{-1})
Natural	Oxineur	16	+2	8.84	1996.8969	26.76
	NN-32	10	+2	9.95	1173.6923	8.55
	Crotalicidin (Ctn)	34	+15	12.59	4149.6388	34.39
	Crotamine	41	+8	9,79	4723.2543	48.85
	CTNsen1	60	+6	8.70	6768.2528	38.84
	CTNsen2	60	+8	9.18	6819.3549	36.01
	CTNsen3	60	+6	8.70	6852.2747	36.56
	CTNanc1	60	+6	8.70	6692.2829	43.31
	CTNanc2	58	+6	8.87	6636.2431	40.42
	CTNanc3	60	+6	8.69	6867.3106	40.72
	Toxin F-VIII	37	+5	9.76	4137.1292	33.65
	Toxin C13S1C1	37	+6	10.03	4303.3411	30.52
	pEM-2	13	+7	14.00	1740.0798	15.94
	pepBthTX-I	13	+6	10.55	1737.9837	21.78
	pBmje	17	+7	10.30	2171.1751	30.89
	p-AppK	13	+8	10.76	1674.0137	23.60
	p-Acl	13	+7	10.55	1708.9822	23.14
	pepMTX-I	13	+5	10.55	1670.9449	15.35
	pepMTX-II	13	+6	10.55	1703.9993	22.24
Synthetic	AACT	31	+2	8.53	3709.8013	18.72
	3-NAntC	14	0	6.27	1644.7002	18.28
	BF-30	30	+11	12.29	3636.2324	31.59
	Cbf-K_{16}	30	+13	12.82	3635.2847	30.76
	Ctn [1–14]	14	+8	11.99	1797.1473	23.72
	Ctn [15–34]	20	+8	11.95	2369.5180	18.57
	ΔPb-CATH4	24	+9	13.03	3050.6986	19.30
	Obtustatin peptide	11	+1	9.07	1311.5899	10.84

researchers propose that these chemical properties impart selectivity to peptides, enabling differential activity on cancerous versus healthy membranes due to variations in lipid composition. This principle has guided efforts to engineer peptide charge and hydrophobicity for enhanced selectivity toward cancer cell membranes. Nonetheless, achieving the optimal balance remains complex. Previous reviews have explored membranolytic mechanisms in greater depth.

A detailed analysis of snake venom-derived peptides at the compositional level is presented in the heat map (Fig. 4). Notably, these peptides are enriched with positively charged amino acids, predominantly lysine (K). They also exhibit higher frequencies of phenylalanine (F) and leucine (L), alongside a moderate presence of cysteine (C), alanine (A), and proline (P). Negatively charged amino acids are rare within the sequences and, when present, occur at lower densities. A similar trend has been reported in other studies on anticancer peptides derived from natural sources, highlighting the predominant focus on cationic and membranolytic peptides [280,281]. While membrane-active molecules are promising candidates, exploring alternative mechanisms of action through high-throughput assays targeting other intracellular pathways could uncover additional patterns and possibilities. Moreover, establishing correlations between the physicochemical properties and sequences analysed here and their anticancer activity remains challenging due to the limited dataset and the heterogeneity of cells used in the studies.

5. Peptide venom discovery in the AI era

Artificial intelligence has dynamically transformed numerous fields, including peptide-focused drug discovery, driving significant advancements [282]. However, despite its vast potential and opportunities, its application to snake venom-derived peptides remains limited, with only a few small-scale examples reported. The advent of AI in utilizing snake venom as a source of anticancer peptides has focused on miniming individual proteins to identify molecular fragments with these properties. Notably, two studies have employed AI-based tools to predict the activity and toxicity of 13-mer peptides designed from viper PLA_2 sequences and *in vitro* evaluation [121,250]. A third study has adopted the computational route to guide the design of potential anticancer peptides based on the sequence of snake venom metalloproteases [283]. However, no experimental evidences were presented to validate the findings. Transitioning from the individual screening of a single toxin or toxin family to analysing thousands of molecules within the snake venom proteome presents significant challenges. However, with the advancements in computational power, this approach has become feasible and is beginning to deliver exciting results [284]. On a larger scale, the Venomics AI study analysed 16,123 venom proteins from different animal sources [285]. Although this study primarily emphasised antibiotic properties, it represents the first large-scale integration of AI into the pipeline for mining venom proteomes. This work signifies a paradigm shift, showcasing the potential AI-driven approaches, which can be extended to anticancer screening.

As discussed in the previous sections, there is a gap between the identification of numerous sequences through venomics and the pre-clinical evaluation of candidates, highlighting the need for high-throughput assays and innovation. The high cost and time-consuming nature of experimentation, combined with the limited availability of material for certain venom proteins and peptides, underscore the need to rethink venom screening systems. In this context, AI-driven approaches have a transformative potential to redesign the roadmap from venomics to pre-clinical validation with options to be implemented in different steps. To enhance understanding, we present a comparative analysis in Fig. 5, contrasting traditional step-by-step screening methods based on

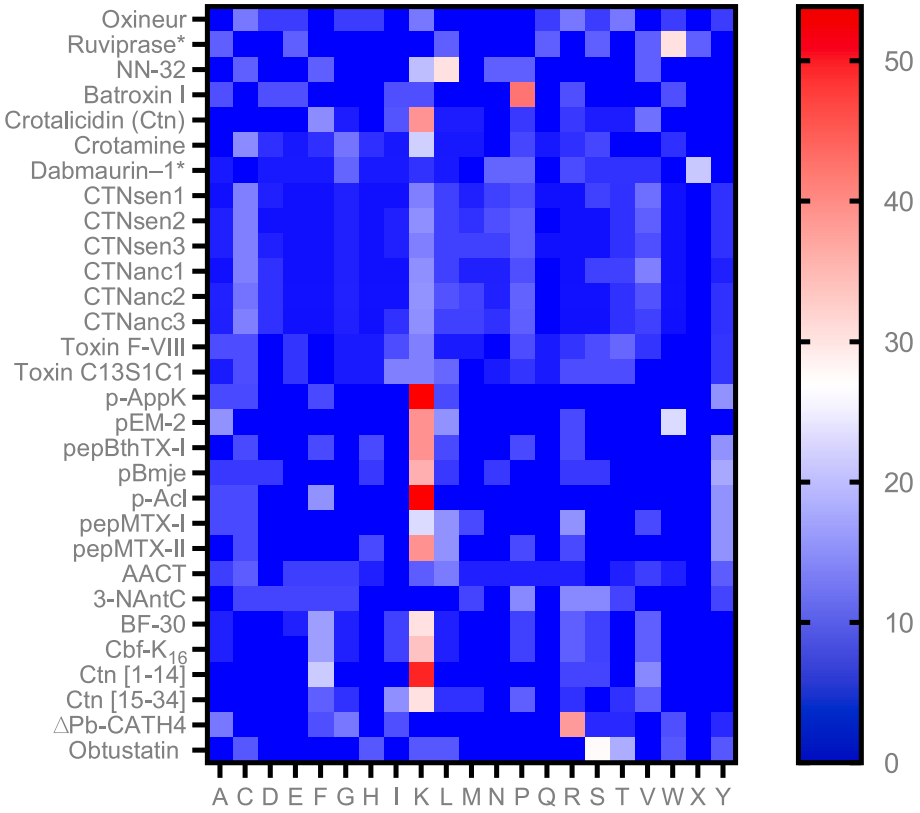

Fig. 4. Compositional patterns of snake venom-derived peptide sequences. The frequency analysis of amino acid composition in snake venom-inspired peptides is illustrated as a heat map. A double gradient was applied to visualise the *in silico* analysis of the primary structure. Darker red shades indicate higher prevalence, while deeper blue tones represent lower occurrences. The frequency of amino acid occurrence is expressed as a percentage (%). *Peptides with sequences containing the letter X, indicating that the full sequence remains unknown.

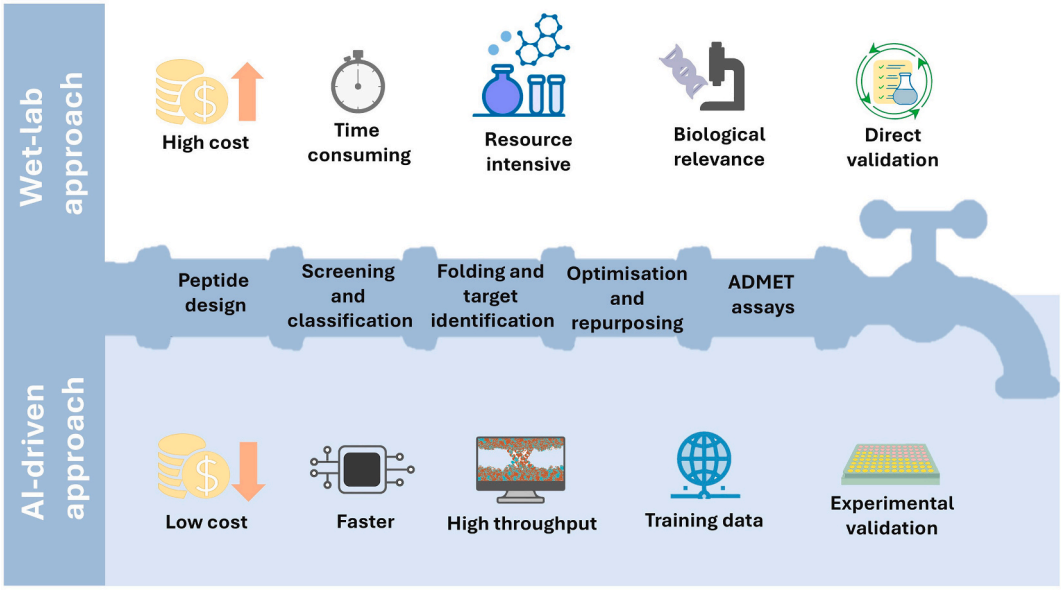

Fig. 5. AI-based tools can reshape many steps in drug peptide discovery. From the design to ADMET analysis, the conventional journey of finding lead peptides for animal validation is multi-layered with many obstacles. From the design to ADMET analysis, AI-driven tools can act in all steps, promising to reduce the time needed to find candidates for preclinical validation. This simplified view highlights points where AI-based algorithms can offer alternative routes in the drug discovery process.

repetitive wet-lab approaches with AI-driven technologies. Additionally, we outline our perspective on how and where AI-driven solutions can currently be integrated into this workflow.

The transition from thousands of sequences from venom proteomes to successful *vivo* experimentation of active anticancer peptides is a lengthy process filled with numerous challenges associated with speed and accuracy. In this study, we identified five key steps in this journey: (1) peptide design, (2) *in silico* screening and classification, (3) folding and target identification, (4) lead optimisation and repurposing, and (5) ADMET analysis, which encompasses Absorption, Distribution, Metabolism, Excretion, and Toxicity evaluation. AI-based tools provide an accelerated, smarter and more accurate pathway, maximising the potential to explore broader chemical spaces of bioactive peptides and achieve improved outcomes [286]. Below, we examine the challenges associated with conventional methods and highlight the opportunities for integrating AI at various stages of the peptide drug discovery process, ultimately leading to safer and more effective preclinical candidates.

In the first step, designing or selecting potential peptides for screening remains a challenging task, primarily due to the limited possibility of the experimental-based approach to explore the vast chemical and biological space. In other words, screening whole proteomes and peptide fragments across various cancer cell lines demands substantial investment in resources, infrastructure, and time, resulting in slower progress [287]. Conventional approaches have relied on literature-based insights, the analysis of physicochemical properties, activity-guided fractionation and the study of more abundant venom components to guide the selection of peptide sequences [287,288]. In contrast, AI-based tools offer significant advantages by enabling the exploration of large databases, establishing homology comparisons, predicting activity, and generating novel sequences [289]. These capabilities optimise the process by reducing the number of molecules requiring *in vitro* evaluation. This approach has already been incorporated into the pipeline design for anticancer peptides [290,291] and is expected to expand into the exploration of large datasets of venom proteomes in the near future.

In the second step, peptide evaluation and classification into anticancer and non-anticancer categories are already performed by numerous algorithms and models at a much higher speed compared to the time-intensive toxicity profiling methods, such as cell- and absorbance-based assays [292,293]. Similarly, AI-driven hemolytic and cancer toxicity prediction tools have been developed, offering an initial assessment of therapeutic and safety profiles [294,295]. Table 5 provides a list of AI-based tools available for this purpose. We identified over 50 tools for anticancer prediction and more than 30 for analysing haemolysis and the toxic properties of peptides. This illustrates how AI-based methods have permeated therapeutic peptide discovery. These data-driven approaches can recognise particular molecular and structural patterns based on sequences or biochemical parameters and predict biological activities or therapeutic applications [55]. However, their accuracy depends on the quality and domain knowledge of the large datasets used [296].

There are many available databases of anticancer, haemolytic and toxic peptides used to develop other AI models [297–299]. Although they can be repurposed to mine venom proteomes, such datasets may introduce biases. One significant challenge in venom screening is the lack of extensive databases containing snake venom-derived peptides and non-anticancer peptides from the same source. VenomZone (https://venomzone.expasy.org/1877) and the Snake Venom Database (https://www.snakevenomdb.org.) are valuable resources that could be further explored in the future as sources of anticancer templates for virtual screening, or as repositories of experimentally validated peptides or toxins to develop algorithms or models [300]. Data generation plays a vital role in ensuring the quality and accuracy of novel models [301]. An adequate volume of data produced under standardized conditions, such as consistent cell lines, assays, and media, is essential for achieving strong performance metrics [302]. Our literature search and review of currently available databases focused on snake venom-derived peptides revealed a restricted sequence space. Therefore, the discovery of additional sequences is an urgent and necessary task. One key takeaway is the need to enhance our capacity for screening venom proteomes. This expansion would increase the volume of sequences available, enabling the creation of more diverse and representative training and test datasets. Such datasets are crucial for developing robust AI models to explore snake venom libraries effectively.

Subsequently, in the traditional approach, the identification of peptide structure, targets, and mechanisms of action relies on various experimental methods, which are both resource- and time-demanding [296,395]. In contrast, the integration of AI enables faster identification of structures and targets [396]. AlphaFold 2 and machine/deep

Table 5
AI-driven tools in the peptide drug discovery landscape. This table compiles useful AI-based tools available for predicting the anticancer properties, toxicity, structure and ADME properties of peptide candidates. This table provides an overview of AI-based tools designed for predicting the anticancer properties, toxicity, structure, and ADME characteristics of peptide candidates. Additionally, it examines the algorithms and models employed in their development. The last column details key evaluation metrics used to assess the performance and effectiveness of AI-driven tools. The symbol – indicates that the metrics were either undetermined or unavailable. All abbreviations in the table are defined at the bottom.

Tools	Year	Links	Algorithms/models	Evaluation metrics				References
				SV	SP	MCC	ACC	
Predictive tools for anticancer peptide candidates								
AntiCP	2013	http://crdd.osdd.net/raghava/anticp/	SVM	0.89	0.93	0.83	0.91	[303]
Hajisharifi et. al	2014	NA	SVM	0.85	0.93	0.78	0.90	[304]
ACPP	2014	http://acpp.bicpu.edu.in/predict.php; https://github.com/brsaran/ACPP	SVM	0.95	0.97	0.92	0.96	[305]
iACP	2016	http://lin-group.cn/server/iACP	SVM	0.93	0.92	0.85	0.93	[306]
Li & Wang	2016	NA	SVM	0.90	0.96	0.87	0.94	[307]
MLACP	2017	http://www.thegleelab.org/MLACP/MLACP.html	RF and SVM	0.89	0.98	0.89	0.95	[308]
Khan et al.	2017	NA	KNN and SVM	0.86	0.98	0.86	0.93	[309]
iACP-GAEnsC	2017	NA	ML models	0.95	0.97	0.91	0.96	[310]
ACPred-FL	2018	http://server.malab.cn/ACPred-FL	SVM	0.84	0.98	0.83	0.91	[311]
SAP	2018	NA	Hybrid model (amino acid composition, and average chemical shifts)	0.86	0.96	0.83	0.92	[312]
TargetACP	2018	NA	SVM, PNN, and KNN	0.99	0.98	0.97	0.99	[313]
ACP-DL	2019	https://github.com/haichengyi/ACP-DL	Deep LSTM model	0.85	0.90	0.71	0.85	[314]
ACPred	2019	http://codes.bio/acpred	RF and SVM	0.96	0.99	0.95	0.98	[315]
mACPpred	2019	http://www.thegleelab.org/mACPpred	SVM	0.89	0.94	0.83	0.91	[316]
MAMPs-Pred	2019	NA	ML and SVM	0.93	0.95	0.88	0.94	[317]
AntiCP2.0	2020	https://webs.iiitd.edu.in/raghava/anticp2/	SVM	0.92	0.92	0.84	0.92	[318]
cACP-2LFS	2020	https://github.com/shahidawkum/cACP-2LFS	KSAAP features, 2LFS, and ML models	0.91	0.96	0.87	0.94	[319]
EnACP	2020	https://github.com/greyspring/EnACP/tree/master	LightGBMs and SVM	0.93	0.98	0.91	0.95	[320]
ACP-GCN	2020	NA	GCN	-	-	-	-	[321]
ACPred-Fuse	2020	http://server.malab.cn/ACPred-Fuse	MvRL	0.77	0.88	0.65	0.82	[322]
CancerGram	2020	http://biongram.biotech.uni.wroc.pl/CancerGram/; https://github.com/BioGenies/CancerGram	RF	0.71	0.85	0.57	0.79	[323]
DeepACP	2020	https://github.com/jingry/autoBioSeqpy/tree/master	Deep learning and DNN	0.78	-	0.66	0.83	[324]
DLACP	2020	NA	Dictionary learning	0.89	0.95	0.84	0.92	[325]
DRACP	2020	NA	Deep belief network with RRVM	0.78	-	0.66	0.83	[326]
Li et al.	2020	NA	SVM	0.89	0.95	0.84	0.92	[327]
ACHP	2021	http://118.178.58.31:9801/	SVM, KNN, RF, and SVM-RFE	0.86	0.99	0.87	0.94	[328]
ACP-DA	2021	https://github.com/chenxgscuec/ACPDA	AAindex features	0.88	0.88	0.77	0.88	[329]
ACP-MHCNN	2021	https://anticancer.pythonanywhere.com/	Multi-headed CNN model	0.98	0.84	0.82	0.91	[330]
DLFF-ACP	2021	https://github.com/wame-ng/DLFF-ACP	Deep learning and CNN	0.83	0.86	0.32	0.86	[331]
iACP-DRLF	2021	https://github.com/zhibinlv/iACP-DRLF	LSTM and LightGBM	0.90	0.96	0.86	0.93	[332]
iACP-FSCM	2021	https://github.com/Shoombuatong/Dataset-Code/tree/master/iACP-FSCM	FSCM-derived propensity scores	0.88	0.90	0.78	0.89	[333]
iAMP-CA2L	2021	http://www.jci-bioinfo.cn/iAMP-CA2L	CNN-BiLSTM-SVM	0.97	0.94	0.92	0.96	[334]
MLBP	2021	https://bioinfo.ahu.edu.cn/MLBP/	Multi-Label deep learning (CNN and BiGRU layers)	-	-	-	0.71	[335]
PreTP-EL	2021	http://bliulab.net/PreTP-EL/	ML models	0.84	0.89	0.73	0.86	[336]
xDeep-AcPEP	2021	https://app.cbbio.online/acpep/home	CNN-based deep learning	-	-	-	-	[337]
CL-ACP	2021	https://github.com/zjlyn1314/CL-ACP/tree/main	Combined network with attention mechanisms	0.91	0.85	0.77	0.88	[338]

(continued on next page)

Table 5 (*continued*)

Tools	Year	Links	Algorithms/models	Evaluation metrics				References
				SV	SP	MCC	ACC	
ACP-2DCNN	2022	NA	Deep learning	0.92	0.80	0.73	0.86	[339]
ACP-check	2022	http://www.cczubio.top/ACP-check/	BiLSTM	0.93	0.93	0.86	0.93	[340]
ACP-MCAM	2022	NA	Multi-kernel CNN	0.85	0.96	0.82	0.91	[341]
ACPNet	2022	https://github.com/abcair/ACPNet	Hybrid deep learning	0.88	-	0.79	0.90	[342]
ME-ACP	2022	https://github.com/hyao1/ME-ACP	LightGBMs and a hybrid DNN	0.92	0.95	0.87	0.93	[343]
MPMABP	2022	https://github.com/Good-Ly/MPMABP	Deep learning model combining CNNs and BiLSTM,	-	-	-	0.72	[344]
Pep-CNN	2022	https://github.com/alivelxj/Pep-CNN	CNN	0.96	0.97	-	0.97	[345]
MLACP 2.0	2022	http://thegleelab.org/MLACP/	ML	0.75	0.77	0.51	0.76	[346]
PreTP-Stack	2022	http://bliulab.net/PreTP-Stack/	Multi-view learning meta-model	-	-	-	-	[347]
StackACPred	2022	https://github.com/Muhammad-Arif-NUST/StackACPred-	SVM-RFE+CBR	0.87	0.86	0.72	0.86	[348]
TPpred-ATMV	2022	https://github.com/cokeyk/TPpred-ATMV	Multi-view learning and tensor learning frameworks	0.82	0.79	0.61	0.81	[349]
AI4ACP	2022	https://axp.iis.sinica.edu.tw/AI4ACP/helppage.html	Deep learning	0.90	0.92	0.83	0.91	[208]
ACP-BC	2023	NA	LSTM and BERT	0.90	0.89	0.78	0.90	[350]
ACP-MLC	2023	https://github.com/Nicole-DH/ACP-MLC	RF and binary relevance	0.76	0.84	0.60	0.80	[351]
ACP-GBDT	2023	https://github.com/jingry/autoBioSeqpy/tree/master	Gradient boosting decision trees, AAIndex and SVMProt-188D features.	0.90	0.93	0.83	0.91	[352]
iACP-GE	2023	https://github.com/yunyunliang88/iACP-GE	GBDT and ET	0.93	0.89	0.82	0.91	[353]
ANNprob-ACPs	2024	https://circular-palatable-term.anvil.app/	ANN	0.95	0.94	0.87	0.94	[354]
Predictive tools for peptide-induced haemolysis								
HemoPI	2016	https://webs.iiitd.edu.in/raghava/hemopi/	ML algorithms (SVM^{light}, IBK, Multilayer Perceptron, Logistic, J48, and RF	0.96	0.99	0.93	0.96	[355]
HemoPred	2017	https://github.com/chaninn/HemoPred	RF	0.96	0.97	0.92	0.96	[356]
HemoPImod	2020	https://webs.iiitd.edu.in/raghava/hemopimod/	2D/3D fingerprints and atom compositions.	0.80	0.77	0.57	0.78	[357]
HAPPENN	2020	https://research.timmons.eu/happenn	ANN	0.85	0.86	0.71	0.86	[358]
Plisson et al. model	2020	https://github.com/plissonf/ML-guided-discovery-and-design-of-non-hemolytic-peptides	ML models	-	-	0.93	0.97	[359]
HLPPredFuse	2020	http://thegleelab.org/HLPpred-Fuse/	ML models	0.84	0.96	0.82	0.90	[360]
AMPDeep	2022	https://github.com/milad73s/AMPDeep	AMPDeep learning pipeline	0.97	-	0.97	0.99	[361]
Hemolytic-Pred	2023	http://ec2-54-160-229-10.compute-1.amazonaws.com/	ML models	0.97	0.94	0.89	0.96	[362]
EnDL-HemoLyt	2023		BiLSTM, BiTCN, and 1D-CNN	0.85	0.86	0.73	0.87	[363]
Peptide Dashboard	2023	https://github.com/ur-whitelab/peptide-dashboard	RNN	-	-	-	0.84	[364]
PeptideBERT	2023	https://github.com/ChakradharG/PeptideBERT	Deep learning	-	-	-	0.86	[365]
HemoDL	2024	https://github.com/abcair/HemoDL	LightGBM	0.85	0.90	0.76	0.88	[366]
QSVM-PEPTIDE	2024	https://github.com/sxxnz/QSVM-PEPTIDE	QSVM	0.94	-	-	0.95	[367]
Multi-Peptide	2024	https://github.com/srivathsanb14/MultiPeptide	GNN	-	-	-	0.88	[368]
HemoFuse	2024	https://github.com/z11code/Hemo	Word embeddings, hand-crafted features, and multi-head cross-attention	0.87	0.89	0.76	0.88	[369]
HemoPi2	2025	https://webs.iiitd.edu.in/raghava/hemopi2/; https://github.com/raghavagps/HemoPI2?tab=readme-ov-file	Hybrid approach (Motif and SVM)	0.80	0.88	0.68	0.84	[370]

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Table 5 (*continued*)

Tools	Year	Links	Algorithms/models	Evaluation metrics				References
				SV	SP	MCC	ACC	
Predictive tools for peptide-induced toxicity								
ClanTox	2009	http://www.clantox.cs.huji.ac.il/	ML	-	-	-	-	[371]
ToxinPred	2013	http://crdd.osdd.net/raghava/toxinpred/	ML models	0.75	0.99	0.81	0.96	[372]
ToxClassifier	2016	http://bioserv7.bioinfo.pbf.hr/ToxClassifier/	SVM, GBM and GLM	0.97	0.99	0.89	0.99	[373]
TOXIFY	2019	ttps://www.github.com/tijeco/toxify	Deep learning	0.76	0.96	0.74	0.86	[374]
NNTox	2019	http://www.github.com/kiharalab/NNTox	Deep learning	0.90	-	-	0.88	[375]
ToxDL	2020	http://www.csbio.sjtu.edu.cn/bioinf/ToxDL/	Deep learning with CNN	-	-	0.79	-	[376]
ATSE	2021	http://server.malab.cn/ATSE	GNN	0.96	0.94	0.90	0.95	[377]
ToxIBLT	2022	https://server.wei-group.net/ToxIBTL	Deep learning	0.96	0.95	0.92	0.96	[378]
ToxinPred2.0	2022	https://webs.iiitd.edu.in/raghava/toxinpred2/	ML models	0.94	0.97	0.91	0.95	[379]
Toxicity-vib	2022	https://github.com/khanhlee/toxicity-vib	Deep learning	-	-	0.95	0.95	[380]
CSM-toxin	2023	https://biosig.lab.uq.edu.au/csm_toxin/	Deep learning	0.75	-	0.67	-	[381]
VISH-Pred	2024	http://ec2-35-170-123-194.compute-1.amazonaws.com:7860/	ESM2 and ML	0.81	-	0.74	0.96	[382]
tAMPer	2024	https://github.com/bcgsc/tAMPer	Graph-based peptide representations from ColabFold structures	0.82	0.89	0.62	-	[383]
ToxinPred3.0	2024	https://webs.iiitd.edu.in/raghava/toxinpred3/	SVM	0.92	0.93	0.86	0.93	[384]
ToxTeller	2024	https://github.com/comics-asiis/ToxicPeptidePrediction	ML models	0.72	0.92	0.63	0.80	[385]
MultiToxPred 1.0	2024	https://github.com/jfbldevs/MultiToxPred/tree/master	LightGBM and QDA	-	-	-	0.85	[386]
ToxGIN	2024	https://github.com/cihebiyql/ToxGIN	GIN	0.80	-	0.69	-	[387]
ToxDL 2.0	2025	http://www.csbio.sjtu.edu.cn/bioinf/ToxDL2/	GCN	0.89	-	0.87	-	[388]
PLPTP	2025	https://www.bioai-lab.com/PLPTP; https://github.com/birdsmart/PLPTP	ESM2, BiLSTM, and DNN	0.97	0.98	0.94	0.98	[389]

Predictive tools for peptide structures			Algoritms/Models	Highlights	References
Pep-FOLD	2009	https://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD/	SA-HMM	PEP-FOLD predicts 3D structures of 9–25 residue peptides using a structural alphabet and coarse-grained force field, generating 50 models to identify low-energy, representative conformations. On a 25-peptide benchmark, PEP-FOLD achieved an average Cα RMSD of 2.6 Å from NMR structures, demonstrating reliable prediction of low-energy peptide conformations	[390]
Pep-FOLD2	2014	https://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD2/	SA-HMM	PEP-FOLD2 improves peptide structure prediction over PEP-FOLD1 and outperforms Rosetta, generating near-native models for 95% of 56 peptides (25–52 residues) in benchmark tests	[391]
Pep-FOLD3	2016	https://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD3/	SA-HMM	PEP-FOLD3 enables fast de novo prediction of 5–50 residue peptides and models peptide–protein interactions, achieving experimental-like structures for 80% of 56 tested peptides	[392]
ColabFold (v1.5.5)	2022	https://github.com/sokrypton/ColabFold	MSAs (MMseq2) and python library	Accelerated prediction of protein structures. Free and accessible platform. Designed to be used in Google Colab	[393]

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Table 5 (*continued*)

Tools	Year	Links	Algorithms/models	Evaluation metrics				References
				SV	SP	MCC	ACC	
PEP-FOLD4	2023	https://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD4/	SA-HMM	Predict peptide structures. Describe the conformations of four consecutive residues, couples the predicted series of SA letters to a greedy algorithm and a coarse-grained force field				[394]

Abbreviations: 2LFS: Two-level feature selection, ACC: accuracy, ANN: Artificial neural network, BERT: Bidirectional encoder representations from transformers, BiGRU: Bidirectional gated recurrent units, BiLSTM: Bidirectional long short-term memory, BiTCN: Bidirectional temporal convolutional network, CBR: Case-based reasoning, CNN: Convolutional neural network, DNN: Deep neural network, ESM2: Evolutionary scale modeling 2, ET: Extra tree, FSCM: Frequency of solvent contacted motifs, GBDT: Gradient boosting decision tree, GBM: Gradient boosting machine, GCN: Graph convolutional network, GIN: Graph isomorphism network, GLM: Generalized linear model, GNN: Graph neural network, HMM: Hidden markov model, IBK: Instance-Based K-nearest neighbor, KNN: k-Nearest Neighbors, KSAAP: K-spaced amino acid pairs, LightGBM: Light gradient boosting machine, LSTM = Long short-term memory, MCC: Matthew's correlation coefficient, ML: Machine learning, MSAs: Multiple sequence alignments, MvRL: Multiview representation learning, PNN: Probabilistic neural network, QDA: Quadratic discriminant analysis, QSVM: Quantum support vector machine, RF: Random forest, RNN: Recurrent Neural Networks, RRVM: Random relevance vector machines, SA-HMM: Structural alphabet hidden markov model, SP: Specificity, SV: Sensitivity, SVM: Support vector machines and SVM-RFE: Support vector machine - recursive feature elimination.

learning-driven (quantitative structure–activity relationship QSAR models) are potential resources to predict how snake venom-derived peptides may interact with specific biological targets, helping to clarify the mechanisms of action [397]. For the structural analysis of shorter peptides (fewer than 40 amino acids), PEP-FOLD4 stands out as an innovative strategy, enabling simulations under diverse conditions, such as different pH levels and ionic strengths. This represents significant progress, as the heterogeneous nature of the tumour environment can pose challenges to peptide activity [394]. Usually, cancer cells typically establish an acidic extracellular zone due to metabolic shifts, while also exhibiting ionic strength variations resulting from hypoxia, altered ion transport, and metabolic changes [398]. These challenges, however, present opportunities for the development of pH-responsive or ion-sensitive drug delivery systems [399]. Lastly, tools discussed in this third phase can be incorporated into the initial step to promote a more target-centric approach for identifying anticancer peptides. We aimed to present a logical and sequential perspective based on the authors' experience. However, readers should also consider the possibility of applying these tools in parallel at different steps or in varying orders.

Once peptide leads are identified and their mechanisms elucidated, an optimization step becomes essential to fine-tune their desired effects while minimising side effects, ultimately producing more promising preclinical candidates [400]. In the traditional pathway, this involves the large-scale synthesis of molecules and the evaluation of numerous candidates while exploring optimisation possibilities. Various peptide sequence reconstruction/engineering approaches can be employed, but selecting the most effective method remains a significant challenge [400]. At this stage, AI-driven models can play a pivotal role in guiding the process [400]. However, a major limitation is the small number of available models, largely due to the scarcity of data. Most existing tools primarily focus on analysing peptide analogues, often restricted to substitutions of natural amino acids [318,346].

A shorter pathway that bypasses the multiple steps of this workflow has been employed in some studies [401,402]. Repurposing strategy is also a valuable strategy in peptide drug discovery [403]. This phenomenon has been observed primarily with antimicrobial peptides (AMPs) [404]. Various studies have characterised the dual or multiple actions of AMPs, making them promising candidates for anticancer applications [404,405]. A similar approach has been documented in snake venom, where certain antimicrobial toxins or peptides exhibit combined effects [159,250]. This dual functionality is particularly promising, as it offers the potential to combat infections and cancer simultaneously, a valuable advantage in clinical settings, given the frequent co-occurrence of these conditions in oncology patients [406]. Thus, repurposing existing selective peptides can accelerate progress, eliminating the need for extensive assessments of toxicity or other parameters, as these peptides have already been well-characterised during their development for prior applications.

Lastly, the progress of one peptide candidate is beyond its activity and toxicity, as they also need to meet drug-like properties [407,408]. Basically, the experimental assessment of ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) is complex due to its multicomponent nature and demands resource-heavy investments, specialised and high-cost equipment and long durations [409]. Pharmacokinetics and pharmacodynamics, encompassing various aspects such as stability, absorption, distribution, metabolism, excretion and toxicity, represent critical barriers to achieve incremental discovery gains [410]. However, in recent years, significant efforts have been made to capture ADMET profiles using AI-driven approaches [411]. Several algorithms have been developed to evaluate individual parameters, and examples of these methods are emerging [301]. Although more complex, some researchers have begun exploring multicomplex systems to provide comprehensive ADMET profiling [301,412]. Despite these advancements, further refinement and the generation of more data are essential to expand the training and testing datasets, ultimately achieving improved performance metrics.

From a broad perspective, wet-lab approaches for studying snake venom-derived peptides provide high biological relevance and direct validation, but they are slow, costly, and resource-intensive [287]. On the other side, AI-driven methods accelerate discovery, reduce costs, and enable high-throughput screening, but they require extensive training data and experimental validation to ensure accuracy [413]. With this in mind, a hybrid approach combining AI predictions with wet-lab validation may offer the most effective strategy for venom peptide screening and drug discovery

Our critical analysis of the available tools suggests that the rise of AI in peptide discovery has not been matched by efforts in experimental validation. Our observations reveal that while many available tools demonstrate high performance metrics, they often lack an essential *in vitro* or *in vivo* confirmation step [324,414,415]. In this context, we utilised the sequences of previously characterised anticancer snake-venom peptides along with AI-based tools to cross-check the correlation between AI predictions and experimental findings. To achieve this aim, we used freely accessible tools with user-friendly interfaces to evaluate the potential activity, toxicity, and structure of snake venom-derived peptides. We selected at least two predictors for comparative analysis of each peptide's properties. These included Colab-Fold2 [393] and PEP-FOLD4 [394] for secondary structure analysis; AntiCP2.0 [318], MLACP2.0 [346], and AI4ACP [416] for anticancer predictions; HemoPi2 [370] and HLPpred-Fuse [360] for haemolytic assessments; and CSM-toxin [381] and ToxinPred3.0 [384] for toxicity predictions. All *in silico* findings are summarised in the Table 6.

Table 6
Practical applications of AI-based tools in anticancer snake venom-derived peptides. The sequences of snake venom-derived peptides, identified in the literature as anticancer molecules, were screened using AI-based tools to predict their anticancer properties, haemolytic activity, toxicity, and structure. At least two software tools from each category were employed for comparative analysis. The colours represent the structure or activity of the snake-venom derived peptides as predicted by computational approach: pink indicates β-sheets, purple represents α-helices, yellow denotes non-anticancer activity, green signifies anticancer activity, blue indicates non-haemolytic activity, red represents haemolytic activity, orange denotes non-toxic peptides, and grey indicates toxic peptides.

Peptides	Secondary structure		Anticancer activity			Haemolytic activity			Toxicity				
	Colab- fold (1.5.5)	Pep-Fold 4	AntiCP 2.0	MLACP 2.0	AI4ACP	HemoPi	HemoPi 2	HLPpred-Fuse	Toxin Pred1.0	ToxDL	Toxin Pred2.0	CSM -toxin	Toxin Pred 3.0
Oxineur	α-helix	α-helix	Non-ACP	ACP	Non-ACP	Non-Haem	Non-Haem	Non-Haem	Toxic	Toxic	Toxic	Non-toxic	Toxic
NN-32	ND	ND	ACP	ACP	Non-ACP	Non-Haem	Non-Haem	Haem	Toxic	Toxic	Toxic	Non-toxic	Toxic
Crotalicidin (Ctn)	α-helix	α-helix	ACP	ACP	ACP	Haem	Haem	Haem	Non-toxic	Toxic	Non-toxic	Non-toxic	Toxic
Crotamine	β-sheet	β-sheet	ACP	ACP	ACP	Non-Haem	Haem	Haem	Toxic	Toxic	Toxic	Non-toxic	Non-toxic
pEM-2	α-helix	α-helix	ACP	ACP	ACP	Haem	Non-Haem	Haem	Non-toxic	Toxic	Toxic	Non-toxic	Toxic
pepBthTX-I	α-helix	α-helix	ACP	ACP	ACP	Non-Haem	Non-Haem	Haem	Non-toxic	Toxic	Toxic	Non-toxic	Toxic
pBmje	α-helix	α-helix	Non-ACP	ACP	Non-ACP	Non-Haem	Non-Haem	Haem	Non-toxic	Toxic	Toxic	Non-toxic	Toxic
p-AppK	α-helix	α-helix	ACP	ACP	ACP	Non-Haem	Non-Haem	Haem	Non-toxic	Toxic	Toxic	Non-toxic	Toxic
p-Acl	α-helix	α-helix	ACP	ACP	ACP	Non-Haem	Non-Haem	Haem	Non-toxic	Toxic	Toxic	Non-toxic	Toxic
pepMTX-I	α-helix	α-helix	Non-ACP	ACP	ACP	Non-Haem	Non-Haem	Haem	Non-toxic	Non-toxic	Toxic	Non-toxic	Toxic
pepMTX-II	α-helix	α-helix	ACP	ACP	ACP	Non-Haem	Non-Haem	Haem	Non-toxic	Toxic	Toxic	Non-toxic	Toxic
AACT	β-sheet	β-sheet	Non-ACP	Non-ACP	Non-ACP	Non-Haem	Haem	Non-Haem	Non-toxic	Toxic	Toxic	Non-toxic	Non-toxic
3-NAntC	β-sheet	β-sheet	Non-ACP	Non-ACP	Non-ACP	Non-Haem	Non-Haem	Non-Haem	Non-toxic	Toxic	Toxic	Non-toxic	Non-toxic
BF-30	α-helix	α-helix	Non-ACP	ACP	ACP	Non-Haem	Haem	Haem	Non-toxic	Toxic	Toxic	Non-toxic	Toxic
Cbf-K_{16}	α-helix	α-helix	Non-ACP	ACP	ACP	Haem	Haem	Haem	Non-toxic	Toxic	Toxic	Non-toxic	Toxic
Ctn [1-14]	α-helix	α-helix	ACP	ACP	ACP	Haem	Non-Haem	Haem	Non-toxic	Toxic	Toxic	Non-toxic	Toxic
Ctn [15-34]	α-helix	α-helix	ACP	ACP	ACP	Non-Haem	Non-Haem	Haem	Non-toxic	Toxic	Non-toxic	Non-toxic	Non-toxic

The structural analysis highlighted a predominance of α-helix peptides, consistent with trends commonly reported in anticancer peptide discovery. Both tools produced similar predictions. However, this level of agreement was not observed for anticancer, haemolytic, and toxicity predictions. Computational discrepancies may arise from differences in training datasets, testing datasets, and performance metrics. Notably, significant differences were identified between AI predictions and experimental findings, particularly in anticancer predictions. While all evaluated peptides demonstrated *in vitro* activity as described in the literature, some software tools inaccurately predicted non-activity. These observations underscore several key takeaways. First, as previously discussed, the quality and quantity of data are critical [417]. Variability in the datasets used to train these models, including cell lines and experimental conditions, likely contributes to the observed discrepancies [418]. Some models may exhibit biases toward specific cell lines, whereas the testing of snake venom-derived peptides was conducted on different ones. Second, these findings emphasise the need for more extensive experimental validation. Although AI-based tools show great promise, additional efforts are necessary to create robust and representative datasets to advance their development. Third, the threshold used in selecting anticancer peptides can be a critical factor. For example, pBmje exhibits activity, but only at higher concentrations [121]. This suggests that some AI models may primarily capture anticancer peptides that exhibit stronger activity at lower concentrations. Finally, while AI tools can greatly enhance peptide development, leveraging human expertise in synergy with these emerging technologies is essential to overcome current limitations. This small-scale analysis presented in this review highlights both the potential and limitations of AI. Undoubtedly, the peptide drug discovery agenda stands to benefit significantly from the ongoing AI-driven revolution. Concurrent advancements in data generation through high-throughput screening will enable more accurate and realistic training scenarios, ultimately enhancing the robustness, efficiency, and cost-effectiveness of AI applications.

6. Cutting-edge approaches applied to venom research: Expanding the horizons in anticancer peptide discovery and development

The success in identifying anticancer peptides within snake venom proteome libraries will rely on multidisciplinary approaches that integrate multiple systems. The conceptual framework must evolve to incorporate novel technologies for the obtention of peptides and also for their evaluation. In the previous section, we reviewed the virtual screening process powered by the progressive incorporation of AI. In this section, we explore innovative approaches that have been applied to

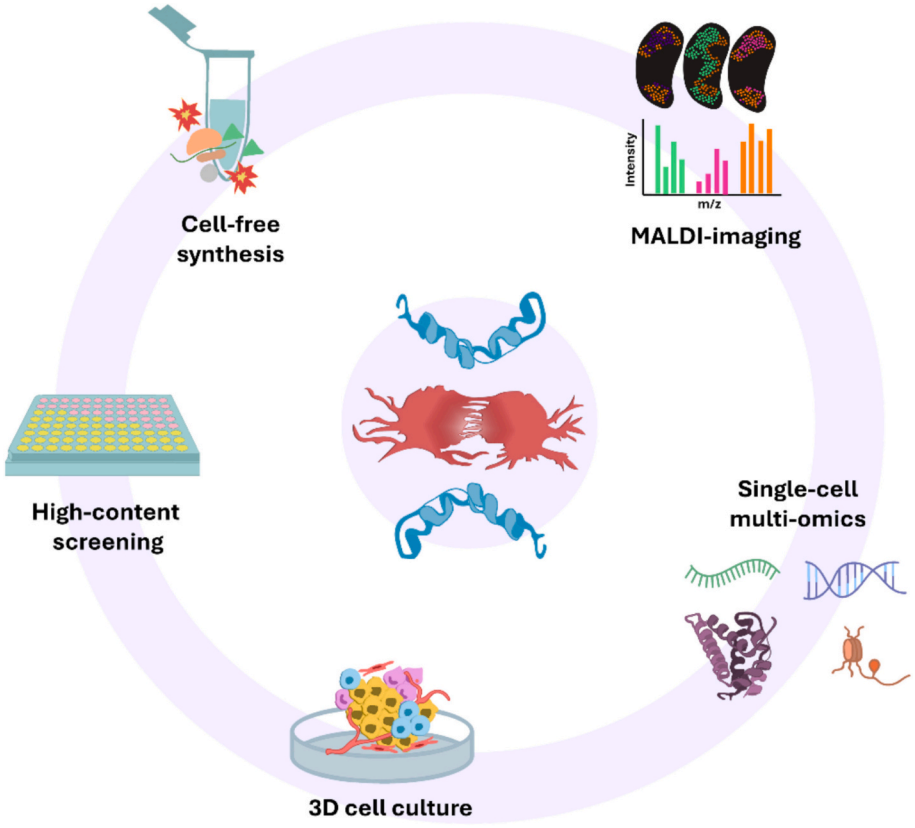

Fig. 6. The future experimental landscape of venom-based anticancer research. Cutting-edge technologies can be implemented in venom screening of anticancer candidates to capture tissue responses to snake venom-derived peptides and disease-related molecular events at the single-cell level. Broadly, these tools generate multichannel molecular readouts, offering a more detailed picture of cellular diversity, pathological states, and responsiveness to anticancer candidates.

cancer drug discovery and can be repurposed to better capture the potential snake venom-derived peptides. From our perspective, repurposing the principles and capabilities of these approaches can help identify optimal candidates, thereby enhancing the accuracy and success of snake venom screenings.

Fig. 6 outlines five technical avenues with the disruptive potential to influence the discovery of anticancer peptides from snake venoms. Our focus includes cell-free synthesis, MALDI imaging, single-cell multi-omics, high-content analysis, and 3D cell culture techniques. The application of these methods can expand the scope and depth of information obtained, enabling the screening of a larger number of peptides while providing insights within a more realistic pathological context. We provide a concise overview of the principles underlying these technologies, accompanied by some examples of their practical applications in cancer drug discovery. Lastly, we explore how they can be integrated into the peptide discovery pipeline to highlight their potential contributions.

6.1. *Cell-free synthesis*

Cell-free synthesis is a promising DNA-based bioproduction platform, where biomolecules can be produced under *in vitro* conditions without using intact cells [419]. The principle behind this application involves the reproduction of key biochemical processes, such as transcription and translation, in an open reaction environment [420]. Two main approaches have emerged: one based on the use of purified recombinant elements (bottom-up), and the other relying on crude cell extracts (top-down) [421]. Both approaches share the characteristic of offering an open system where enzymes operate and biochemical processes occur, which can be easily manipulated for biotechnological applications. The applicability of this synthetic tool has expanded beyond their initial purpose of deciphering genetic information, evolving into a versatile platform for the production of bioactive molecules with therapeutic potential [422]. In fact, cell-free synthesis overcomes the challenges associated with chemical peptide synthesis and DNA recombinant cell-based systems, enabling the production of sufficient quantities of material for high-throughput assays [423].

The great potential of this technique has been explored to produce anticancer agents. One example is the "just-add-water" lyophilized cell-free system, developed for the rapid production of onconase (ranpirnase), an anticancer candidate currently undergoing phase III clinical trials as a novel therapy for mesothelioma [424]. By harnessing the open and stable nature of this approach, the authors successfully obtained a final product with high solubility and an active form, eliminating the need for expensive purification processes. Notably, the lyophilised form retains its activity even after being stored above freezing for up to one year.

To the best of our knowledge, this innovative technology has yet to be applied in anticancer peptide discovery. However, as a proof-of-principle, a pioneer study has combined deep learning with cell-free synthesis to discover antimicrobial peptides [245]. The authors have screened 500 potential AMP. Six novel peptide templates with broad-spectrum antibacterial activity were reported, showing no evidence of bacterial resistance. The findings validate the ability of these biotechnological tools to efficiently produce and screen a large number of peptides within a short timeframe. The advancements achieved in antimicrobial peptide research may offer valuable solutions for the discovery of snake venom-derived peptides with anticancer properties.

6.2. *MALDI Imaging mass spectrometry (MALDI IMS)*

A second methodological approach with potential to bring the

screening of snake venom-derived peptides to the next level is MALDI IMS. This *in situ* approach has actively transformed our understanding of tissue-based research, providing spatial maps of the distribution of biomolecules and metabolites within the analysed samples [425]. The operation of MALDI imaging systems involves the sequential acquisition of single mass spectra across a tissue section at specific spatial locations. Generally, in the first step, thin sections of tissues are collected and mounted onto glass slides. Then, they are coated with a light-absorbing matrix to enable the desorption and ionisation of analytes. Finally, ions are generated by laser irradiation at each position, producing informative spectra that are used to build representative spatial distribution maps of molecules of interest [425]. More details on sample preparation and workflow can be found in the following review articles [426–429]. Of particular note, the region-specific molecular measurements are invaluable for characterising heterogeneous tissues, such as tumours [430].

Historically, the principles of this molecular imaging technology have formed the basis of many diagnostic projects aimed at identifying key differential biomarkers for the early diagnosis of cancer [431]. However, the versatility and richness of the information can also be explored in anticancer drug discovery [432]. Gradually, we have observed its use to catalogue the distribution of drugs, assess responses, and evaluate toxicity. Although no examples have been found for anticancer peptides, its application has proven useful in the assessment of other anticancer candidates or existing drugs [433,434]. Therefore, these applications in cancer research open avenues for its routine use in peptide-treated cancer tissues to understand their actions, distribution, and spatial responses.

6.3. Single-cell multi-omics

The study of complex networks in heterogeneous cancer tissues demands high-resolution analytical techniques to provide an integrative view of multiple cellular events. One front that addresses this involves single-cell multi-omics. This approach harnesses the methodological and technological advances in the toolbox of omics modalities, such as transcriptomics, genomics, proteomics, metabolomics, and other emerging omics technologies, to explore multiple layers of information at the cellular levels [435]. Basically, they are designed to identify and quantify thousands of cellular components resulting in a system-level view of biological processes [436]. Given the inherent cellular complexity and diversity, single-cell omics tools have been integrated into platforms for dissecting molecular programs and creating data-rich contexts that provide a more holistic snapshot of the cellular landscape with intricate details [437].

Multi-omics approaches continue to be developed, but they have already been adopted in anticancer screening to interrogate how cancer tissue responds to existing drugs or potential novel anticancer candidates. For instance, Veggvari et al. (2022) utilized a single-cell proteomics platform to achieve cellular resolution of the time-resolved responses of adenocarcinoma A549 cells to three anticancer agents: camptothecin, methotrexate, and tomudex. This workflow offered a temporal perspective on the emergence of heterogeneous cellular populations following drug treatment and successfully corroborated drug targets previously identified in other studies [438]. Moving from cell culture under *in vitro* conditions, single-cell omics has also found applications in screening the responses of patient tumours, facilitating the identification of therapeutic candidates [439].

The impact of peptides on cancer cells continues to be predominantly analysed using bulk omics technologies, with limited advancements toward achieving a more granular perspective [440]. Regarding snake venom-derived peptides, our bibliographic search did not reveal the application of either single-cell approaches or bulk omics technologies. However, the expanding repertoire of experimental protocols for single-cell omics analysis, coupled with the successful characterisation of therapeutic responses in heterogeneous cell populations, offers novel opportunities and dimensions to enhance snake venom profiling. This advancement could lead to a precision-level understanding of the mechanisms underlying anticancer peptide candidates.

6.4. High-content screening

High-content imaging is a cell-based approach built upon advancements in automated microscopy, fluorescence detection, advanced imaging, data analytics and multiparameter algorithms, with notable progress in resolution capabilities [441]. This technology enables the monitoring of phenotypic alterations in cell populations [442]. With its ability to accurately capture spatio-temporal changes when cells are exposed to drug candidates, it represents a promising tool for early-stage discovery efforts [443]. The large volume of imaging data associated with phenotypic patterns can be efficiently managed using AI-based models, which aid in optimising the anticancer screening process and successfully identifying superior candidates [444].

The potential in anticancer drug discovery has been illustrated in some studies. In a large-scale screening of a library comprising 349 compounds, high-content analysis was used to facilitate the identification of lead candidates for neuroblastoma treatment [445]. The examination of this extensive chemical library focused on the viability of 3D multicellular spheroids, employing a cell-permeant dye (Calcein-acetoxymethyl) that is enzymatically converted into green fluorescent calcein exclusively in viable cells. Images of the treated spheroids were captured, and both the area and intensity were analyzed. This initial layer of experimentation guided the selection of hits, ultimately leading to the repurposing of a tyrosine kinase inhibitor for subsequent preclinical investigations in neuroblastoma animal models. In a similarly high-throughput manner, an efflux assay was developed to examine the potential interactions of 386 anticancer agents with multidrug resistance protein 1 [446].

In summary, high-content imaging-based assays have significantly enhanced our capacity for drug screening. Although not yet applied in the anticancer peptide field, they offer many reasons for a proof-of-concept study. Their robustness, cost-effectiveness, and efficiency make them well-suited for screening platforms designed to evaluate complex mixtures, such as snake venoms. Integrating automated image acquisition and analysis into early discovery workflows for snake venom-derived peptides could facilitate the screening of a greater number of candidates.

6.5. 3D cell culture systems

For decades, 2D-based systems have been the cornerstone of anticancer screening due to their ease of implementation, low cost, and well-established protocols [447]. However, recent studies have highlighted the inability of these models to replicate the metabolic and proliferative gradients characteristic of the tumour microenvironment [448]{Abbas, 2023 #430]}. Indeed, their morphology and functional properties differ significantly from those *of in vivo* tissues [449]. Consequently, the predictive accuracy of this approach remains limited. To address these shortcomings, various 3D models have been developed, offering a more accurate representation of tissue architecture and a physiologically relevant platform for screening novel anticancer agents [450,451].

In the field of anticancer peptide discovery, a comparative analysis has highlighted the differential sensitivity of spheroids and monolayers to the action of synthetic peptides against breast cancer [452]. The 3D environment required a higher concentration of peptides compared to the simplistic nature of the 2D model system. Along the same lines, another study evaluated the effects of lactoferricin-inspired peptides on melanoma using both 2D and 3D models [453]. Although some peptides influenced the survival of both cell models, no direct correlation was observed, as a peptide demonstrating high activity in monolayer cultures did not exhibit the same efficacy in a more complex environment. Taken together, these studies emphasise the need to incorporate robust

models during the early stages of anticancer peptide drug discovery.

Although progress in snake venom bioprospecting has been slow, there are notable examples of the adoption of 3D microenvironment cell cultures [454]. Large venom biomolecules, such as PLA_2s [157,455,456], metalloproteases [457], and L-amino oxidases [457], have been evaluated using 3D tumour spheroid models. Shifting to smaller components, a synthetic analogue of crotamine, a cell-penetrating peptide, demonstrated the ability to infiltrate melanoma-based spheroid models [458]. This property is particularly valuable for the development of drug delivery carriers and as a research tool to investigate tumour microenvironments [459].

Overall, by combining the potential of these multiple approaches discussed above and integrating them into the anticancer screening of snake venoms, pharmaceutical companies and researchers can make significant progress in identifying more suitable candidates and reducing the risks of failure. The multilayered biological information provided by these emerging technologies is already appearing in the anticancer discovery pipeline and should benefit the development of "oncovenomics." These methodological options highlight both promising opportunities and the necessity of rethinking the experimental approach to discovering and developing snake venom-derived peptides.

7. Translational challenges and strategies in snake venom-derived peptide development

Despite the pharmacological potential of snake venom–derived peptides, their translation from discovery to clinical application remains slow and challenging, with important obstacles comparable to those encountered by other peptides of natural origin [460]. Understanding and addressing these barriers is essential to promote the transformation of venom-derived peptides into viable anticancer agents, mirroring the success already achieved in cardiovascular and haematological medicine, where venom-inspired drugs have been approved [92,99]. In this section, we explore translational challenges, such as toxicity, the *in vitro–in vivo* gap, immunogenicity assessment, and regulatory hurdles, and summarises strategies aimed at overcoming them.

7.1. Inherent cytotoxic properties of venom peptides

A significant obstacle to the clinical translation of some venom-derived peptides in oncology is their inherently cytotoxic nature [97]. Snake venoms comprise a mixture of toxic molecules that act rapidly on tissues, leading to cell death [97,461]. Despite evidence of partial selectivity in some snake venom peptides and toxins, fine-tuning their toxicity to maximise therapeutic benefit remains a critical barrier to increase drug productivity discovery and development [93]. Many of these molecules, disrupt cell membranes, modulate ion channels, or interfere with signalling cascades conserved across different cell types [92]. While such mechanisms can effectively kill cancer cells, they also risk damaging healthy tissues, thereby limiting their therapeutic window [95].

To mitigate this challenge, strategies have been employed, including shortening peptide sequences or designing smaller peptide analogues based on toxin fragments, with the aim of maximising therapeutic activity while reducing toxic effects [121,250]. On a broader scale, emerging approaches already applied in cancer drug development, such as the conjugation of peptides with tumour-specific ligands (e.g., monoclonal antibodies, aptamers, or receptor-specific peptides) offer avenues to enhance selectivity [462]. Similarly, nanoparticle-based delivery systems [463] could serve as tools to improve the delivery and therapeutic index of venom-derived peptides. Collectively, these strategies provide opportunities to advance snake venom peptides towards safer therapeutic applications.

7.2. Bridging the in vitro–to–clinic gap

Our previous analysis of current research on venom-derived peptides revealed a predominance of *in vitro* investigations, with comparatively few studies progressing to *in vivo* evaluation. The transition from promising *in vitro* findings to successful clinical translation remains a major bottleneck in the field. Although these peptides frequently demonstrate potent biological activity in cell-based assays, their advancement into animal-based studies and clinical trials is often limited by challenges common to peptide therapeutics, such as poor pharmacokinetic performance, susceptibility to enzymatic degradation, and short systemic half-life. These limitations collectively reduce efficacy in *in vivo* contexts, underscoring the need to enhance peptide stability and bioavailability for translational success [464].

To address these constraints, snake venom–derived peptides may benefit from the chemical optimisation strategies that have enabled other therapeutic peptides to achieve clinical use in oncology, as illustrated in Table 1. Peptides used in clinical settings are usually chemically modified to improve their properties. The discovery phase of oncolytic peptides from snake venoms has identified several promising candidates; however, greater effort is required during the optimisation phase, which should incorporate chemical modifications aimed at improving the stability, bioactivity, and formulation of these peptides. Advances in peptide chemistry have introduced a range of versatile modifications to improve stability and anticancer activity of peptide candidates [465]. Cyclisation, either through head-to-tail linkages or the introduction of disulphide bonds, can confer conformational rigidity and resistance to proteolysis [466]. Another approach involves replacing L-amino acids with their D-enantiomers or incorporating non-natural amino acids, which can protect peptides from enzymatic degradation while preserving their anticancer properties [275]. Additional alternatives, such as PEGylation and lipidation, enhance solubility and extend circulation time, thereby improving pharmacokinetic profiles [467]. From our perspective, when combined with targeted delivery systems, these chemical strategies hold promise for bridging the gap between laboratory discovery and clinical application of venom-derived peptides. Greater emphasis on peptide engineering will be essential to fully harness the anticancer potential of these short molecules and bring them to the market. Theoretically, peptide engineering could address the main barriers preventing snake venom–derived peptides from advancing to the market, similar to its role in the development of other FDA-approved oncolytic peptides.

7.3. Immunogenicity considerations for snake venom–derived peptides

Immunogenicity is often overlooked in the evaluation of anticancer snake venom–derived peptides, as noted in our review. Owing to their relatively short amino acid sequences, these peptides are generally assumed to exhibit low immunogenic potential, similar to other therapeutic peptides [61]. However, an assessment of their immunogenicity, integrating *in silico* epitope prediction, *in vitro* immune assays, and *in vivo* antibody monitoring, remains largely lacking for most venom-derived candidates. Implementing this approach would provide insights into their safety profiles and inform the rational design of next-generation snake venom–derived peptide therapeutics.

Within this context, multiple strategies, including AI models [468], can be integrated into the evaluation of venom-derived peptides to mitigate immunogenicity risks. Rational sequence engineering can attenuate immunodominant epitopes while preserving anticancer efficacy [469]. On the other hand, humanisation of peptide motifs represents an alternative approach to minimise immune recognition [470]. Similarly, encapsulation within liposomal or biodegradable nanoparticle formulations may serve to reduce systemic exposure and subsequent antigen presentation [471]. Irrespective of the strategy adopted, the incorporation of early immunogenicity assessment into preclinical development pipelines is crucial for the identification and management

of immune-related risks, thereby strengthening the translational potential and clinical viability of venom-derived peptide therapeutics.

7.4. From snake venom to bedside: regulatory and developmental perspectives

The clinical translation of venom-derived peptides requires adherence to regulatory frameworks that ensure safety, efficacy, and quality, similar to other anticancer drugs [472]. Regulatory oversight begins at the sourcing stage, as many countries that are signatories to the Nagoya Protocol require permits to access biological materials and genetic information from snake venoms [473]. From venom extraction to market approval, these molecules follow a process that includes preclinical studies and phased clinical trials, consistent with the development pathway of other pharmaceuticals.

Preclinical development of venom-derived peptides involves toxicological profiling, safety pharmacology, and pharmacokinetic studies to define safe dosage ranges and identify off-target effects using cell-based and animal-based assays. Only a few snake venom–derived peptides have undergone preclinical evaluation to date. Regulatory agencies require detailed dose–response data and toxicity assessments before first-in-human trials. Clinical development follows the standard phased approach: Phase I safety and dose-escalation studies, Phase II efficacy and dosing trials, and Phase III confirmatory trials in large groups. Lastly, phase IV of clinical development takes place once the drug has entered the pharmaceutical market [474].

Despite these challenges, successful examples provide a path forward. Captopril, derived from bradykinin-potentiating peptides in *Bothrops jararaca* [146], and eptifibatide, based on a disintegrin from *Sistrurus miliarius*, show how snake venom-inspired molecules can become approved drugs [92]. In oncology, crotoxin from *Crotalus durissus terrificus* reached Phase I clinical trials for advanced solid tumours, demonstrating the potential of venom-derived peptides despite toxicity-related limitations [475].

8. Concluding remarks and forward-looking perspectives

Snake venoms represent a promising and valuable peptide-based cancer drug discovery and development platform. However, to fully harness the inherent cytotoxic potential of snake venom-derived peptides, key lessons from developing licensed peptide-based drugs must be applied to overcome existing bottlenecks (toxicity and low translational success rate). First, while membrane-active and direct-acting peptides are attractive anticancer candidates, the early stages of discovery should prioritise exploring intracellular mechanisms that align with the first-line actions of currently FDA-approved peptides. Second, rational peptide design and engineering must be employed to modify and optimise natural sequences, enhancing their stability and efficacy for routine therapeutic implementation.

Adopting a pathway-centric high-throughput approach integrated with super-resolution imaging, and single-molecule methodologies can drive the emergence of the “oncovenomics” field. The adoption of 3-D physiologically relevant cancer models, co-cultures, exploration of a broad range of venoms beyond the membrane-active and abundant components, together with a wider range of cancer and healthy cells, can represent a transformational step with more translatable findings. The integration of multisystem approaches and a broader perspective can enhance the success of snake venom-derived peptides as practical solutions to combat various malignancies. The consolidation of “oncovenomics” demands a multidisciplinary approach and an integrative perspective, bringing together teams primarily composed of toxinologists, biochemists, medicinal chemists, pharmaceutical scientists, organic synthetic chemists, molecular biologists, cancer biologists, clinicians, and computer scientists.

The large-scale discovery of anticancer venom-inspired peptides requires automation and advanced tools to accelerate the transition from venom toxin identification to vitro/pre-clinical screening, thereby maximising the chances of success. AI-driven approaches serve as a critical bridge, linking libraries of venom components identified through transcriptomics and proteomics and the advantages stage of drug discovery. In this era, algorithms and models can capture biochemical and structural patterns relevant to bioactivity prediction, guiding the selection of promising peptides from broad-spectrum venom toxin libraries. A key challenge remains the limited number of anticancer venom toxins and peptides identified to date, as highlighted in our review. However, exploring databases of anticancer peptides from diverse sources can facilitate this process and support the effective integration of AI into the “oncovenomics” platform.

The venom-based drug discovery agenda is heavily influenced by legal frameworks, which can slow the development of novel therapeutics. Accessing the genetic information of snake venoms is subject to various regulations. For instance, many countries require official permits, ethical approvals, and agreements with local communities or institutions for the collection and study of snake venoms. The Nagoya Protocol serves as the primary legal instrument, though national laws are also enforced in some countries. Another challenge is that regions with high snake biodiversity are predominantly located in tropical and developing countries, where research funding is often limited. In this context, extensive legal knowledge, bioprospecting agreements, and international research partnerships are essential to ensuring compliance while advancing venom-inspired therapies. Additionally, the inclusion of lawyers and marketing specialists is crucial in the team developing venom-derived peptides as anticancer agents, aiding in regulatory navigation and commercialisation strategies.

Collectively, snake venom-inspired peptides are poised for a golden era of discovery, facilitated by versatile computationally-based and high-throughput innovative screening systems. As outputs, novel specific molecular targets, fast-acting and effective killing mechanisms, and unique chemical structures will serve as the foundation for a more successful advancement of snake venom-derived peptides in anticancer drug discovery. These innovations can unlock exciting possibilities and revolutionise our clinical capacity to combat the societal impact of cancer diseases.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review article.

Data availability

The data supporting the findings of this review article are available within the article.

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