Biomedicine & Pharmacotherapy 163 (2023) 114832

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

Evolving strategies and application of proteins and peptide therapeutics in cancer treatment

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ARTICLE INFO

Keywords:
Protein
Anticancer
Targets
Therapeutics
Immune checkpoint

ABSTRACT

Several proteins and peptides have therapeutic potential and can be used for cancer therapy. By binding to cell surface receptors and other indicators uniquely linked with or overexpressed on tumors compared to healthy tissue, protein biologics enhance the active targeting of cancer cells, as opposed to the passive targeting of cells by conventional small-molecule chemotherapeutics. This study focuses on peptide medications that exist to slow or stop tumor growth and the spread of cancer, demonstrating the therapeutic potential of peptides in cancer treatment. As an alternative to standard chemotherapy, peptides that selectively kill cancer cells while sparing healthy tissue are developing. A mountain of clinical evidence supports the efficacy of peptide-based cancer vaccines. Since a single treatment technique may not be sufficient to produce favourable results in the fight against cancer, combination therapy is emerging as an effective option to generate synergistic benefits. One example of this new area is the use of anticancer peptides in combination with nonpeptidic cytotoxic drugs or the combination of immunotherapy with conventional therapies like radiation and chemotherapy. This review focuses on the different natural and synthetic peptides obtained and researched. Discoveries, manufacture, and modifications of peptide drugs, as well as their contemporary applications, are summarized in this review. We also discuss the benefits and difficulties of potential advances in therapeutic peptides.

1. Introduction

Cancer is the primary concern for public health authorities worldwide due to its high mortality rates [1,2]. The cell surfaces receptors like metalloproteases (MMPs) and extracellular matrix (ECM) remodelling develop aggressive and metastatic cancers [3,4]. The main reason behind cancer progression is the blocking of chemotherapeutic drugs from reaching the target site [1]. Hence, several proteins and peptides involved in tumor progression and cancer metastasis can be identified and targeted for cancer therapy. Peptides are small-sized molecules, around 40 amino acids or less, which can be derived either naturally or developed synthetically [5-10]. Mainly, the naturally derived peptides must be modified using several chemical processes to use them in cancer therapeutics. These peptides can target the tumors at their specific site

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https://doi.org/10.1016/j.biopha.2023.114832
Received 9 February 2023; Received in revised form 18 April 2023; Accepted 30 April 2023
Available online 5 May 2023

or deliver a particular anticancer drug to the tumor site, becoming one of the most promising ways to treat cancer. Several types of peptides can be created, and the focus can be made towards targeting the homing ability of the mesenchymal stem cells (MSCs), targeting the function of the ligand/receptor, targeting a particular organelle like the mitochondria, or directly entering into the nucleus of the tumor cells to induce apoptosis and cell death [6]. Hence, these techniques can be utilized to develop peptide conjugates that can enhance the tumor cells' apoptosis and help in cancer therapy.

Proteins' advantages over small-molecule medications have contributed to their meteoric rise in the pharmaceutical industry. Compared to small molecule medications, the binding surface area of protein therapies is much larger, making it possible to access a broader set of protein targets [11,12]. On the other hand, small molecule medicines are generally buried within a hydrophobic pocket of their protein binding partner to optimize hydrophobic interaction and generate a more stable complex [13]. It effectively eliminates pockets in inaccessible proteins from becoming a target. Second, enhancing their present capabilities or installing new activities is a standard method of protein therapeutic adaptation [14,15]. Protein treatments, not often taken orally like small molecule medications, can benefit from significantly less frequent dosages due to their longer blood circulation duration [16].

Historically, monoclonal antibodies (mAbs) have been demonstrated to have approximately double the overall approval rate and much faster USA FDA approval success times than small compounds [17-19]. Twenty percent of small molecule medications made it through Phase II trials in 2015, compared to forty percent of large molecules. Phase III approval rates for small-molecule medications were also lower than those for large molecules (79% vs 65%). Although protein treatments have many advantages, small-molecule medications also have several advantages, including oral bioavailability, intracellular targeting, simplicity of production, and relatively extended shelf life. Nonetheless, there is great interest in further developing this class of medications because of the enormous promise of protein therapies in cancer treatment [20,21]. Therefore, these therapies using proteins can be a promising, therapeutic, highly effective, efficient, and safe treatment method for cancer patients and enhance the therapeutic efficacy of the anticancer drugs utilized in cancer treatment.

This review explains the significance of identifying the proteins involved in cancer progression and developing treatments that can help in accurately targeting the tumor site, proteins, miRNAs, and transcription factors and increasing the efficiency of cancer therapy. Understanding the therapeutic peptides utilized for cancer treatment includes anticancer agents like pro-apoptotic and D-peptides. Tumour-targeting peptides can enhance cancer treatment via newer techniques – cell penetration peptides (CPP) at a nuclear and mitochondrial level, exosomal proteins, immune checkpoint proteins such as PD-1/PD-L1 proteins, CTLA-4 proteins, VISTA proteins, and tumor microenvironment targeting peptides for targeting the tumor vasculature, the extracellular matrix, tumour-associated macrophages (TAMs) and the response of the tumor microenvironment by altering the pH and temperature. The molecular-based targeted therapies where mAb, epigenetic alterations, and RTKs can weaken cancer cells from within and prevent tumor metastasis [22-24]. These can act as drug-delivery systems for several types of anticancer drugs like paclitaxel and cisplatin and can help in the specific drug release to the target tumor site [22,25,26]. These receptor-mediated drug delivery technologies can help treat cancer cells in vitro and in vivo [27-29]. These drug-delivery systems can be incorporated to function as a ligand, a conjugated chemical with anticancer drugs, and a type of drug-delivery vehicle [28,30]. This work further sheds light on the targets for cancer therapy, including the Wnt, Hedgehog, and NOTCH signaling pathways, the cell cycle progression, the apoptotic pathway, and the role of MDM2, p53, and tumor suppressor proteins, which have been altered due to cancer.

2. The importance of peptide therapeutics and their potential mechanism of action

The therapeutic peptides exhibit antitumor activity through various mechanisms such as membrane disruption, apoptosis, inhibition of tumor angiogenesis, immune regulation, or inhibition of specific internal targets [31,32]. Numerous peptides exert their mechanism of action by creating pores or channels within the cellular membrane. The presence of pores can lead to the internalization of the peptide. However, it can also serve as a mechanism for cell death due to membrane disruption. The determination of the impact of a specific peptide in this aspect necessitates experimental investigation due to the limited comprehension of the phenomenon. Various models have been put forth to elucidate the underlying mechanisms, such as the barrel-stave, carpet, and toroidal pore models, which have been extensively examined in numerous scholarly articles [33,34]. The aforementioned models explicate the peptide aggregation and organization process, which culminates in the formation of channels within the cell membrane. This process is facilitated by the amphipathic properties of the peptide and the phospholipid bilayer. The peptide undergoes conformational changes that facilitate its penetration into the hydrophobic core of the membrane. This penetration can lead to membrane disruption, causing either internalization of the peptide or cell breakage and necrosis due to dysregulated osmotic pressure. The occurrence of cell death through membrane disruption is noteworthy due to its ability to bypass conventional chemotherapy approaches, despite growth rate or multidrug resistance mechanisms. Additionally, cationic residues in the peptide facilitate selective targeting of cancer cells' relatively anionic cell membrane. Peptides can cause disruption not only in the cell membrane but also in the mitochondrial membrane potential. It can lead to the release of cytochrome c, activation of caspases, and, ultimately, the induction of apoptosis [33,35,36].

Specific peptides induce antitumor effects by disrupting the vascularization of neoplastic cells, thereby impeding their proliferation rather than inducing direct apoptotic cell death. The peptides can impede the signaling of vascular endothelial growth factor (VEGF), a process that typically triggers the formation of new blood vessels in tumors. The peptides can impede tumor growth and metastasis by hindering VEGF signaling while exerting negligible impact on normal cells with low neovascularization demands. Peptides can serve as an anticancer therapeutic by inducing a tumour-specific immune response. In a recent instance of this methodology, a peptide capable of penetrating cells, known as cytosol localizing internalization peptide 6 (CLIP6), was linked to a representative antigen, ovalbumin (OVA) [37]. The CPP known as CLIP6 exhibits a noteworthy feature of direct translocation through cell membranes, as opposed to endocytosis, frequently resulting in endosome entrapment. The researchers discovered that the CLIP6-OVA complex exhibited efficient cellular entry and led to increased uptake of antigens by antigen-presenting cells, specifically dendritic cells. The researchers observed that the CLIP6-OVA complex, administered in vivo along with CpG, an immune adjuvant, elicited a robust antigen-specific immune response in mice. The researchers utilized the B16/OVA mouse model, a melanoma cancer model that expresses OVA on its cell surface, to investigate the efficacy of CLIP6-OVA/CpG immunization. The results indicated that two out of six mice who received the aforementioned immunization became tumour-free.

Conversely, mice receiving OVA or CLIP6-OVA immunization did not survive beyond 31–39 days post-inoculation with tumors. The findings of this research demonstrate the involvement of CPPs in the creation of prophylactic or remedial cancer immunizations. Therapeutic peptides have the potential to selectively target crucial internal cell systems and structural proteins that are integral to various cellular processes, such as signal transduction pathways, cell cycle regulation, DNA repair pathways, and cell death pathways [38].

3. Protein and Peptides as direct anticancer agents and their importance in targeted therapy

Targeted therapy utilizes peptides that can straightforwardly target disease cells without influencing normal cells and is advancing as a substitute system to standard chemotherapy. By explicitly focusing on malignant growth cells, the peptide can be used as a carrier of cytotoxic drugs or as a direct cytotoxic agent and radioisotopes. Peptide-based hormonal treatment or therapy has been widely read and used to treat prostate and breast cancer [39]. Overexpressed receptors are regulated in cancer treatment by targeting molecules, such as peptides, antibody fragments, or antibodies that directly bind to these receptors, preventing downstream mechanisms obstructing cancer progression. Different methodologies included using receptor overexpression to deliver biologically active compounds or anticancer medications that could not tell the difference between healthy and cancer cells [40]. Some examples of tumour-targeting therapies are peptides, proteins, antibodies, glycopeptides, aptamers, peptidomimetics, and peptoids. Tumour vascular endothelial cell surface receptors, the tumor's extracellular matrix, and cancer cell surface receptors are all common targets for tumour-targeting ligands [41].

Cancer cells consist of cell surface receptors, which can be well-targeted for cancer therapies [42,43]. One of the best methods is the surface receptor-dependent endocytosis of the cancer cells by binding macromolecular drug ligands that will release a peptide for the targeted killing of the cancer cells at a particular tumor site and prevent tumor metastasis [43]. The central concept behind this is to transport the active drugs to cancer cells, which can have a suitable ligand to link to the surface receptors of cancer cells [43]. Specific cell surface receptors of cancer cells include VEGFR, EGFR, chemokine receptor, folate, integrins, mannose receptor, carbonic anhydrase IX receptor, biotin receptor, interleukin receptor, estrogen receptors, and intracellular adhesion molecules. The study by X. Deng et al. [22] shows how the peptide-drug conjugate called LTP-1 can bind with the anticancer drug paclitaxel, improve its functioning, and help direct the drug to the specific tumor site. Due to their high concentration, the cell surfaces receptors like LHRH-R and MMPs facilitated the conjugate to identify these receptors and used paclitaxel to block its function [44,22,45]. Hence, by using these modeling techniques, we can modify the drug delivery systems and optimize their functioning using simulation-related approaches, focusing on factors like ligand, density, and spacing orientation and develop an effective vehicle design having no side effects on the patients being treated for cancer [46,28,47].

3.1. Cell penetration peptides (CPPs)

CPPs can be used for tumor-targeted delivery of several anticancer and natural drugs to treat cancer at the nuclear and mitochondrial levels.

3.1.1. In nucleus

The role of CPP in the nucleus is essential as it can help target several DNA and RNA molecules which can help in tumour-targeted cancer therapy. The experiment by Y. Cheng et al. [48] utilized an integrin-targeting peptide-conjugate called AIEgen, which can help deliver the antisense single-stranded DNA oligonucleotide (ASO) and help in gene-targeted sequential therapy at the nuclear level. It can help enhance the treatments of serious diseases using gene therapy [48-52]. CPP and their role as effective drug delivery systems, such as liposomes, oligonucleotides, etc., can play a significant role in solid tumor therapy [53-57]. Using advanced imaging technologies, like the phage display technique, will help the CPPs to show the peptide-conjugate and ligand interactions at the tumor site, which can help in tumour-targeted therapies and help in the effective treatment of cancer patients [58,40,59]. One of the experiments developed a nucleus-targeting-TAT peptide which is conjugated with IR780. A near-infrared fluorescence dye was utilized to enhance photodynamic therapy for breast cancer treatment [60-65]. Later, this TAT-IR780 conjugate was combined with the anticancer drug doxorubicin, where it further enhanced the photodynamic therapy of breast cancer in such a way that only the targeted breast cancer cells were induced with apoptosis and damaged other genetic alterations around the tumor site and killed the cancer cells [64,66]. A research study by Gronewold et al., [67] exhibited that the s18 CPP, when modified by linking nuclear localization sequence N50 and nucleoli targeting sequence NrTP, increased the transporting efficiency of the s18 CPP into the nuclei and helped in cancer therapy [68,67,69-71]. Lastly, when the doxorubicin drug was combined with the lysine-rich CPP called KRP, it could penetrate the nuclei of the tumor cells and cause internal death of the cancer cells. It exerted a tumour-killing and chemotherapeutic effect over solid tumors, increased the drug's therapeutic index, and helped in cancer therapy [72-77].

3.1.2. In Mitochondria

In general, the mitochondria and the cell membrane play a significant role in maintaining the cell's stability and all the functional and metabolic activities [78-82]. The same applies to cancer cells. There are specific differences in the functioning of healthy and cancerous mitochondria in energy production and gene mutations, and they can be used as a target for cancer treatments [83,84,81]. Nevertheless, the mitochondria-targeting peptides approach is a highly effective method for cancer treatments [85-87,35]. The peptide hexokinase-II was engineered at the N-terminus by inserting a 15 amino acid sequence called pkv and a lipid Pal at the N-terminus end of the hexokinase-II scaffold. This peptide-conjugate interacted with the voltage-dependent anion channel-1 (VDAC-1) of the mitochondria and successfully induced apoptosis in lung cancer cells and hence is a promising therapy for cancer treatment [88,35,89,90]. A study by Jeena et al. explained that the amphiphilic peptides within the mitochondria are similar to hexokinase-II peptide conjugation [91]. They created a heterochiral peptide assembly that could quickly enter the mitochondria and disrupts its functioning. Mitochondria penetrating tri-peptide along with diphenyl alanine mito-FF and its mirror pair mito-ff, which, when co-assembled, could completely disrupt the mitochondrial function in the cell. Hence, it can be used for tumour-targeting in cancer therapy [92,91,93,82,94]. Lastly, an experiment by Rizvi, Mu, Wang, Li, and Zhang [95] used pro-apoptotic peptide conjugates combined with fluorescent-RGD tripeptide as a probe for targeting the mitochondria in tumor cells. Here, the RGD was also linked with the KLAK tetrapeptide, where the RGD was able to target the MSCs involved in the homing of the tumor cells, and the KLAK was able to enter the mitochondria and cause the apoptosis of the cancer cells [96-98,95]. The fluorescence tag was used to image the anticancer activities caused by the peptide conjugates in both in vitro and in vivo conditions. Hence, they were found to thrive in targeting the α,β integrins and prevent cancer progression, thereby being a promising technique for cancer therapy [99-101,95,102,103].

3.2. Pro-apoptotic peptides

Apoptosis is the cell's natural death mechanism and is a prospective anticancer therapeutic target. Caspases are used in both the extrinsic and intrinsic pathways to carry out apoptosis by cleavage of numerous proteins. Various mechanisms frequently suppress the apoptotic process in cancer, including proapoptotic protein under-expression and anti-apoptotic protein overexpression [104].

According to A. Hazafa et al., Humanin have the same proapoptotic activity as TNF-α in cancer, making it a new and effective therapeutic agent for cancer treatment. It has also been suggested that in addition to Humanin, the innovation of some other mitochondrial-derived peptides could be a feasible therapeutic option for various diseases related to apoptosis and oxidative stress [105]. Humanin is a crucial cytoprotective polypeptide generated from small mitochondria and transcribed

by mtDNA. Humanin modulates cytoprotection by coupling soluble extracellular proteins like IGFBP3 ad VSTM2L [106]. Humanin protects different cell types, notably leukocytes, germ cells, neurons, and tissues, against apoptosis and cellular stress by modulating multiple signaling systems, like the interplay of the BCL-2 family of proteins and the JAK/STAT pathway [107]. Humanin interacts with G protein-coupled formyl peptide receptor-like 1 (FPRL1/2) to drive the c-Jun N-terminal kinase (JNK) and apoptosis signal-regulating kinase (ASK) signaling pathways when released from cells as a secreted peptide. It also activates JAK2/STA3 signaling by interfacing with CNTFR-/gp130/WSX-1 trimeric receptors [106].

Humanin inhibits apoptosis in various cell types, including pancreatic β cells, anterior pituitary gland secretory cells, germ cells, endothelial cells, and neurons. Humanin has been shown to have cytoprotective properties in various species, including mice, humans, and rats [108]. Even though Humanin was postulated as a possible oncopeptide about two decades ago, its significance in cancer development and treatment is still not adequately known. Humanin upregulation has been linked to carcinogenesis after being found in bladder tumor cells, gastric cancer, and pituitary tumor cells [109]. Humanin peptide, according to studies, successfully inhibits glucocorticoid-induced bone development retardation. However, the mechanism by which Humanin prevents osteoporosis is unknown. Humanin does not interfere with the anti-inflammatory effects of glucocorticoid medication; instead, it suppresses apoptosis [105].

Apoptosis malfunction has been linked to many different diseases. Acquiring resistance to apoptosis is a crucial aspect of malignant transformation, especially for cancer, marked by aberrant and unlimited cell development. As a result, a promising approach to cancer therapy is the induction or restoration of the apoptotic machinery in cancer cells. Several of the essential apoptosis regulators have been found. Among these are death receptors, Bcl2 inhibitors (pro- and anti-apoptotic), IAPs, caspases, and p53. Their identification has encouraged drug candidates that could directly work with the critical apoptotic regulators. In particular, much focus has been on pro-apoptotic proteins and peptides (Fig. 1) [110].

The potential of peptides that resemble intrinsic death receptor ligands as anti-cancer medicines have been investigated. Peptides like TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) derivatives, TRAIL-R2 binding peptides [111,112], and the multimeric FasL mimetic peptide (FRAP- 4)$_8$-MAP [113] are all examples. Both natural TRAIL and FasL are expressed as multimeric forms on the cell surface (TRAIL is trimeric; FasL is hexameric) and contain pro-apoptotic activity, but only when attached to the membrane [114]. Released into the cytosol, soluble TRAIL or FasL loses its ability to induce apoptosis and can even block the action of membrane-bound forms [114]. Curiously, researchers discovered that cross-linking these proteins could revive their ability to induce cell death. Antibody cross-linking and nanoparticle hybrids are two methods that have been tried in this direction [115].

Researchers have paid much attention to compounds that mimic the BH3 domains of the pro-apoptotic Bcl-2 family proteins because of their potential as anti-cancer therapeutic candidates [116-119]. Several attempts have been made to develop peptides that mimic BH3, including TLS peptide [118], mitochondria Ca^{2+} overload-inducing peptide composed of NOXA and IDP [120,121], Bim, and derivatives such as TAT-Bim peptide [122,123], hydrocarbon-stapled peptides derived from BH3 domains of BCL-2 proteins and several other BAX derived peptides [116,124-126].

The preservation of p53 integrity plays a crucial role in preventing tumors. Therefore, it is prevalent in numerous human cancers that there is a genetic mutation of p53, accounting for over 50% of human cancers. Alternatively, the functionality of p53 may be impaired, as reported by Hollstein et al. [127], Haupt et al. [128], and Cho [129]. The overexpression of the p53 protein mutation in human tumors results in the loss of its tumor suppressive function. Additionally, it exhibits dominant

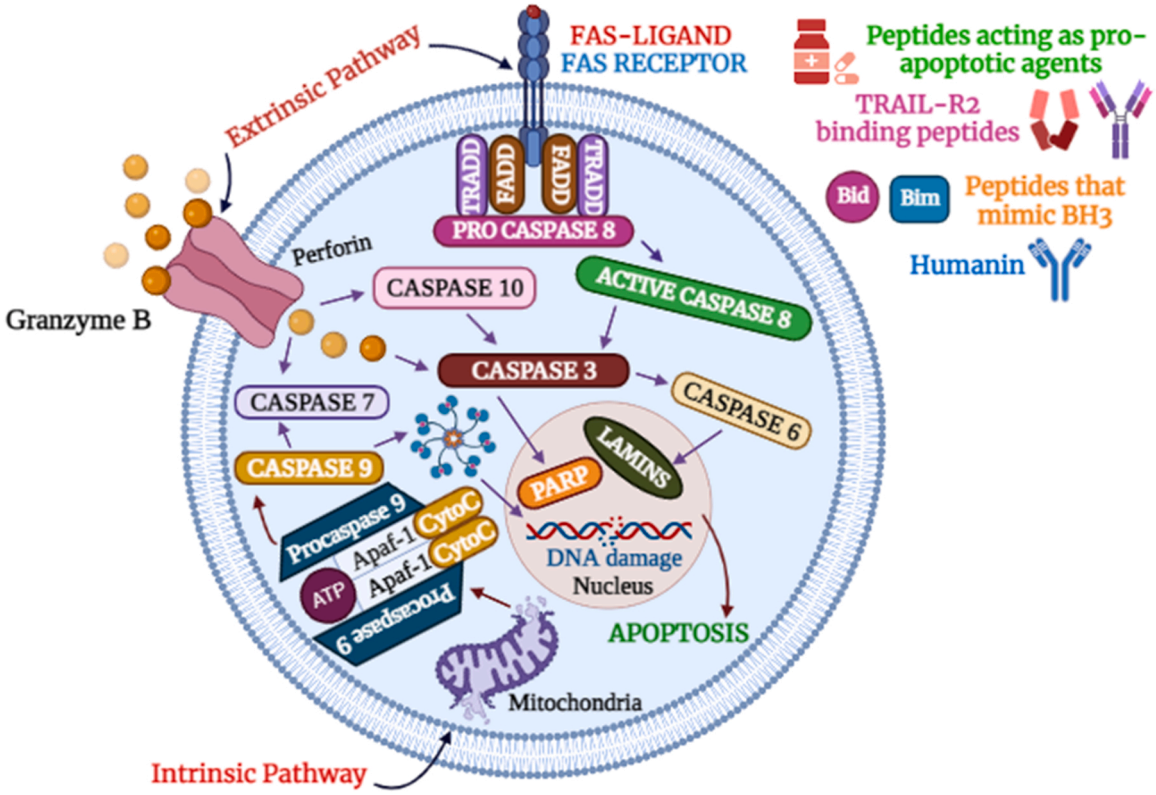

Fig. 1. Intrinsic and extrinsic pathways of pro-apoptotic agents of anticancer proteins and peptides. This diagram explains the caspase activation pathways. It includes the role of drugs in activating the pathways.

negative activity and gains oncogenic properties. Various therapeutic strategies have been developed to address this issue, including gene delivery of functional p53 protein or peptides, inhibition of MDM2-p53 interaction, restoration or elimination of mutant p53, and p53-based vaccine therapy. The p53 synthetic long peptide vaccine is a type of peptide vaccine that comprises long synthetic peptides (SLPs) sourced from the central region of p53. The administration of the p53 SLPs vaccine can induce an immune response mediated by cytotoxic T cell lymphocytes (CTLs) against tumor cells that express the p53 protein [130-133].

Several therapeutic strategies involving caspase have been investigated, such as administering active caspase executioners or activators through direct delivery. The RGD peptide is considered a noteworthy illustration of caspase activators. The RGD peptide has been primarily recognized as a ligand for targeting tumor cells due to its ability to bind with integrin receptors. However, a collection of research studies have demonstrated that the RGD peptide can also directly stimulate the activation of pro-caspase 3 and reduce the activation threshold of caspases, as reported by Buckley et al. in 1999 [134].

3.3. Antimicrobial peptides as anticancer agents

One of the issues with anticancer drugs is their resistance to cancer cells and the toxic side effects it brings to the patient. Hence, a new class of drugs has been produced with anticancer and antimicrobial activity. These are called antimicrobial Peptides (AMPs). They are a group of peptides with a strong electrostatic interaction with the negatively charged bacterial membrane containing glycoproteins and glycolipids [135]. Cancer cells possess these glycoproteins and glycolipids on the outer membrane, and these AMPs can prove highly therapeutic. The cationic antimicrobial peptides (ACPs) are potential AMPs for cancer treatment as they are selective, penetrate through the cell membrane, and lyse the cell [136,137,135].

3.4. D-peptides

D- Peptides and other natural peptides from plants and marine environments can have excellent anticancer properties. First, D-melittin is a peptide compound of 26 amino acids of honeybee venom. It has been established with anti-tumor activity for breast, liver, and prostate cancers. Nevertheless, a proper delivery system is required here since mellitin has high intrinsic instability and non-hemolytic activity and needs to be safely delivered. This delivery is possible after several molecular formulations by converting the L-amino acids to D-amino acids and transporting them via conjugates. It can help increase the drug's anticancer activity and efficacy [138-144]. A study was conducted by Russell et al. [145], where they determined the efficacy of immunoconjugates cross-linked with synthetic MEL against human prostate cancer. It inhibited tumor growth in mice and improved their survival ability [143,146,145]. The use of a naturally occurring compound, chitosan, as a drug-delivery carrier for therapeutic drugs required in breast cancer treatment [147-149]. Third, deriving the small peptides from marine organisms can produce highly effective cancer treatment drugs due to their excellent fast absorption properties and less complex bonds, making it easy to modify and synthesize them. Along with the treatment, they provide nutrients to the body, providing dual benefits. Some examples include the marine organism *Sacrophytan glaucum*, which has three new cytotoxic peptides from the papain hydrolysate AGAPGG, AERQ, and RDTQ. They show high cytotoxicity toward human cervical cancer cells [150,151]. *Diplosoma virens* release the peptides Verenamides A-C, which inhibit the topoisomerase II activity and present anticancer and apoptotic effects over human colon cancer cells and kidney cells [151,152]. Lastly, an actinomycete (fungal) organism, *Nocardiopsis lucentens*, releases the Lucentamides A – D peptides, which showed in vitro cytotoxicity toward human colon cancer cells [151,153].

3.5. Exosomal proteins

Exosomes are extracellular molecules about 30–150 mm in size in the tumor microenvironment. They help cell-to-cell communication between cancer cells via signaling pathways [154-157]. [158-161]. These nano-sized molecules are derived from extracellular vesicles and released by several cell types [157,162]. They help in the chemo-resistance of cancer cells, and therefore they can be utilized as biomarkers and as excellent nano-delivery systems of other anticancer agents (Fig. 2) [163,164,158,165,166]. Exosomal proteins can be modified into essential delivery systems for molecules and anticancer agents for chemotherapies and exhibit low toxicity with no side effects. These naturally derived, nano-sized particles or membrane-bound vesicles can help in targeted photodynamic therapies [167-173]. The chimeric peptide-engineered exosomes (ChiP-Exo) were found to be successful delivery systems in both in vitro and in vivo techniques and inhibited tumor progression. These bio-derived systems can be excellent for precise individualized tumor therapy [174]. An experiment using arginylglycylasparatic acid (RGD) peptide in an exosome-mediated siRNA delivery system to inhibit the tumor immune checkpoints governing colorectal cancer, was very effective in inhibiting FGL1 and TNF-β1, which helped the tumor cells to evade the immune system. Under both in vitro and in vivo conditions, immunotherapy is highly effective in inhibiting tumor growth [175-177]. However, some studies have found the difficulty of using exosomes over other artificial nanoparticles due to the difficulty in isolating and extracting purified exosomes [154]. Scaling up the exosomes is challenging, and there is also a risk of contamination during manufacturing [178,179]. Therefore, more clinical and pre-clinical experiments will be required to understand their utility in cancer therapy and personalized cancer treatment for patients [180,154,181,182]. Recently, tumor-derived exosomes (TEX) have been under extensive study as they are crucial mediators for cancer initiation, followed by tumor progression and metastasis. This mediation is done via many ligands such as FAS, TNF-β, prostaglandin E2, and heat shock proteins such as HSP70 and 90, which help to enhance the tumor microenvironment and prevent the immune response against cancer. Therefore, these TEXs can be a potential biomarker in cancer diagnosis and can develop therapies using the TEXs and other ligands and proteins associated with them for cancer treatment [183-185,162,186-188]. Similar to this concept, another study used melanoma cell-derived exosomes (MTEX) on its influence over the tumor microenvironment by combining it with photodynamic therapy (PDT). This combined treatment can effectively inhibit the EMT transition and have a chemotherapeutic effect on cancer [189-192].

3.6. Tumor suppressor proteins and peptides

The tumor suppressor genes losing function are part of a more extensive signaling system, and that pathway's hyperactivation causes cancer. The inactivated tumor suppressor genes can be therapeutically addressed by blocking the relevant pathway further downstream. PTEN, one of the most typically changed tumor suppressor genes throughout human malignancies, is an example of this paradigm. PTEN is inactivated by deletion or mutation in many cancers, including breast, endometrial, uterine, prostate, glioblastoma, and melanoma [193,194].

Tumor necrosis factor-induced protein 1 (TNFAIP1) causes cancer cell apoptosis and is commonly downregulated in cancer cell lines. TNFAIP1 is a single-copy gene identified in human umbilical vein endothelial cells that is very conservative. The protein expressed by this gene is comparable to the potassium channel tetramerization domain containing 13 (KCTD13) and potassium channel tetramerization domain containing 10 (KCTD10), both of which are constituents of the polymerase delta-interacting protein 1 (PDIP1) family [195]. Studies showed that by altering the NF- κB/CSNK2B/TNFAIP1pathway, TNFAIP1 can be a tumor suppressor in hepatocellular carcinoma, meaning TNFAIP1 could be a therapeutic target and a promising marker for hepatocellular

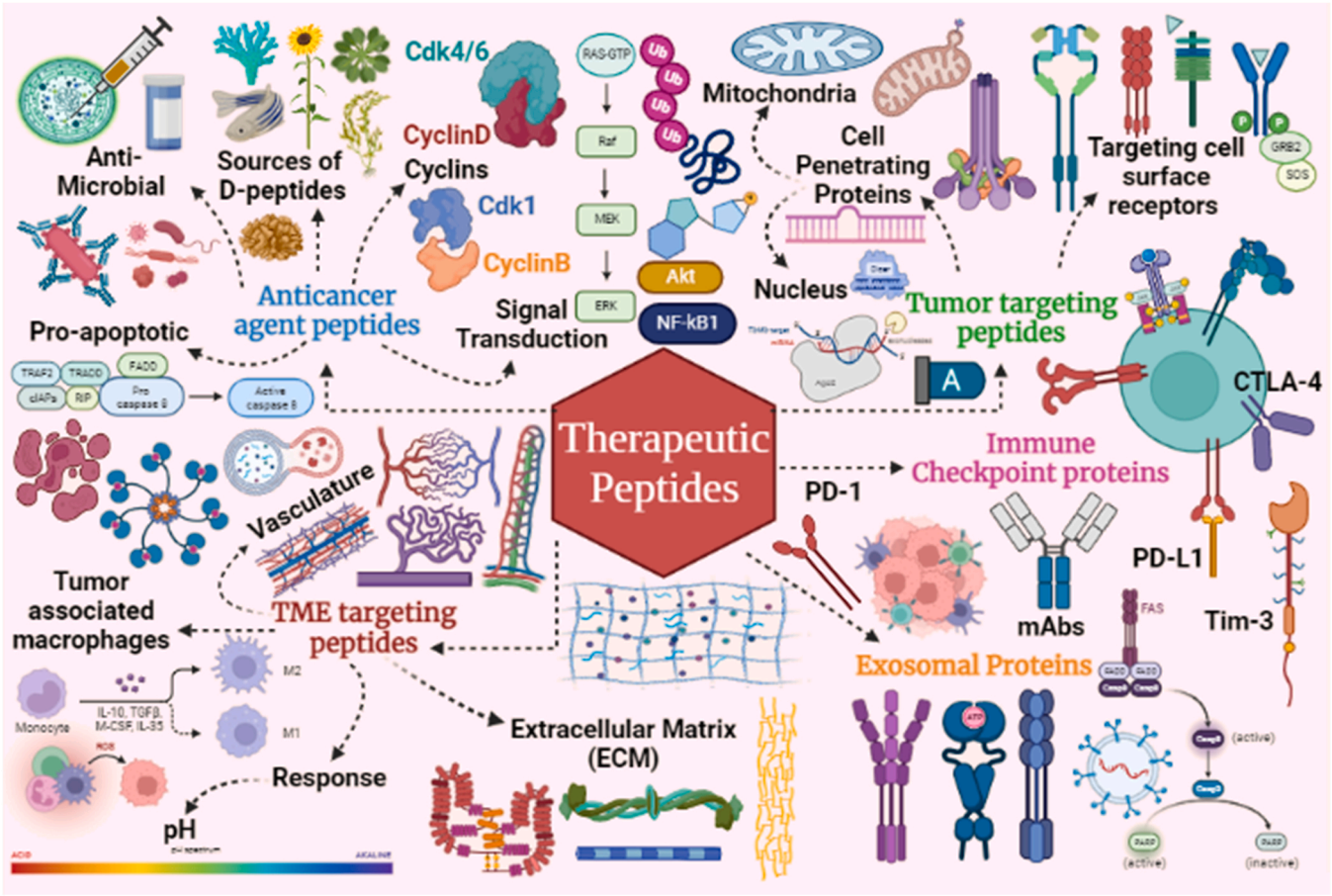

Fig. 2. The potential uses of different therapeutic peptides for treating different cancers. It includes anticancer agents containing natural and lab-made sources, tumor-targeting peptides for targeting cell surface receptors and cell-penetrating peptides in the nucleus and mitochondria, tumor microenvironment (TME) targeting peptides targeting the ECM, vasculature, tumor-associated macrophages (TAMs) and response to pH and finally utilization of exosomal proteins and immune checkpoint proteins.

carcinoma [196]. Even though ASPP2 acts as a tumor suppressor, the exact mechanism by which it does so and how it is regulated are still unknown. Alternative splicing truncates the C-terminal TP53 binding protein, resulting in the ASPP2 isoform. Furthermore, ASPP2 is commonly expressed in acute leukemia blasts but is also found in other solid and hematologic tumors, suggesting that it functions in human cancer [197].

In vitro, Dnmt3b$^{CI/CI}$ MEFs are more vulnerable to oncogenic transformation and tumor development than in vivo. The authors then apply the MLL-AF9 model of AML and the Myc overexpression model of Myc-induced T-cell lymphomagenesis to the haematological setting. It was found that Dnmt3b$^{CI/CI}$ mice have shorter survival periods in both circumstances. These models support the catalytic-dependent tumor suppressive effect of DNMT3B in oncogenesis [198].

3.6.1. *p53and MDM2*

The tumor suppressor p53 controls various biological processes, including DNA repair, apoptosis, genomic stability, and cell cycle arrest. This gene is commonly changed in human tumors by deletions or point mutations. The MDM2 protein acts as a negative regulator of the p53 inhibitor. It reduces p53's transcriptional activity, promotes its breakdown, and enhances nuclear export after binding [199]. MDM2 inhibitor compounds can block the connection between MDM2 and p53, allowing p53 to regulate tumor suppressor transcription and trigger apoptosis. In acute lymphoblastic leukemia, the P53 pathway is frequently changed, owing to the deletion of CDKN2A and overexpression of MDM2, the two primary regulators of p53. As a result, targeting the MDM2-p53 axis as a cancer therapy strategy in acute lymphoblastic leukemia could be appealing [200]. MDMX is a prominent cancer therapeutic target for its capacity to function in the MDM2/MDMX complex and suppress p53, particularly in malignancies where MDMX amplification is more common than MDM2 [201].

MDM2's E3 ubiquitin ligase can bind to the p53 protein and ligate it, which can then be transported to the cytoplasm and digested by proteasomes. As a result, MDM2 can keep the p53 signaling pathway stable [202]. In epidermoid carcinoma, the MDM2–p53 loop leads to cisplatin resistance. Cisplatin triggers p53 protein phosphorylation that can diminish cisplatin resistance, whereas cisplatin-resistant tumor cells had increased MDM2 expression and non-phosphorylated p53. This process could be linked to the p73 loop auxiliary factor's regulation [203]. MDM2 overexpression leads to classical radiotherapy and chemotherapy resistance via the EMT and MDM2–p53 loop-dependent pathway, indicating a possible tool for identifying therapeutic resistance in malignancies and a potential new therapeutic intervention. Furthermore, combining MDM2 inhibitors with radiotherapy or chemotherapy may improve therapeutic efficacy and benefit the patients [204].

3.7. *Peptide hormones in cancer treatment*

The use of LHRH (luteinizing hormone-releasing hormone) agonists introduced by Schally et al. as a therapy for prostate cancer is the most classic example of the application of peptides in cancer treatment [205-207]. Since then, depot formulations of LHRH agonists have been created, including buserelin, leuprolide, goserelin, and triptorelin, to

treat prostate cancer more effectively and conveniently [208-210]. When these peptides are administered, the pituitary's LHRH receptors are downregulated, which inhibits the release of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone at the same time. It provided patients with prostate cancer with a novel approach to androgen deprivation therapy. Due to their competitive blockage of the LHRH receptors, LHRH antagonists immediately and dose-dependently decrease LH and FSH production, providing therapeutic advantages over agonists. Many potent LHRH antagonists are currently available for clinical usage in patients. The first LHRH antagonist to receive marketing approval and become commercially available was Cetrorelix [211]. New-generation LHRH antagonists like abarelix and degarelix have since been approved for human usage [212,213,39].

3.8. The importance of peptides as cytotoxic drug carriers

Several peptide receptors can potentially serve as drug targets in cancer treatment [214-219]. A peptide has the potential to be linked with a cytotoxic agent to transport it to a cancerous cell that exhibits the corresponding peptide receptor. Peptides with the ability to selectively target a cell expressing its receptor are called cell-targeting peptides. Compounds with cytotoxic properties associated with analogs of hormonal peptides such as LHRH, bombesin, and somatostatin can be directed towards specific tumors that possess receptors for said peptides, resulting in a higher degree of selectivity in the eradication of cancerous cells [220,221]. One drug candidate, AEZS-108, utilizes a peptide LHRH and doxorubicin, a chemotherapeutic agent, to selectively target cells expressing LH-RH receptors, such as prostate cancer cells [222,223]. Most of the research conducted thus far has focused on radionuclide therapy and imaging, with a limited number of studies exploring the transportation of cytotoxic drugs, such as AN-201 and doxorubicin [224]. However, these receptors offer a promising platform for the targeted delivery of chemotherapeutic agents to specific cells. In addition to peptides that exhibit selective binding to peptide receptors, a multitude of peptides with relevance to cancer therapy have been identified in recent times. The peptides acquired through in vivo phage display methodology are commonly referred to as homing peptides due to their precise targeting of normal organs or diseased tissues [225-227]. The utilization of homing peptides as delivery mechanisms has proven to be effective in directing imaging agents, drug molecules, oligonucleotides, liposomes, and inorganic nanoparticles toward tumors and other types of tissues, as evidenced by various studies [228,229,225]. The utilization of RGD and NGR peptides has facilitated the administration of tumor necrosis factor-α (TNF-α), a highly effective antineoplastic agent, as a drug [230,231]. The utilization of TNF-α as an anticancer agent in clinical settings is restricted to localized treatments owing to its systemic toxicity that limits the dosage. Using RGD and NRG peptides as targeting agents for TNF-α treatment resulted in reduced tumor growth with lower dosages compared to the administration of unbound TNF-α [39].

4. Targeting tumor microenvironment, immune checkpoint proteins, and signal transduction pathways as anti-cancer therapeutic strategies

4.1. Targeting the tumor microenvironment (TME)

TME-targeting peptides can be an excellent tumor-targeting agent to help inhibit tumor progression and cancer metastasis. Here, the extracellular matrix (ECM) surrounding the tumor site plays a significant role in maintaining the tumor stemness and allowing the cell-to-cell and cell-to-matrix interactions, thereby helping in cancer progression. Recently, there has been a shift in the study towards the role of tumor vasculature in causing cancer and how it can be targeted for cancer therapy using angiogenesis inhibitors and vascular disrupting agents. The targeting of tumor vasculature can help in better treatment of cancer due to two primary reasons – one is the direct contact of the chemotherapeutic drug with the vascular endothelial cells that will not require to penetrate towards the inner side of the tumor site, and second, lesser ability of the endothelial cells to cause drug resistance since these cells have high genetic stability [232-234]. An experiment was done by Yarong Liu et al. [235], where they proved that combination therapy transported via the multilamellar liposomal vesicles could quickly help target the tumor cells along with the tumor vasculature [236-240,235,241,242]. This transportation mechanism of the combination therapy by the vesicle could be a potential technique to improve cancer therapy results [240,235,243]. In another experiment by W. Zhang et al. [244], an orthotopic model from a mouse was used to understand the effect of targeting the BB2r receptor, which plays an essential role in the propagation of prostate cancer. Here, they observed that by targeting the BB2r receptor via the BB2r therapeutic agent, there was increased tumor vasculature perfusion, and the impact was observed by lowering the hypoxic conditions and vascular density surrounding the tumor cells [245-249,244]. Neuropilin-1 and 2 (NRP1 and NRP2) are co-receptor parts of the tyrosine kinase and integrin receptors and regulate angiogenesis. In the case of tumor cells, the mutated NRP1 and NRP2 can also play a significant role in the angiogenesis of the tumor cells and tumor vasculature, which can help in cancer progression and metastasis [250-254]. Hence, NRP can potentially be a specific tumor target for cancer therapy, and cytostatic drugs can effectively target the NRP receptor and promote tumor therapy [253,255,256]. Lastly, an experiment conducted by He et al. [257] demonstrated that transforming the tumor vasculature using a combination of LIGHT (lymphotoxin β receptor mediated by herpes virus entry) and vascular-targeting peptide (LIGHT-VTP) can help to modulate the tumor vasculature in such a way that the metastasis is reversed and it exerts anti-tumor effect, thereby preventing cancer metastasis and enhancing immunotherapy treatment of lung cancer [257-260].

The macrophages are essential in increasing the tumor progression and creating a TME, eventually producing carcinogenesis. Based on the type of tumor, the macrophages and the monocytes are the first cells to be incorporated to create a strong TME for the tumor. There are two types of macrophages: the activated macrophages called M1 and the alternatively activated M2 [261-265]. The M2 macrophages are called tumor-associated macrophages (TAMs) and are responsible for tumor progression. Several anti-tumor drugs and therapeutic systems are available for targeting the TAMs for tumor therapy [265,266]. In one experiment, the calcium/calmodulin-dependent protein kinase II (CAMKII) inhibitor, KN93, helped reprogram the TAMs to inhibit the tumor cells and enhance cancer immunotherapy with an injectable hybrid peptide hydrogel. It increased immunogenic cell death significantly in tumor cells and prevented cancer progression [267-271]. The epithelial-to-mesenchymal transition (EMT) caused due to the TME and TAMs developing more aggressive tumors and increasing chemoresistance exponentially [272-274]. Here, lipid metabolism plays a crucial role in enhancing cancer progression. Hence, a combination of drugs called simvastatin and paclitaxel was found effective in reversing the EMT transition, suppressing the integrin β3/FAK signaling pathway and helped in the conversion of the TAMs to the M1 phenotype, which brought the TME towards the normal form and prevented cancer progression [275,276,273].

The TME depends on the ECM because it regulates cell-to-cell and cell-to-matrix interactions and supports tumor growth and expansion. This communication or interaction of the TME is regulated by ECM macromolecules or angiogenic growth factors called matrikines and matricryptins. When the tumor progression becomes more robust, the ECM also undergoes alterations due to hypoxia and acidosis conditions and, in turn, secretes free radicals [277-280]. These free radicals result in cell inflammation and further enhance tumor metastasis. Therefore, ECM macromolecules can be used as a biomarker to diagnose cancer and understand its progression strategies [277,281]. In an experiment conducted by Senthebane et al. [282], they used the esophageal cancer cell

lines and 3D cell-derived ECMs, to develop a model to understand how the ECM proteins influence the response of these esophageal cancer cells and increase the chemoresistance of cancer cells towards treatment. The results showed an increase in the ECM proteins like fibronectin, collagens, and laminins and enhancement of the specific signaling pathways like the PI3K/Akt and MAPK/ERK, which prevented the interaction of the chemotherapeutic drugs with the cancer cells and hence increased cancer cell migration [283,284,282,285,286]. Therefore, the ECM proteins can be targeted to prevent cancer progression. Another study was done where they directly targeted the ECM of the tumor cells via targeted drug-delivery mechanisms. The ECM protein targets, such as tenascin-C, fibronectin-fibrin complex, collagen, galactan-1, aggrecan, heparin sulfate, etc., could be used to detect the site of the tumor cells. The chemotherapeutic drug delivery mechanisms combined with immunotherapy are promising techniques to prevent tumor progression and help in cancer therapy [287-294].

4.2. Targeting the immune checkpoint proteins and peptides

The approval of cancer therapy drugs by the FDA for PD-1 and CTLA-4 immune checkpoint proteins has increased the significant role of antitumor immunotherapy in protein and peptide therapeutics for cancer treatment [295]. Immune checkpoint blockade drugs are clinically beneficial for patients who suffer from melanoma, renal carcinoma, and other types of tumors; hence, cancer immunotherapy has emerged as a potential therapeutic technique for cancer treatment [296].

4.2.1. PD-1 protein

Programmed death – 1 (PD-1) / programmed death-ligand 1 (PD-L1) is an immune checkpoint that can be targeted via immunotherapy to prevent tumor progression [297-301]. PD-1/PD-L1 is one of the immune checkpoint pathways that allows the immune cells to evade the consequences of immune surveillance and escape the immune response. Therefore, PD-1/PD-L1 immune checkpoints can reduce tumor progression and could be targeted for cancer therapy. It includes pembrolizumab and nivolumab mAbs that display the potential for tumour-targeted treatments/therapies [302-304,299,305]. Several studies are being done on other mAbs, molecular pathways, and peptides, making use of different properties of these proteins like post-translational modification regulation, allosteric effects, and direct inhibition of the receptor or ligand, providing insights into the control of many factors and the tumor microenvironment while developing the tumour-targeted therapy. It is one of the ways to strategize and increase the rate of cytotoxic immunity toward cancer cells and develop safe therapeutic approaches [306-310]. The IgG4 mAbs such as pembrolizumab and nivolumab are FDA approved, have good binding efficacy with PD-1, and are highly effective PD-1 inhibitors [311,312]. Pembrolizumab was the first clinically approved anticancer treatment for all types of carcinomas. It was the first immune checkpoint inhibitor that prevented immune suppression and immune cell deactivation for patients with either higher levels of PD-1 or PD-L1. Nivolumab successfully disrupted the action of PD-1 and produced strong responses even in heavily mutated carcinomas like melanoma and hepatocellular carcinoma [312,313]. Atezolizumab, a human IgG1 mAb, was the first approved drug for PD-L1 inhibition and was found effective in treating TNBC, NSCLC, and small-cell lung cancer [312,314]. As per J. Yang and Hu [315], the mAbs showed limitations such as poor pharmacokinetics and were expensive to manufacture. Hence, they mainly focused on immunomodulators to inhibit the PD-1/PD-L1 immune checkpoints via protein-protein interaction. These peptides can help improve cancer immunotherapy treatments and prevent cancer progression [316–319, 315]. A study by D'Alterio et al. [320] showed that targeting the CXCR4 surface receptor on cancer cells could enhance the efficacy of the PD-1/PD-L1 inhibitors. The use of the CXCR4 antagonist called Peptide-R54, along with PD-1 inhibitors, as found in the results conducted on murine models of colon cancer and B16 human-melanoma cells, demonstrated its effectiveness against melanoma [321,320, 322-330]. Small inhibitory molecules targeting the transcription, translation, degradation, signaling pathways, and protein-protein interaction blockage of PD-1 can be highly effective for cancer treatment [331-337]. Another experiment was conducted by Zhai et al. [338], where they developed a new cyclic peptide inhibitor called C8 to block the PD-1/PD-L1 interactions and improve cancer immunotherapy treatment. By blocking these interactions, tumor cells could directly interact with the immune cells and did not escape immune surveillance. The results showed effective activation of $CD8^+$ T-cells and disrupted the PD-1 interactions in vitro and in vivo conditions. Therefore, the C8 peptide also can be used in cancer immunotherapy and aid in cancer treatment [339-342,338].

4.2.2. CTLA-4 proteins

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is one of the co-stimulatory molecules that help regulate the body's immune response [295,299]. This receptor is mainly found in T cells and helps regulate the early activation of T cells. Hence, CTLA-4 is mainly utilized to inhibit any immunological response that activates the T helper cells and interacts with the T regulatory cells to maintain the inhibition of T cells. However, within the tumor microenvironment, they increase the tumor resistance toward T cell and further metastasizes cancer [312]. An experiment conducted by Fang et al. [296] found that the expression levels of both CTLA-4 and TIGIT exhibited a better prognosis for breast cancer [296]. Hence, immune checkpoint blockades are essential to prevent cancer progression and can help treat cancer [312]. The action of CTLA-4 can be targeted for melanoma using the FDA-approved mAb drug, Ipilimumab [299,315]. However, as per Granier et al. [295], patients receiving such therapies are likely to suffer from adverse immune events, especially with the anti-CTLA-4 antibody, compared to other anti-PD-1 therapies [295,343]. Tremelimumab, a human Ig2 mAb, is another CTLA-4 inhibitor that effectively blocks the interaction between CD28 of T cells and CTLA-4, preventing the deactivation of the T cells. Tremelimumab, combined with other immunomodulatory agents, is currently being studied to test the clinical efficacies in many types of cancer [344,312,345].

4.2.3. Lymphocyte activation gene-3 (LAG-3) proteins

LAG-3 is one of the potential targets for cancer immunotherapy [299]. It is one of the co-inhibitory molecules currently under study for developing cancer treatments in the form of individual antibodies or combination with PD-1 antibodies. Their primary function is hypothesized to be a competitive inhibitor in the interaction between antigen and the T-cell receptor of $CD4^+$-T cells. They can also act on $CD8^+$-T cells and are mostly co-expressed with PD-1 proteins and on tumour-infiltrating lymphocytes (TILs), helping the cells to escape from the immune mechanism [346,295,301]. Nevertheless, they can also cause T cell dysfunctioning in the TME, which can increase inflammation and cause severe autoimmune reactions and tumor formation. These checkpoints are primarily expressed in human breast cancer cells and signify a good patient prognosis [347]. The LAG-3 blockage antibodies can be combined with anti-PD-1 or PD-1 blockage antibodies as it provides lower toxicity compared to a combination with CTLA-4 and PD-1 blockage antibodies. The combination of LAG525 and PDR001 (anti-PD-1 Ig4 antibody) effectively prevents advanced TNBC and is currently being recruited for ongoing trials to treat breast cancer. Another combination of IMP321, a LAG-3 Ig fusion protein with eftilagimod alpha and pembrolizumab (anti-PD-1), is currently recruited and can treat advanced non-small lung carcinoma and head and neck squamous cell carcinomas [348,347,349]. The mAb, Ieramilimab, is under study for monotherapy and as a combination with PDR001 in patients with small-cell lung cancer and neuroendocrine tumors [346]. Another combination of an anti-LAG-3 mAb called Relatlimab and nivolumab (anti-PD-1) has been recruited for clinical trials with the ability to treat microsatellite stable (MSS) colorectal carcinomas, other

advanced solid tumors and is also under study to be used as neoadjuvant therapy for early-stage NLCSC patients [346,347].

4.2.4. T-cell immunoglobulin and mucin domain 3 (TIM-3) proteins

TIM-3 normally functions as an immune checkpoint molecule that regulates the functions of the immune system and prevents autoimmune reactions. However, when there is an irregularity in the form of cancer, these molecules are overexpressed; hence, it is crucial to inhibit their actions [335]. It is expressed mainly by the T cells, NK cells, and monocytes and has been found to play a crucial role in inflammation as it is influenced by interferon-β and IL-27. It is a key checkpoint molecule that helps in suppressing anti-tumor immunity [350]. It is another co-inhibitory molecule under study to be utilized as a potential therapeutic target using antibodies since TIM-3 regulatory cells are primarily identified in advanced cancer stages and are hence found in other cancer types like cervical, colon, ovarian carcinomas, etc. [295,350,351]. There have been eight anti-TIM-3 mAbs registered for clinical trials as of now. In 2016, the mAb Cobolimab (TSR-022), an IgG4 anti-TIM-3 mAb (NCT02817633) developed by Tesaro, was approved for the first phase-I clinical trial, both as a monotherapy and as a combination therapy with TSR-042, i.e., anti-PD-1 mAb for patients with advanced tumor [352,353]. Another anti-TIM3 antibody is called MBG453 (NCT02608268), developed by Novartis, that is currently under study for the treatment of advanced malignancies both as a monotherapy and as a combination therapy with PDR001 (anti-PD-1 mAb) [353,354].

4.2.5. V-domain Immunoglobulin suppressor of T-cell activation (VISTA) proteins

VISTA and two other co-inhibitory molecules, LAG-3 and TIM-3, are currently being studied and investigated to become potential targets for cancer treatment, individually or in combination with anti-PD-1 antibodies [295,299]. It is also known as PD-1 H and functions as a co-inhibitory ligand against APCs by suppressing the T-cell responses and, in turn, induces the Foxp3 expression in cells [295,355]. CA-170 is a small immune checkpoint oral inhibitor for PD-1, PD-L1, and VISTA proteins that can help in T cell proliferation and cytokine production

Table 1
Classification of the different anticancer peptide agents with their functions, the benefits and drawbacks of each type of drug, and the feasibility of its application.

S. No.	Peptide or Protein	Function	Benefits	Drawbacks	Feasibility	References
1.	Cell surface receptors	Present on the surface of the cell, involved in protein-ligand interactions.	It can be targeted for cancer therapies. No side effects on patients.	Not specified.	Under study	[22,43,28]
2.	Cell peptide penetration in the nucleus	Help in the targeting of DNA and RNA molecules.	Highly effective in tumor-targeted therapies.	Require drug delivery systems for targeted therapy.	Widely studied, have effective formulations for targeted therapy.	[48,67,56,64,76]
3.	Cell peptide penetration in mitochondria	Play a significant role in maintaining the stability of the cell and helps in the cell's metabolic activities.	It works well with combination therapy and helps effectively function with other types of cancer therapy, like immunotherapy.	Requirement of drug delivery system for effective transport to the target site.	Under study, it works well with other formulations.	[48,91,81,35,95]
4.	Tumor vasculature	Essential for maintaining the TME.	The drug does not require nanoformulations since it can directly interact with endothelial cells and is effective for cancer therapy.	Not specified.	Under the study, however, smart nanotherapeutic technology can help bring it to the market.	[257,233,235,253,244]
5.	Tumor-associated macrophages	The most important part of the TME is that it helps in tumor cell proliferation and cancer progression.	Easy to change the phenotypes of TAMs to M1, which helps to bring the pH to the neutral range.	Not specified.	Under study and has excellent potential for cancer treatment, works well with nanotherapeutic technology, and enhances immunotherapy.	[267,273,265]
6.	Extracellular matrix	TME is dependent on the ECM for cell-to-cell and cell-to-matrix communication.	It can be well-targeted for cancer therapy. Excellent biomarker for diagnosis of cancer.	Not specified.	Under study	[277,294,282]
7.	Exosomal Proteins	Present in the TME and help in the cell-to-cell interactions and signal transduction pathways.	Low toxicity with less to no side effects. It can be used as a biomarker to diagnose cancer.	Scaling up and manufacturing exosomes is difficult.	Not so feasible, but it can work out with drug delivery systems.	[48,154,158,189,177,162]
8.	PD-1 or PD-L1 proteins	Immune checkpoints can help to reduce tumor progression.	Reduce tumor progression, acts as an immunomodulator, enhances immunotherapy, and aids in cancer treatment.	Not specified.	Pembrolizumab, Nivolumab, and Atezolizumab are FDA-approved drugs and are effective for cancer treatment.	[320,307,299,312,335,315,338]
9.	CTLA-4 proteins	Regulates immune response. Blocks the interaction between CD28 of T cells and CTLA-4 proteins.	The therapeutic target for melanoma treatment. Anti-CTLA-4 inhibitor called Ipilimumab.	Side effects are possible. Other mAbs and anti-CTLA-4 agents are under study.	Ipilimumab is an FDA-approved drug available for the treatment of melanoma. Other drugs under clinical studies.	[296,295,299,312,345,315]
10.	TIM-3 proteins	Immune checkpoint protein prevents autoimmune reactions.	The potential therapeutic target for cancer treatment.	Currently under clinical studies	Not feasible. No available treatments.	[295,350,354,353,335]
11.	VISTA proteins	Also known as PD-1 H, it is a co-inhibitor ligand against APCs and regulates the T cell immune responses.	Potential therapeutic target for cancer treatment.	The mAbs are under clinical trial.	Currently, no available treatments.	[295,350,354,353]
12.	TIGIT proteins	It acts as an inhibitory immune checkpoint molecule and has binding capacity with 3 ligands – CD155, CD112 and CD113.	A therapeutic target for cancer treatment.	Under study and clinical trials	The tiragolumab and atezolizumab approved for BTD by the FDA.	[346,347]
13.	LAG-3 proteins	Inhibits the interaction between antigens and T cell receptors. They are also expressed on TILs.	A potential target for cancer immunotherapy.	No treatment is available yet under clinical trials.	Currently recruited for clinical trial studies.	[346,295,299,347]

and is under the clinical recruiting stage (NCT02812875). This oral inhibitor exhibited anti-tumor properties in the phase-I clinical trials and was bearable for patients suffering from advanced solid tumors and lymphomas [350,354]. Another drug under study is the JNJ-61610588, a fully human anti-VISTA mAb made by Johnson and Johnson, which is under phase-I clinical trials and is currently in recruiting stage (NCT02812875) [353,354].

4.2.6. T cell immunoreceptor with Immunoglobulin and ITIM domains (TIGIT) proteins

TIGIT is another inhibitory immune checkpoint molecule currently under study to be utilized as a potential target of immune checkpoint blockade drugs [347]. This receptor type is expressed in T cells, T regulatory cells, and activated natural killer (NK) cells. It has a binding capacity with three ligands, CD155, CD113, and CD112. In the tumor cells, the CD155 ligand is overexpressed and upregulates the TIGIT expression in TILs, primarily identified in NSCLC [346,356]. Many mAbs are being studied to target the TIGIT in cancer cells and help in treatment. The mAb, Etigilimab, was tested individually and in combination with nivolumab and was found effective in evading advanced solid malignancies. Even though the phase I clinical trials were positive, it was discontinued. Other mAbs under study include tiragolumab and atezolizumab, evaluated in 2018 in a phase II clinical trial to test the safety and efficacy of the combined therapy toward NSCLC. It was found that both the mAbs improved the objective response rate and had a safe and favorable profile. In 2021, it was granted a breakthrough therapy designation (BTD) by the FDA and was to be utilized for first-line treatment for patients with metastatic NSCLC [346,357] (Table 1).

4.3. Targeting epigenetic regulators via PROTACS and CRISPR/Cas9

Wang et al. [358] validated that CRISPR/Cas9-mediated site-specific target methylation facilitated the monitoring of gene silencing in vivo and in vitro. They have also demonstrated that combining CRISPR/Cas9 components, the long methylated homology-directed repair template, and SCR7 treatment can improve CRISPR/Cas9-directed epigenomic editing effectiveness while inducing consistent impacts on transcriptional suppression and methylation modifications [358]. Fusion enzymes like DNA methylases, deacetylases, and histone acetyltransferases, can be targeted to change the epigenetic state at specific sites in the genome by using inactive dCas9 as a DNA-binding domain platform [359]. EpiCas9s, Cas9 epigenetic effectors, can be employed for genome-wide screening to identify new connections between chromatin states, epigenetic modifications, and phenotypes like disease progression or cellular differentiation. It would provide a more adaptable platform to investigate the causal roles of epigenetic modifications in forming the regulatory networks of the genome because it is possible to artificially add or remove specific epigenetic marks at specific loci [360].

Proteolysis targeting chimeras (PROTACs) are heterobifunctional molecules that target the natural ubiquitin proteasome mechanism to enable selective protein degradation [361] in order to inhibit tumor growth [362]. By modifying gene expression and protein functions, the various types of epigenetic enzymes, such as "readers," "writers," and "erasers," contribute to various cellular processes and pathogenesis. All three categories of epigenetic proteins have been addressed by PROTACs [361]. Numerous PROTAC degraders have been extensively developed in epigenetic cancer therapy, and recent rapid advancements in PROTACs have made it easier to investigate targeting epigenetic proteins. Additionally, PROTACs that target epigenetic proteins can effectively exploit target druggability and advance the understanding of the epigenetic regulation of cancer [363]. Studies by ARV-471 have unequivocally demonstrated that PROTAC, combined with kinase inhibitors, including CDK4/6 inhibitors, could synergistically affect tumor inhibition. It implies that using PROTAC combined with targeted inhibitors, chemotherapeutics, and antibody drugs may be an excellent alternative to treating cancer [362].

4.4. Targeting the signal transduction pathways

Several studies have targeted several signal transduction pathways to treat cancer. GSK-3β is a regulator of the signaling pathway which can be targeted for cancer therapy. As per an experiment conducted by Abrams, Akula, Meher, et al. [364], a link has been found between K-Ras and GSK-3β and is responsible for causing pancreatic cancer [365,366]. GSK-3β inhibitors can be utilized to degrade the GSK-3β in order to prevent this severe form of cancer [367-369]. More studies are needed to assess the role of GSK-3β in other types of cancers, so that it can be utilized as an effective chemotherapeutic drug [364]. Also, the mutations caused in the tumor suppressor TP53 gene are responsible for causing cancer and activating the K-Ras signaling pathway resulting in tumorigenesis [370,371]. Using miRNAs that can help reverse the mutation in TP53 and bring back its cell growth regulatory function can help prevent the progression of pancreatic ductal adenocarcinoma (PDAC) and increase the survival rate of the patients. However, further studies will be required to identify those miRNAs [370,372]. Another experiment was done on the colon cancer cells to understand the role of the neurokinin-1 receptor, which enhanced tumor metastasis, angiogenesis, and cancer progression [373]. The ligand involved in the tumor progression was substance P which was part of the tachykinins family [373-376].

Oncogenic mutations can develop mutant proteins whose action is dysregulated, for example, fusions, truncations, and point mutations, and generate overexpression of the afflicted genes, such as gene amplification. Models incorporate proteins engaged with signaling pathways that are typically enacted in numerous physiological reactions, such as threonine/serine kinases, for example, Akt and Raf; growth factor receptor tyrosine kinases (RTKs), for example, EGFR (epidermal growth factor receptor); small GTPases such as Ras; cytoplasmic tyrosine kinases, for example, Abl and Src; nuclear receptors which include the ER (estrogen receptor); as well as lipid kinases such as PI3Ks (phosphoinositide 3-kinases). Parts of formative signaling pathways, such as Notch, Hedgehog, Wnt, and Hippo, can likewise be impacted, as can downstream nuclear targets of signaling pathways—for instance, chromatin remodelers like EZH2, transcription factors, for example, NF-κB and Myc and cell cycle effectors such as cyclins [377].

4.4.1. Wnt/ β-catenin signaling pathway

Integrin-linked kinase (ILK) is a serine/threonine kinase that interfaces with the cytoplasmic domains of b3 and b1 integrins. It contains ankyrin repeats. ILK is also thought to function in the growth factor and Wnt signaling pathways, as well as the signaling pathways that control the activity of NFKB [378]. Cancer, human birth abnormalities, and other disorders are frequently associated with mutations in the Wnt pathway. Canonical Wnt signaling controls the release of the transcriptional co-activator β-catenin, which affects essential developmental gene expression processes, and is one of the most researched Wnt pathways [379].

In most inherited and sporadic Colorectal Cancers, the initial event is assumed to be the mutational inactivation of the APC (Adenomatous Polyposis Coli) tumor suppressor. When APC is perturbed, the Wnt Signaling pathway is activated, and wnt hyperactivation is the primary oncogenic driver in most malignancies, mainly in colorectal cancers [380]. Metastasis is a defining feature of delayed-stage cancer and a significant therapeutic obstacle. Inhibition of PI3K-Akt signaling pharmacologically causes a nucleus buildup of FOXO3a and β-catenin in colon cancer cells with hyperactivated canonical Wnt signaling, resulting in enhanced metastasis and cell scattering. A particular antibody targeting Fzd2 lowers colon cancer metastasis and tumor growth [381] (Fig. 3).

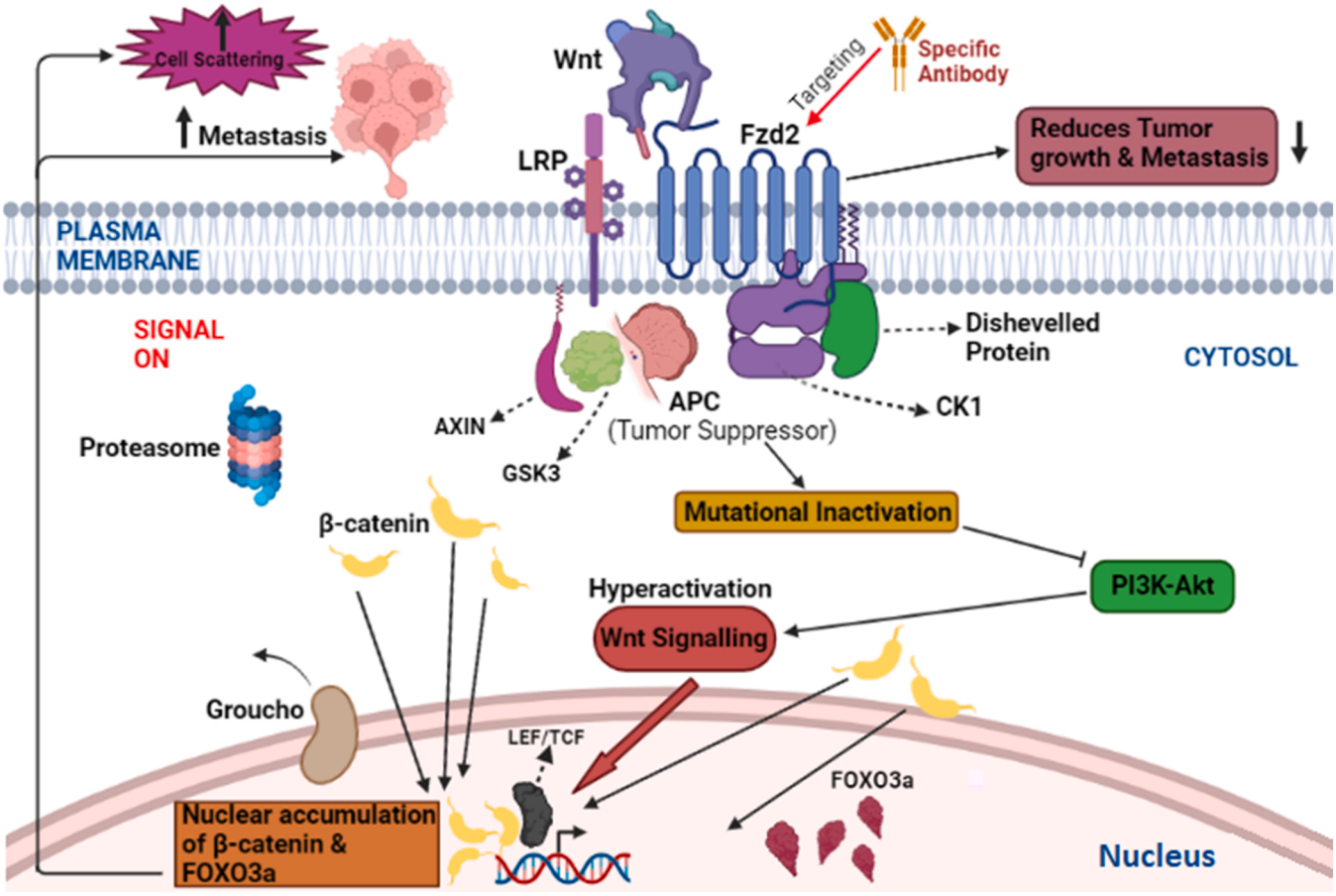

Fig. 3. Hyperactivation of Wnt Signalling leading to colorectal cancer and reduced metastasis by targeting Fzd2 with specific antibodies.

4.4.2. Hedgehog Signaling Pathway

If there is abnormal activation of the Hedgehog pathway, it may lead to tumorigenesis and cancer maintenance in various malignancies. Therefore, tackling it could lead to new treatment prospects. In contrast to the high positive outcomes in Basal Cell Carcinoma, Hedgehog inhibition fails to show promising effects in various cancer types, such as pancreatic cancer, lung cancer, and leukemia, underscoring the need for a deeper study of Hedgehog signaling in cancer [382].

The biological effects of the hedgehog signaling pathway are mediated by a signaling cascade that shifts the balance of activator and repressor forms of glioma-associated oncogene (Gli) transcription factors. Smoothened (SMO)-Gi-RhoA, SMO-SUFU-GLI, and signaling cascades receive hedgehog signals via Patched receptors [383]. The Hh signaling pathway's essential target genes are GLI1, PTCH1, and PTCH2. The end effectors of the Hedgehog pathway, the GLI1 zinc-finger transcription factors, are liberated from SUFU (suppressor of fused) mediated cytoplasmic sequestration, allowing target gene activation and nuclear translocation [384]. Downregulation of the Hh signaling pathway has been linked to spontaneous malignancies, notably medulloblastoma, small cell lung carcinomas, basal cell carcinoma, ovarian, pancreatic, colon, and breast cancers, and developmental defects and cancers like Gorlin syndrome. Excessive production of Hedgehog signaling molecules (ligand-dependent signaling – paracrine or autocrine) or mutations in related genes (ligand-independent signaling) or induce abnormal activation of the Hedgehog signaling pathway [385]. Some proteins like F-box and leucine-rich repeat protein 17 (Fbxl17), RARα2, IL-27, IL-6, PPKCI, HDAC6, SCUBE2, CK2α, RUXN3, USP48, GALNT1, WIP1, Vasohibin 2 (VASH2), p65, forkhead box C1 (FOXC1) and BCL6; lncRNA HDAC2 and microRNAs (miR-326, miR-122, and miR-324–5p) are associated in the Hedgehog pathway during its activation to affect the growth of cancer stem cells [386].

4.4.3. NOTCH signaling pathway

Notch signaling is a fundamental, evolutionarily conserved cell fate-determination system, similar to the Wnt and Hedgehog pathways. The connection between adjacent cells is predominantly mediated by Notch signaling via receptors and transmembrane ligands [387]. Crosstalk with the Wnt and Hedgehog pathways could also influence Notch signaling's long-term effect, adding another degree of intricacy [388]. The expression of multiple genes, including Shh, c-Myc, NF-κB, and β-catenin, is upregulated when the Notch signaling pathway is activated. Oral squamous cell carcinoma tumor aggressiveness has been demonstrated to be enhanced by associations between the Notch signaling system and other pathways. Crosstalk, among such pathways, promotes the survival of cancer stem cells and governs the motility of oral squamous cell carcinoma cells [389].

A fully functional Notch receptor attaches to a ligand Jag1–2 or Dll1–4 provided by a neighboring cell, causing the receptor's conformation to shift, exposing the recognition site for cleavage by γ-secretase and ADAM, culminating in the release of the functional Notch intracellular domain. The Notch intracellular domain is then translocated to the nucleus, forming a complex with the DNA-binding protein CSL, which activates target gene transcription [390]. Since the E-cadherin/catenin complex has been linked to the progression of HCC, it was hypothesized that inhibiting Wnt/-catenin signaling might be employed as a target complex for developing anti-HCC therapeutics. The notch-1/NF-kB signaling pathway has also been considered a target for EMT-related targeted therapy [391]. In the Notch signaling cascade, there are both canonical and non-canonical mechanisms. The five classic Notch ligands identified are the Delta-like ligands DLL1, DLL2, DLL3,

and DLL4, as well as Jagged1 and Jagged2. Notch1, Notch2, Notch3, and Notch4 are the four Notch receptor paralogues identified thus far. Distinct cells can express different Notch ligands and receptors, indicating that the Notch pathway is diverse and versatile. Non-canonical Notch pathways may be relevant to cancer onset and maintenance [392].

4.4.4. Cell cycle

Profound cell cycle egress with combinations of CDK4/6 inhibitors, preferentially targeting malignancies that have depleted RB1, and widening the therapeutic index by reducing side effects associated with such therapies are all possible therapeutic methods. RB1 also affects the tumor microenvironment and immunology, which can improve immunotherapy sensitivity [393]. Without RB1, multiple interferon-response genes cannot be adequately activated. This trait of "non-inducibility" is thought to be one of the most critical consequences of RB1 disruption by viral oncoproteins such as HPV-E7, which enables immune surveillance to be bypassed. RB1 is involved in the activity of NF-kB and CIITA, which are essential indicators of such responses [394,395]. Many disorders, particularly cancer, deregulate the TGF-β signaling pathway. This pathway possesses tumor-suppressor activities in early-stage cancer cells and healthy cells, involving apoptosis and cell-cycle arrest [396].

The cell cycle is regulated by several mechanisms that ensure proper cell division. Mechanisms include CDK (cyclin-dependent kinases) inhibitors, cyclins' regulation of CDK, and phosphorylation processes. CDK dysregulation is a feature of cancer, and suppression of particular members is a promising target for cancer therapy [397]. Fundamental changes in the genetic regulation of cell division occur in cancer, leading to unregulated cell proliferation. Tumor suppressor genes and proto-oncogenes are the two types of genes where mutations are most common. The products of protooncogenes activate at various stages along the pathways that trigger cell proliferation in normal cells. Proto-oncogenes or oncogenes that have been mutated can increase tumor growth. When tumor suppressor genes like p53 and pRb are inactivated, proteins that usually control cell cycle progression become dysfunctional. Mutations cause cancer-related cell cycle dysregulation in proteins crucial at different stages. Cyclins, CDK, CKI, CDK activating enzymes, CDK substrates, and checkpoint proteins have all been found to have mutations in cancer [398]. Rather than irreversible allosteric inhibition, reversible, irreversible ATP-competitive (covalent) inhibition, reversible and antibody–drug conjugation, CDK inhibitor medicines have been tested in several clinical trials in breast cancers. These inhibitors target malignant cells' cell-cycle regulators, offering a therapeutic window in which cancer cells' defects can be targeted with bearable side effects from general tissue damage [397].

5. Approaches to improve the pharmacological properties of proteins and peptides

Determining the pharmacokinetic profile of a protein molecule within the body is influenced by various factors, including but not limited to its size, shape, hydrodynamic radius, and charge. Proteins and peptides smaller than the glomerular filtration size cutoff are more prone to elimination via kidney filtration than larger proteins [399]. Additionally, negatively charged proteins may be removed slower due to the repulsion caused by the charged basement membrane of the kidney [400]. These findings have been reported in previous studies. The increasing quantity of protein therapeutics under investigation, along with the emergence of antibody fragments and alternative scaffolds that extend beyond native IgG molecules, has prompted the need for inventive approaches to adjust protein residence time in the bloodstream. A good pharmacokinetic profile can enhance the effectiveness of a compound by prolonging the duration of exposure to the intended target and, in numerous instances, reducing the quantity or frequency of administrations, thereby providing both economic and therapeutic advantages [20].

The feature of stability holds significant importance for any protein therapeutic. It is because the utilization of sophisticated protein engineering techniques to enhance targeting, efficacy, and pharmacokinetic parameters would be rendered futile if the molecule undergoes physical or chemical degradation before executing the intended function. In addition, maintaining stability is of utmost importance in achieving cost efficiency in large-scale goods production. To maintain its potency and prevent degradation or aggregation, a therapeutic agent must maintain its physical and chemical integrity throughout the production and storage processes. In addition, the current scenario of protein therapies being highly competitive necessitates the development of more potent molecules that can be expedited to the market and exhibit extended shelf lives upon arrival. Several engineering techniques have been utilized to enhance the stability of protein therapies. A method that has been demonstrated to correlate with increased thermal stability and recombinant expression yield involves the identification of protein variants that exhibit elevated cell surface expression levels in response to varying temperature stresses [401]. One possible approach entails utilizing spatial aggregation propensity (SAP) technology to identify antibody regions susceptible to aggregation, followed by introducing specific mutations to enhance antibody stability [402]. A contemporary technological advancement pertains to utilizing affinity-capture self--interaction nanoparticle spectroscopy (ACSINS) to scrutinize extensive arrays of antibodies concerning their inclination to self-aggregate [403]. Additional techniques for enhancing protein stability have been examined in recent literature. These methods encompass physical cross-linking, isotype switching, and identification of off-target binding, which may result in prompt protein elimination [404-407].

The potential to elicit an undesired immune response is an inherent risk associated with administering non-native proteins as therapeutic agents in the human body. The effective management of the immunogenicity profile of a therapeutic candidate is a crucial aspect of achieving success in drug development. The immunogenicity of a protein therapeutic is influenced by various factors, including those related to the patient and the product. The latter has been the subject of extensive review in recent literature, as evidenced by sources [408,409]. The current pragmatic strategies for reducing immunogenicity in the development of protein drugs consist of humanization and alteration of the primary sequence to eliminate or conceal potential T and B cell epitopes, as well as thorough immunogenicity assessment. A set of tools has been devised to forecast CD4 + T-cell reactions, encompassing both in silico and in vitro techniques. Furthermore, various in vivo tools have been utilized, including traditional mouse models, immune-tolerant transgenic mice, HLA-immune-tolerant transgenic mice, and non-human primate models [20,410].

6. Challenges to the usage of proteins and peptides therapeutics in cancer treatment

Proteins have been successfully applied in a wide variety of medicinal contexts recently. However, there have been far more failed attempts at using proteins as medicines than triumphs. It is due in part to the numerous obstacles that must be overcome. Protein therapies have not been widely used because of issues with solubility, delivery, distribution, and stability [411,412]. Proteins are large molecules with hydrophilic and hydrophobic qualities that can make entry into cells and other body compartments problematic, and proteases, protein-modifying compounds, or other clearance processes can substantially reduce the half-life of a therapeutic protein. The development of PEGylated therapeutic proteins is one approach to overcoming these obstacles. Polyethylene glycol (PEG) is added to modified forms of interferon to extend their half-lives, diminish their immunogenicity, delay their breakdown by enzymes, and delay their absorption and renal clearance [413].

Notably, the body may develop an immunological response to the therapeutic protein, which presents a further obstacle [414]. This

immune response can inhibit the protein's therapeutic effects or trigger an adverse reaction in the patient. Antifactor VIII antibodies (inhibitors) developed in patients with severe hemophilia-A who were treated with recombinant human factor VIII are an example of an immune response established against a Group Ia therapeutic protein used to replace a factor that has been absent from birth [415,416]. Nevertheless, immunological responses are typically triggered by foreign proteins. Prior to recently, immune responses induced quickly against this type of therapeutic proteins, limiting the widespread clinical application of mAbs. Many other antibody products have been developed using recombinant technology and other innovations that make them less likely to cause an immune response. Entirely human antibodies can be created utilizing transgenic animals or phage display technologies. In contrast, humanized antibodies replace non-essential regions of the antibody with human Ig sequences, which confer stability and biological activity on the protein without provoking an anti-antibody response [417,418].

7. Conclusion

This review summarizes the benefits of protein and peptide therapeutics in treating various types of cancer. Targeting signaling pathways and genetic alterations and using peptide-based anticancer drugs loaded by drug nanocarriers is a highly potential set of techniques that can be used in treating patients individually and promoting personalized cancer treatment for patients. These techniques can help to identify proteins as biomarkers for early diagnosis so that treatment is immediately provided and the patients return healthy. Here, we discussed the various therapeutic peptides and molecular-targeted therapies that can be practiced to target the tumor site and kill the specific cells without affecting the other healthy cells. mAbs, exosomal proteins, immune checkpoint proteins, drug nanocarriers, and drug delivery systems are potential cancer treatments that have proven highly effective under in vitro and in vivo techniques. Hence, ongoing studies and experiments of these proteins and peptide therapy will later help treat cancer more effectively, efficiently, safely, and feasibly.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Abilash Valsala Gopalakrishnan, Achraf El Allali, Alsamman M. Alsamman: Conceptualization. **Achraf El Allali, Alsamman M. Alsamman, Hatem Zayed, C. George Priya Doss**:Resources, Data curation. **Achraf El Allali, Abilash Valsala Gopalakrishnan, Balachandar Vellingiri, Abhijit Dey, Raja Ganesan:** Supervision. **Anirban Goutam Mukherjee, Uddesh Ramesh Wanjari, Pragya Bradu, Antara Biswas**: Writing – original draft preparation. **Anirban Goutam Mukherjee, Uddesh Ramesh Wanjari, Abilash Valsala Gopalakrishnan, Abhijit Dey, Balachandar Vellingiri, Kaviyarasi Renu, Raja Ganesan**: Writing – review & editing. **Abilash Valsala Gopalakrishnan, Achraf El Allali, Alsamman M. Alsamman, Hatem Zayed**: Visualization. **Abilash Valsala Gopalakrishnan, Abhijit Dey, Raja Ganesan**: Supervision. **Abilash Valsala Gopalakrishnan, Balachandar Vellingiri, Abhijit Dey, Raja Ganesan**: Project administration. All authors have read and agreed to the published version of the manuscript.

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 paper.

Data availability

The articles analysed during the current study are available in the literature and listed in the references.

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